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Pincer complexes as advantageous palladium sources for synthetic transformations

MEMORIA PRESENTADA POR

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Ama & Aita

Aitor

“***Si buscas resultados distintos, no hagas siempre lo mismo***”

Albert Einstein (1879 - 1955)

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Parte de los resultados recogidos en esta memoria han sido objeto de las siguientes publicaciones:

1. "*Synthesis, Structure, and Catalytic Applications for ortho- and meta-Carboranyl Based NBN Pincer-Pd Complexes*"

Min Ying Tsang, Clara Viñas, Francesc Teixidor, José Giner Planas, Nerea Conde, Raul SanMartin, María Teresa Herrero, Esther Domínguez, Agustí Lledós, Pietro Vidossich and Duane Choquesillo-Lazarte.

Inorganic Chemistry **2014**, *53*, 9284.

2. "*A Further Decrease in the Catalyst Loading for the Palladium-Catalyzed Direct Intramolecular Arylation of Amides and Sulfonamides*"

Nerea Conde, Fátima Churruca, Raul SanMartin, María Teresa Herrero, Esther Domínguez.

Advanced Synthesis and Catalysis **2015**, *357*, 1525.

Así mismo se han presentado las siguientes comunicaciones a congresos:

1. "*A straightforward access to pyrazolo(benzo)thienoquinolines*"

Susana Hernández, Maria Perea, Fátima Churruca, Raul SanMartin, Nerea Conde, Maria Teresa Herrero, Aimar García, Iratxe Astarloa, Ester Domínguez.

European Symposium on Organic Chemistry (ESOC 2013)

Marsella (France), 7-12 July 2013 (Comun. en forma de Póster)

2. "*Direct arylation of N-aryl-o-halobenzamides as an advantageous protocol for the synthesis of phenanthridinones*"

Nerea Conde, Fátima Churruca, Raul SanMartin, Maria Teresa Herrero, Esther Domínguez.

European Symposium on Organic Chemistry (ESOC 2013)

Marsella (France), 7-12 July 2013 (Comun. en forma de Póster)

3. "*Síntesis de nuevos sistemas poliheterocíclicos a través de reacciones de arilación directa*"

Susana Hernández, Maria Perea, Fátima Churruca, Raul SanMartin, Nerea Conde, Maria Teresa Herrero, Esther Domínguez.

XXXIV Reunión Bienal de laReal Sociedad Española de Química

Santander (España), 15-18 Septiembre 2013 (Comun. en forma de Póster)

4. “Acceso directo a fenantridinonas en ausencia de agentes transmetalantes”

Nerea Conde, Fátima Churruca, Raul SanMartin, Maria Teresa Herrero, Esther Domínguez.

XXXIV Reunión Bienal de laReal Sociedad Española de Química

Santander (España), 15-18 Septiembre 2013 (Comun. en forma de Póster)

5. “*New synthetic methodologies based on sustainable procedures*”

Esther Domínguez, Raul SanMartin, Imanol Tellitu, Maria Teresa Herrero, Isabel Moreno, Maria Jesús Moure, Jokin Díaz de Sarralde, Garazi Urgoitia, Nerea Conde, Iratxe Astarloa, Yuliet A. Rincón, Izaskun Dávila.

IV Jornadas de Investigación de la Facultad de Ciencia y Tecnología

Leioa (España), 12-13 Febrero 2014 (Comun. en forma de Póster)

6. “*Intramolecular direct arylation of amide derivatives*”

Nerea Conde, Fátima Churruca, Raul SanMartin, Maria Teresa Herrero, Esther Domínguez.

1er Workshop UFI-QOSYC PARA JÓVENES INVESTIGADORES

Leioa (España), 11 Abril 2014 (Comunicación Oral)

7. "*A decrease in the catalyst amount for palladium-catalyzed intramolecular direct arylation*"

Nerea Conde, Fátima Churruca, Raul SanMartin, Maria Teresa Herrero, Esther Domínguez.

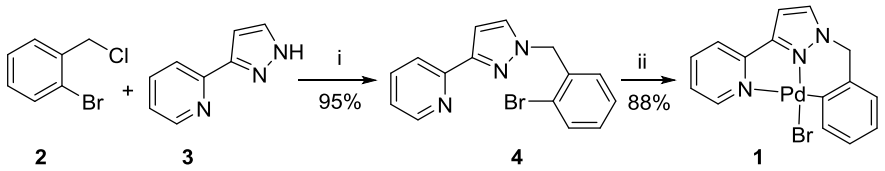
International Symposium on Synthesis and Catalysis 2015 (ISySyCat2015)

Évora (Portugal), 2-4 Septiembre 2015 (Comunicación Oral)

Resumen

El trabajo de investigación que se recoge en la presente memoria se ha centrado en el desarrollo de nuevos catalizadores de paladio tipo pincer y en el estudio catalítico de los mismos en una amplia variedad de transformaciones sintéticas.

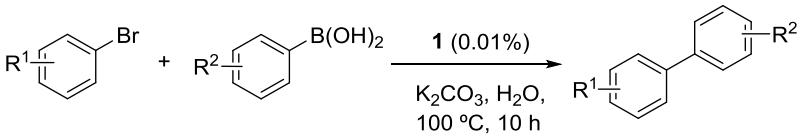
De este modo, en el primer capítulo se describe la preparación de un nuevo complejo de paladio no-simétrico NNC, la cual se llevó a cabo en dos pasos sintéticos. En el primero se realizó una modificación de las condiciones publicadas para la alquilación de pirazoles obteniendo unos resultados excelentes en la formación de intermedio bencílico **4**. Partiendo del mismo, la inserción del paladio tuvo lugar a través de un proceso de adición oxidante + coordinación, dando como resultado el complejo de paladio **1** deseado. La estructura del nuevo complejo pincer se confirmó de manera inequívoca mediante difractometría de Rayos X.



2 **3** **4** **1**

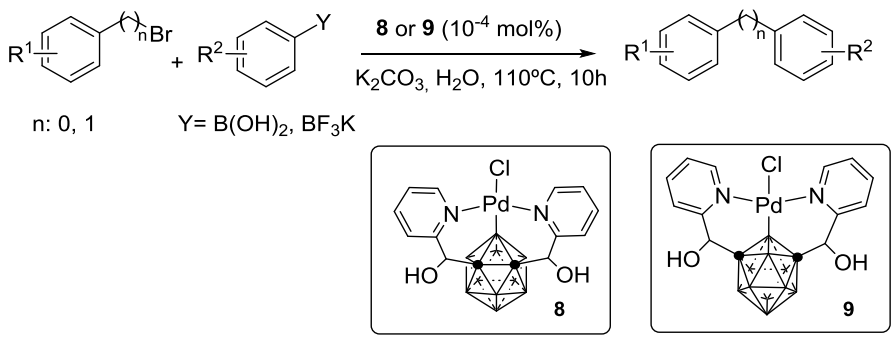
i: aq. NaOH 40%, aq. ^{n}BuNOH 40%, PhMe, 120 ºC, 48 h
ii: $Pd(dba)_2$, THF, 120 ºC, 8h

Una vez sintetizado el pincer **1** se llevo a cabo el estudio catalítico del mismo en la reacción de acoplamiento cruzado Suzuki-Miyaura. Primero, se realizaron varios ensayos para optimizar las condiciones de reacción. A continuación, se ensayaron en una gran variedad de ácidos arilborónicos y bromuros de arilo, obteniendo resultados excelentes tanto desde el punto de vista del rendimiento de los biarilos así preparados como de la carga catalítica empleada en dicha transformación.

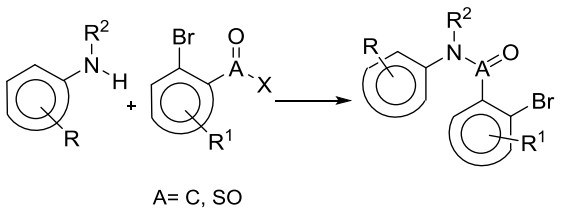


Además, merced a una colaboración con el grupo de Dr. Josep Giner del *Institut de Ciència de Materials de Barcelona*, tuvimos la oportunidad de realizar el estudio catalítico de los pincer de naturaleza carboboránica **8** y **9,** los cuales resultaron ser excelentes catalizadores o pre-catalizadores en varios acoplamientos tipo Suzuki, mostrando una alta tolerancia a la presencia de grupos funcionales. Hay que mencionar que dicha reacción se

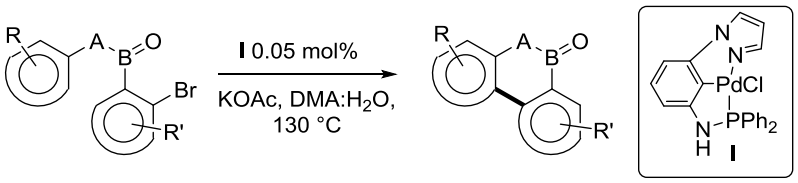
llevó a cabo en un medio acuoso y empleando cargas de catalizador muy bajas.



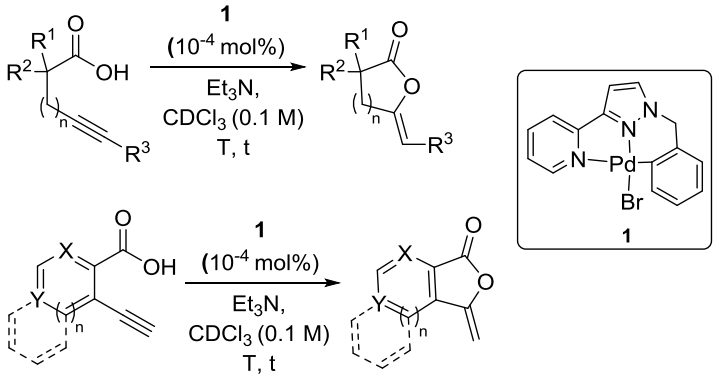
Así mismo, en el segundo capítulo se muestra cómo se llevó a cabo la arilación directa de una serie de *o*-bromo-*N*-arilbenzamidas y *o*-bromo-*N*-arilsulfonamidas previamente sintetizadas a través de distintos procedimientos.



La arilación directa intramolecular en estos sustratos se realizó en presencia del pincer de paladio no-simétrico PCN **I**, dando lugar al desarrollo de un nuevo protocolo muy eficiente para la formación de fenantridinonas, sultamas biarílicas y derivados heterocíclicos afines en presencia de cargas bajas (0.05 mol%) de dicha fuente de paladio **I**.

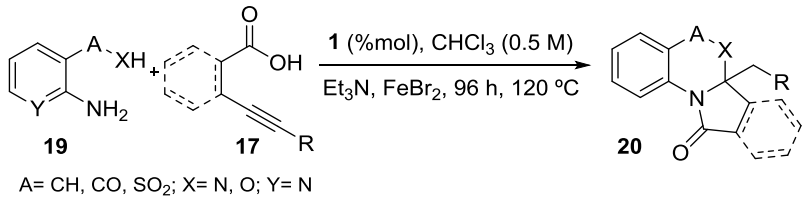


Por otro lado, empleando el catalizador **1** previamente mencionado, en el tercer capítulo se presenta la puesta a punto de las condiciones para llevar a cabo la reacción de cicloisomerización de ácidos alquinóicos, dando así lugar a las correspondientes lactonas vinílicas exocíclicas con muy buenos rendimientos. Este procedimiento además de emplear cargas catalíticas muy bajas del pincer de paladio **1** (10^{-4} mol%) y de cumplir todas las premisas de los postulados de la economía de átomos, presenta una alta tolerancia a la presencia de sustituyentes tanto en la posición α como en la β de los ácidos alquinóicos.



El conocimiento adquirido con la anterior transformación, se aplicó a la reacción entre ácidos alquinóicos y dinucleófilos, accediendo así a sistemas tri- y tetracíclicos con una complejidad media (pirrolo-, inodolo- y piridobenzoxazinadionas, piridoquinazolinonas y benzopiridotiadiazinonas *inter alia*).

Esta reacción en cascada se realizó empleando cargas relativamente bajas del complejo **1** en presencia de $FeBr_2$ como co-catalizador, formando tres nuevos enlaces a través de un proceso tándem.

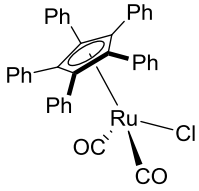


19 **17** **20**

A= CH, CO, SO_2; X= N, O; Y= N

Finalmente, en el último capítulo se describe el trabajo llevado a cabo bajo la supervisión del Profesor Bäckvall en el Departamento de Química Orgánica del Arrhenius Laboratory de la Universidad de Estocolmo. En él, se realizaron ensayos iniciales de reacciones de racemización y resolución cinética, base para el desarrollo de un nuevo método de resolución cinética dinámica de alcoholes alílicos.

Para poder realizar dichos ensayos fue necesaria la síntesis del alcohol racémico **36**, sintetizado en dos etapas de reacción con muy buen rendimiento, y del mismo modo la del catalizador **32** que se empleó en el proceso de racemización.



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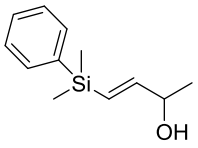

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Nota:

Las referencias bibliográficas de esta Tesis Doctoral se recogen al pie de cada página y son independientes en cada uno de los Capítulos en que se divide la Memoria, por lo que en los casos en que se ha considerado oportuno han sido repetidas para comodidad del lector.

Abbreviations, acronyms and symbols

Ac	Acetyl
Ar	Aryl
br	Broad
Bu	Butyl
^{t}Bu	*tert*-Butyl
^{o}C	Celsius degree
C_{arom}	Aromatic carbon
CTAB	Cetyltrimethylammonium bromide
cyphos	1,2-Bis(dicyclohexylphosphino)ethane
DDA	Dimethyldioctadecylammonium bromide
DMF	Dimethylformamide
δ	Chemical shift
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
DDA	Dimethyldioctadecylammonium bromide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DKR	Dynamic kinetic resolution
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane

EDS	Energy-dispersive X-ray spectroscopy
e.g.	For example
equiv.	Equivalent(s)
Et	Ethyl
et al.	And others
EI	Electronic impact
ESI	Electrospray ionization
FVP	Flash vacuum pyrolysis
g	Gram(s)
GPCR	G protein coupled receptors
h	Hours
$\mathbf{H_{arom}}$	Aromatic hydrogen
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
5-HT	5-Hydroxytryptamine
Hz	Hertz
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
J	Coupling constant
KR	Kinetic resolution
LDA	Lithium diisopropylamide
Lit.	Literature
m	Multiplet
M	Molar
Me	Methyl

mg	Milligram(s)
min	Minute(s)
mL	Mililitre(s)
mmol	Milimol(s)
m.p.	Melting point
MTBE	Methyl tert-butyl ether
NMP	N-methylpyrrolidone
NMR	Nuclear magnetic resonance
PAH	Polycyclic aromatic hydrocarbon
Ph	Phenyl
PVPy	Polyvinylpyridine
Py	Pyridine
q	Quaternary, quartet
r.t.	Room temperature
s	Singlet
t	Time
T	Temperature
tacn	1,4,7-Triazacyclononane
TBAB	Tetrabutylammonium bromide
TCM	Transcyclometallation
TEM	Transmision electron microscopy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TON	Turnover number
TOF	Time of flight

UPLC	Ultra performance liquid chormatography
UV	Ultraviolet
wt.	Weight

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I

Application of two new Pd pincer complexes in Suzuki cross-coupling

1. INTRODUCTION

1.1. Sustainability and catalysts

The first industrial revolution and its technological advances meant a huge change in the world economy and brought along an undeniable impact on the global environment. This revolution involved an overwhelming increase in the world population, changing costumer behaviour and helping the advance of the science. As the population and the technological development were increasing, so did the consumption of natural resources and the contamination from industries.[1]

Nevertheless, until the end of the 20th the idea of sustainable development did not emerge. This "philosophy" was an enormous adjustment for the mentality in society and industry. In the case of the chemical industry, it was not until 1991 that the term "Green Chemistry" appeared. It was defined by Paul T. Anastas as the design of chemical products and processes that reduce or eliminate the amount of dangerous residues.[2] Nowadays, this idea of "Green Chemistry", whose aim is to carry out processes with high atomic economy to avoid the formation of non-desired by-products, thus

[1] A. Valavanidis, T. Vlachogiann in *Green Chemistry and Green Engineering: from Theory to Practice for the Protection of the Environment and Sustainable Development*, Synchrona Themata, Athens, **2012**.

[2] P. T. Anastas, J. C. Warner in *Green Chemistry Theory and Practice*, Oxford University Press, New York, **1998**.

minimizing the contaminating residues, is increasingly accepted by industry.[3]

The use of catalysts provides a useful tool in the search of sustainable processes. These reagents are used in substoichiometric amounts speeding up chemical processes. Sometimes, they can be recycled thereby it is possible to carry out transformations with a lower amount of waste and energy expenditure than in non-catalyzed reactions. Moreover, catalytic chemistry has undergone a great development in recent years, especially in the area of metal catalysis.[4] As it is well-known, at the beginning only pure metal or metal salts were used as catalysts but during the years more sophisticated ones have been reported. A huge step in metal catalysis was made by Cope and co-workers when they first described a metallacycle.[5] These compounds are defined as organometallic complexes with one C-M bond which is intramolecularly stabilized by at least one coordinating donor atom (Figure 1.1).

[3] *Green Chemistry in the Pharmatheutical Industry*, (Eds.: P. J. Dunn, A. S. Wells, M. T. Williams), Wiley-VCH, Weinheim, **2010**.

[4] a) R. H. Crabtree in *The Organometallic Chemistry of the Transition Metals*, *6th ed.*, Wiley, Hoboken, **2014**; b) *Applications of Transition Metal Catalysis in Drug Discovery and Development*, (Ed.: M. L. Crawley, B. M.Trost), Wiley, New Jersey, **2012**.

[5] A. C. Cope, R. W. Siekman *J. Am. Chem. Soc.* **1965**, *87*, 3272.

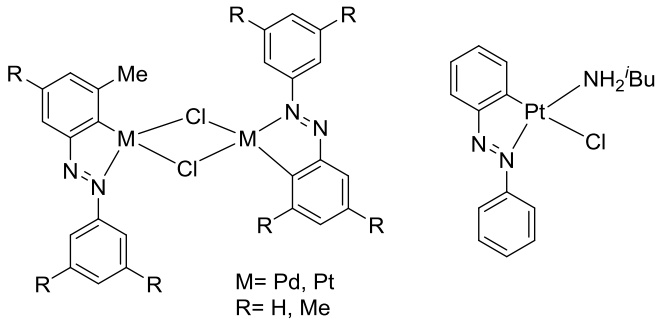


Figure 1.1. Examples of some Pd and Pt metallacycles.

In that context, in the late 1970s organometallic complexes containing an organic tridentate ligand which formed a chelate with the transition metal were prepared for the first time (Figure 1.2). These chelates were named pincer complexes due to their coordination site to the metal.[6]

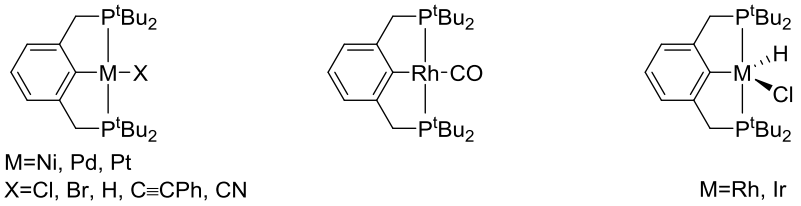


Figure 1.2. Some of the first pincer complexes synthesized by Moulton and coworkers.

1.2. Pincer type complexes

Pincer type complexes consist on a metallic center and a pincer-type ligand containing in its structure the donor atoms, capable of coordinating in a

[6] C. J. Moulton, B. L. Shaw *J. Chem. Soc. Dalton Trans*. **1976**, 1020.

tridentated manner. Metal complexation with pincer ligands usually occurs with formation of two five-membered metallacycles to afford complexes [MX_n(ECE)L_m] (Figure 1.3). A practical way of classifying pincer ligands is based on the three atoms coordinating to the metal center, abbreviated to ECE. For example, if complex **A** bears amino ligands (E = NR_2) in the side arms, it will be called a NCN complex, whereas with phosphines (E = PR_2) would be a PCP complex.

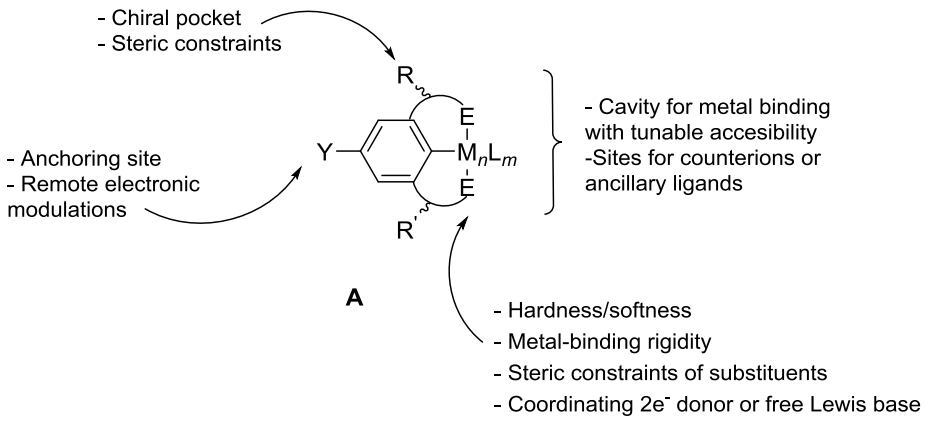


Figure 1.3. Potential modification sites in pincer ligands and their effect on the properties of the metal center.

The basic type of the complexes has a typical ECE architecture in which E are usually a versatile class of neutral species, such as NR_2, PR_2, SR, and SeR. These neutral species (E) with their spacer are usually referred to as the side arms, which stabilize the pincer complexes and strongly affect the electronic properties of the metal. On the other hand, the metal center could

be occupied by a large variety of metals. Thereby, pincer complexes of Fe, Co, Ni, Cu, Pt, Rh, Ru, Ir or Pd they been described (Figure 1.4).[7] The metal plays a key role in the reactivity of the complex and also determines its geometry, which is generally square-planar if the metal has d^8 configuration (Pd^{II}, Ni^{II}, Pt^{II}, Rh^{I}, Ir^{I}) and square pyramidal when the configuration is d^6 (Ru^{II}, Rh^{III}, Ir^{III}).

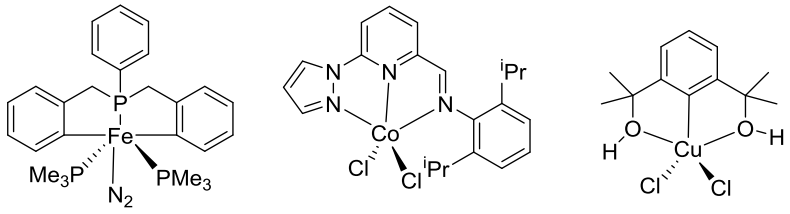


Figure 1.4. Some examples of pincer complexes containing different metals.

There are some reports about new catalytic properties arising from the replacement of the carbon-metal bond with other isoelectronic structure elements,[8] such as silicon-metal or phosphorus-metal bonds. In some cases,

[7] For more information about pincers with different metals, see: Co, Fe complexes: a) H. Sun, N. Liu *J. Organomet. Chem.* **2011**, *696*, 2537*;* b) K-W. Huang, D. Gong *Appl. Catal. A* **2013**, *464*, 35; Ni complexes: c) P. K. Suganthy, R. N. Prabhu *Tetrahedron Lett.* **2013**, *54*, 5695; Cu complexes: d) A. Klein, S. Elmas *Eur. J. Inorg. Chem.* **2009**, 2271; Pt complexes: e) N. Komiya, T. Kashiwabara *J. Organomet. Chem*. **2013**, *738*, 66; Rh complexes: f) G. T. S. Andavan, T. K. Hollis *J. Organomet. Chem.* **2005**, *690*, 5938; Ru complexes: g) S. Maeda, T-A. Koizumi *J. Organomet. Chem.* **2007**, *692*, 5495; Ir complexes: h) X-H. Yang, J-H. Xie *Angew. Chem. Int. Ed*. **2013**, *52*, 7833.

[8] a) M. Mazzeo, M. Lamberti, A. Massa, A. Scettri, C. Pellechia, J. C. Peters *Organometallics* **2008**, *27*, 5741; b) J. Takaya, N. Iwasawa *J. Am. Chem. Soc.* **2008**, *130*, 15254; c) J. Takaya, N. Iwasawa *Organometallics* **2009**, *28*, 6636, d) D. Srimani, Y. Ben-David, D. Milstein *Adv. Synth. Catal.* **2012**, *354*, 2043.

the metal is coordinated to a neutral aromatic nitrogen atom[9] instead of to an anionic carbon. This replacement of carbon in the C-M bond with heteroatoms (such as Si, P, and N) sometimes leads to important improvements of the catalytic activity. Another important strategy to get such improvement is the insertion of two different donors in the side arms (ECE´), creating non-symmetrical pincer complexes.[10] It is worth noting that the insertion of asymmetric moieties in the tridentate framework provides a wealth of opportunities for the development of chiral catalysts. The chiral versions of such complexes commonly contain asymmetric N- or P-based ligand frameworks including those bearing oxazoline-, imidazoline-, imine-, amine-, phosphine-, phosphoramidite- or phosphite-skeletons.[11]

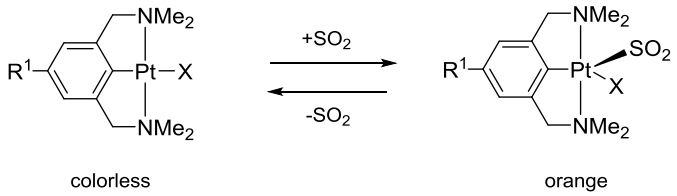
In 1976 Moulton and Shaw[6] synthesized for the first time a pincer type ligand. At that point this ligand and its corresponding complexes only represented some very novel derivatives of a new diphosphine. In the 80's a careful reexamination of the properties of these complexes revealed these compounds to have an extraordinary thermal stability, given their high melting points, property that could enable these complexes to be potentially used in homogeneous catalysis. Nowadays these species have been a driving

[9] a) R. A. Begum, D. Powell, K. Bowman *Inorg. Chem*. **2006**, *45*, 964; b) J. Liu, H. Wang, H. Zhang, X. Wu, H. Zang, Y. Deng, Z. Yang *Chem. Eur. J.* **2009**, *15*, 4437; c) H. Wang, J. Liu, Y. Deng, T. Min, G. Yu, X. Wu, Z. Yang, A. Lei *Chem. Eur. J.* **2009**, *15*, 1499; d) T. Cheisson, A. Auffran *Dalton Trans.* **2015**, in-press DOI: 10.1039/c5dt02789f.

[10] a) I. Moreno, R. SanMartin, B. Inés, M. T. Herrero, E. Dominguez *Curr. Org. Chem*. **2009**, *13*, 878; b) M. Asay, D. Morales-Morales *Dalton Trans*., **2015**, *44*, 17432.

[11] a) *The Chemistry of pincer compounds, 1st ed., (*Eds.: D. Morales-Morales and C. M. Jensen), Elsevier, Amsterdan, **2007**; b) *Pincer and Pincer-type Complexes, 1st ed.,* (Eds.: K. J. Szabó, O. F. Wendt), Wiley-VCH, Weinheim, **2014**.

force for multiple studies beyond catalysis, ranging from application in nanoscience to the development of chemical sensors and chemical switches.[12] For instance, when NCN-platinum pincer designed by van Koten and co-workers is exposed to an atmosphere with SO_2, a pentacoordinate adduct is formed as shown in Scheme 1.1. Upon binding of SO_2, the organoplatinum material undergoes a reversible color change from colorless to bright orange, which confirms the presence of this gas.[13] Thereby, this Pt(NCN) unit is an active site for the construction of novel sensor materials for the detection of SO_2 gas.



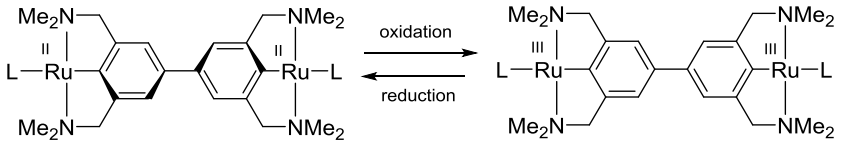
Scheme 1.1. Reversible binding of SO_2 on NCN-Pt complexes.

On the other hand, ruthenium bimetallic complexes (Scheme 1.2) also prepared by this group, change their color and molecular conformation in response to the oxidation state of the metal centers. This is an example of

[12] a) G. van Koten, M. Albrecht *Angew. Chem. Int. Ed.* **2001**, *40*, 3751; b) K. Li, T. Zou, Y. Chen, X. Guan, C.-M. Che *Chem. Eur. J.* **2015**, *21*, 7441.

[13] a) M. Albrecht, R. A. Gossage, M. Lutz, A. L. Spek, G. van Koten *Chem. Eur. J.* **2000**, *6*, 1431; b) M. Albrecht, M. Schlupp, J. Bargon, G. van Koten *Chem. Commun.* **2001**, 1874. For new applications of metal pincer complexes as sensors of several chemical entities (chloride anion, mustard agents *inter alia*), see: c) Q.-Q. Wang, R. A. Begum, V. W. Day, K. Bowman-James *Inorg. Chem.* **2012**, *51*, 760; d) A. Dorazco-González *Organometallics* **2014**, *33*, 868.

molecular switch based on redox activity of ruthenium nuclei that are complexed to NCN pincer dimers.[14]



Scheme 1.2. Redox-active molecular switch.

It has been previously stated that catalysis has been the main application of metal pincer complexes. There are a wide range of transformations catalyzed by these compounds, such as Michael and aldol reactions,[15] allylation of aldehydes[16] or imines[17] or dehydrogenation and hydrogen transfer reactions.[18] As some illustrative examples of the catalytic potential

[14] a) P. Steenwinkel, D. M. Grove, N. Veldman, A. L. Spek, G. van Koten *Organometallics* **1998**, *17*, 5647. For related application of pincer complexes as optical switches, see: b) C.-H. Wang, N.-N. Ma, X.-X. Sun, S.-L. Sun, Y.-Q. Qiu, P.-J. Liu *J. Phys. Chem. A* **2012**, *116*, 10496.

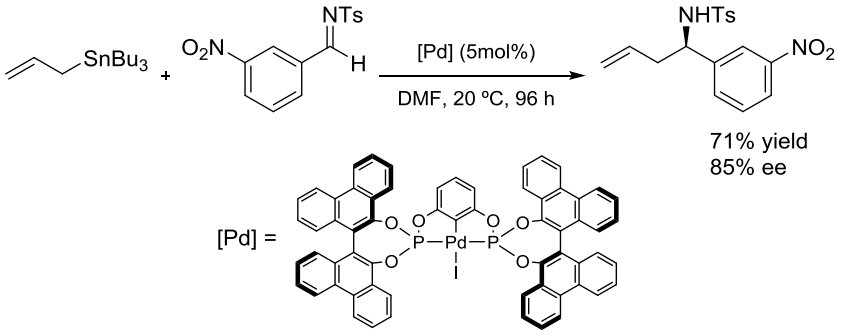
[15] For more information about aldol and Michael reactions catalyzed by pincers, see: a) M. A. Stark, C. J. Richards *Tetrahedron Lett.* **1997**, *38*, 5881; b) B. S. Williams, G. van Koten *Helv. Chim. Acta* **2001**, *84*, 3519; c) K. Takenaka, Y. Uozumi *Org. Lett.* **2004**, *6*, 1833; d) K. Takenaka, M. Minakawa, Y. Uozumi *J. Am. Chem. Soc.* **2005**, *127*, 12273; e) Z.Yang, D. Liu, Y. Liu, M. Sugiya, T. Imamoto, W. Zhang *Organometallics* **2015**, *34*, 1228.

[16] a) J. Kjellgren, K. J. Szabó *Angew. Chem. Int. Ed.* **2003**, *42*, 3656, b) T. Wang, X.-Q. Hao, J.-J. Huang, J.-L. Niu, J.-F. Gong, M.-P. Song *J. Am. Chem. Soc.***2013**, *78*, 8712.

[17] a) J. Aidyn, K. J. Szabó *Org. Lett.* **2008**, *10*, 2881; b) J. Lisena, J. Monot, S. Mallet-Ladeira, B. Martin-Vaca, D. Bourissou *Organometallics* **2013**, *32*, 4301.

[18] For more information about dehydrogenation and hydrogen transfer reactions in the presence of pincer complexes, see: a) J. Choi, A. H. R. MacArthur *Chem. Rev.* **2011**, *111*, 761; b) S. Kundu, M. Brookhart *ACS Catal.* **2013**, *3*, 1768; c) A. V. Polukeev, A. A. Koridze *Organometallics* **2013**, *32*, 1000; d) J. Zhang, D. Milstein *Organometallics* **2013**, *30*, 5716; e) G. Zhang, S. K. Hanson *J. Am. Chem. Soc.* **2013**, *135*, 8668; f) W. Z. Jin

exhibited by those metallocycles, Scheme 1.3 shows the selective allylation of sulfonimines catalyzed by a chiral palladium pincer, published by Szabó and coworkers.[19]



Scheme 1.3. Allylation reaction catalyzed by a chiral Pd pincer complex.

1.3. Palladium pincer complexes

Although a great variety of pincer complexes have been described during the last decades, palladium has been the most used transition metal to prepare these metallocycles (Figure 1.5). It is known that the pincer architecture accounts for many desirable properties of palladium pincer complexes in catalytic transformations. As a consequence of the firm tridentate coordination mode, the palladium pincer complexes show a high thermal stability. In addition, most of the complexes are stable toward

Organometallics **2012**, *31*, 5664; g) H. Dyer, S. Sabo-Etienne *Organometallics* **2011**, *30*, 1478; h) S. Mazza, R. Scopelliti, X. Hu *Organometallics* **2015**, *34*, 1538.

[19] a) J. Aidyn, K. J. Szabó *J. Org. Chem.* **2007**, *72*, 4689, for more information about allylation of sulfoimines, see: b) J.-L. Niu, X.-Q. Hao, J.-F. Gong, M.-P. Song *Dalton Trans.* **2011**, *40*, 5135.

moisture and air, resulting in easy handling and storage. These important aspects may account for high durability of the catalyst and a broad reaction scope.[12]

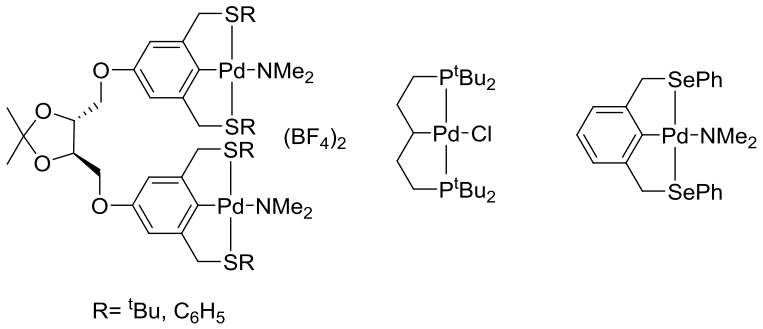


Figure 1.5. Some examples of palladium pincer complexes.

Although almost all pincer compounds are symmetrical, non-symmetrical ECE´and EXY palladacycles have been recently reported (Figure 1.6). In addition to the already mentioned stability, non-symmetrical ligands can feature soft and hard donor atoms in their side arms, providing them hemilabile properties that can facilitate the interaction of the substrate with the metal center, thus stabilizing intermediates of the catalytic cycle.[11]

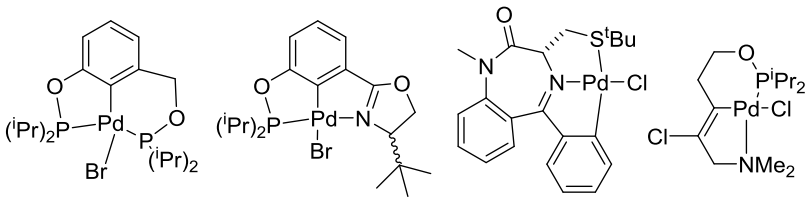


Figure 1.6. Some examples of non-symmetrical palladium pincers.

During the last decades, asymmetric catalysis has experienced a great increase in organic chemistry due to its use in the synthesis of natural products and biologically active compounds. Pincer's chemistry has also spread over this area of catalysis (Figure 1.7).[15,16,20]

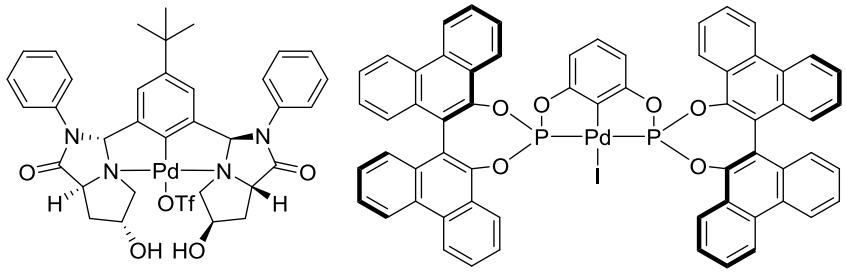


Figure 1.7. Asymmetric palladium pincers.

1.3.1. Synthesis of palladium pincer complexes

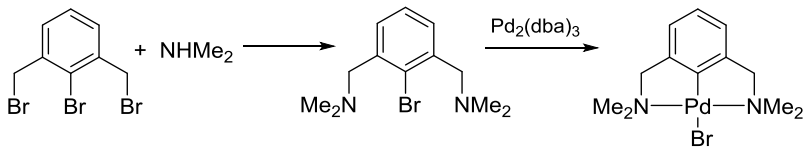
The synthesis of pincer complexes is sometimes considered as a limiting factor for their application in catalysis. Some synthetic precursors of pincer complexes are commercially available; however, development and use of pincer complex catalysis often require synthesis of both the pincer proligands and the complexes. Moreover, the efficient tunability of the complexes is a great advantage, but it requires a set of pincer complexes with widely different substituents (E) in the side arms to be tested in the studied catalytic transformations. There are several methods available for the generation of pincer palladacycles and often two five-membered or, to a

[20] a) J. Li, M. Lutz, A. L. Spek, G. P. M. van Klink, G. van Koten, R. J. M. K. Gebbnik *Organometallics* **2010**, *29*, 1379; b) P. O. Lagaditis, P. E. Sues, J.F. Sonnenberg, K. Y. Wan, A. J. Lough, R. H. Morris* *J. Am. Chem. Soc.***2014**,*136*, 1367.

lesser extent, six-membered chelates are generated as a result of the formation of a stable Pd−C bond, assisted primarily by coordination of one of the two-electron donor groups.

Oxidative addition

Probably the easiest and most efficient way to synthesize pincer complexes is based on an oxidative addition of Pd(0) species, such as $Pd_2(dba)_3$, to the carbon-halogen bond of the pincer proligand. For example, this synthetic route can be employed to obtain the NCN complex shown in the Scheme 1.4.[21]



Scheme 1.4. Synthesis of an NCN complex by oxidative addition.

In this context, a highly modular synthesis of various chiral pincer complexes was reported starting from TADDOL (**B**),[22] and BINOL (**C**)[23] derivatives (Figure 1.8).

[21] a)P. L. Alsters, P. J. Baesjou, M. D. Janssen, H. Kooijman, A. Sicherer-Roetman, A. L. Spek, G. van Koten *Organometallics* **1992**, *11*, 4124; b) C. Tschersich, B. Braun, C. Herwig, C. Limberg *Organometallics* **2015**, *34*, 3782.

[22] a) O. A. Wallner, V. J. Olsson, L. Eriksson, K. J. Szabó *Inor. Chim. Acta* **2006**, *359*, 4689; b) C. Holzhacker B. Stöger M. D. Carvalho L. P. Ferreira, E. Pittenauer, G. Allmaier, L. F. Veiros, S. Realista, A. Gil, M. J. Calhorda, D. Müller, K. Kirchner *Dalton Trans.* **2015**, *44*, 13071.

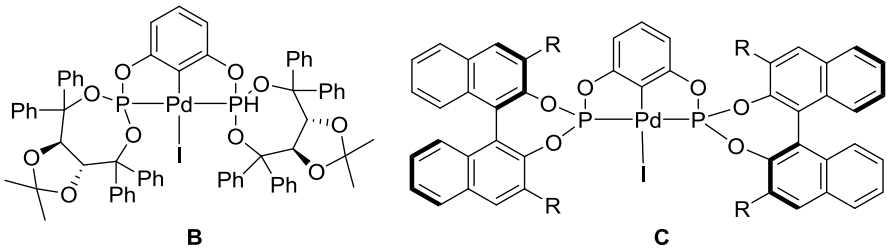


Figure 1.8. Example of chiral pincer complexes accessible by C-I bond metallation.

C-H activation

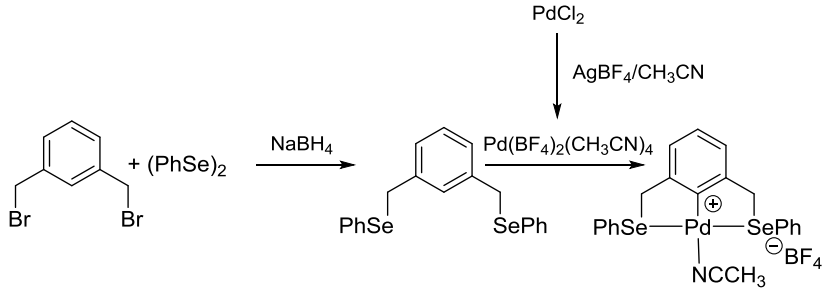
The C-H activation/cyclometallation is also a major strategy for the preparation of palladium pincer complexes.[24] This methodology requires simpler precursors than the above-described procedures based on C-X bond activation. However, the success of these procedures is more dependent on the electronic character and bulkiness of the side arm ligands. Although at the initial reports long reaction times and high temperatures were usually necessary, if electron-donating *tert*-butyl substituents on the phosphorus donors were replaced by weakly electron-withdrawing phenyl substituents (E=PPh_2), milder reaction conditions could be used.[25] Besides, the synthesis of pincer complexes based on C-H activation usually requires more

[23] a) J. Aydin, C. S. Conrad, K. J. Szabó *Org. Lett*. **2008**, *10*, 5175; b) J. Aydin, K. S. Kumar, M. J. Sayah, O. A. Wallner, K. J. Szabó *J. Org. Chem*. **2007**, *72*, 4689.

[24] a) R. A. Baber, R. B. Bedford, M. Betham, M. E. Blake, S. J. Coles, M. F. Haddow, M. B. Hurthouse, A. G. Orpen, L. T. Pilarski, P. G. Pringle, R. L. Wingad *Chem. Commun.* **2006**, 3880, b) T. S. Lobana.*RSC Adv*. **2015**, *5*, 37231.

[25] a) H. Rimml, L. M. Venanzi *J. Organomet. Chem*. **1983**, *259*, 155; b) J.-L. Niu, X.-Q. Hao, J.-F. Gong, M.-P. Song *Danton Trans.* **2011**, *40*, 5135.

experience in organometallic synthesis than other alternative methods. An important difference between the C-X and C-H activation strategies is the different oxidation states of the employed palladium precursor. The oxidative addition to the C-X bond is performed using Pd(0) species, while the C-H activation protocol involves Pd(II) species. This C-H palladation is usually dependent on the ancillary ligands on the Pd(II) precursor. Very efficient C-H activation can be achieved using palladium(II) salts with weakly coordinating ligands, such $Pd(OCOCF_3)_2$[26] or $Pd(BF_4)_2(CH_3CN)_4$.[27] Although these reagents are commercially available, they are rather expensive. However, some of them, (*e.g.* $Pd(BF_4)_2(CH_3CN)_4$) can be easily generated *in situ* prior to the C-H activation process (Scheme 1.5).

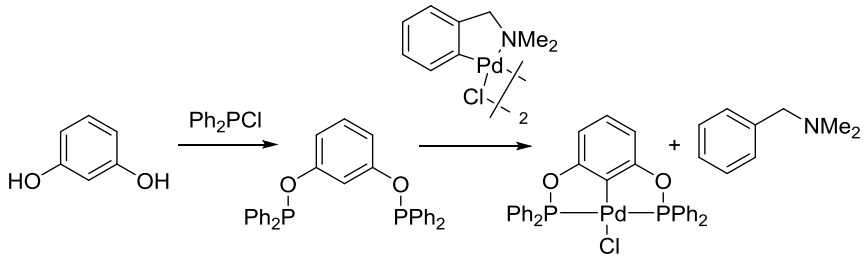


Scheme 1.5. Synthesis of a pincer complex *via* C-H activation by *in situ* generated $Pd(BF_4)_2(CH_3CN)_4$.

[26] R. B. Bedford, S. M. Draper, P. N. Scully, S. L. Welch *New J. Chem.* **2000**, *24*, 745.

[27] a) W. J. Sommer, K. Wu, J. S. Sears, Y. Si, X. Zheng, R. J. Davis, C. D. Sherrill, C. W. Jones, M. Weck *Organometallics* **2005**, *24*, 4351; b) J. Aydin, K. S. Kumar, L. Eriksson, K. J. Szabó *J. Inorg. Chim. Acta* **2006**, *359*, 1767; c) M. Gagliardo, N. Selander, N. C. Mehendale, G. van Koten, R. J. M. Klein Gebbink, K. J. Szabó *Chem. Eur. J.* **2008**, *14*, 4800.

An alternative way of obtaining pincer complexes by C-H functionalization is *via* the so-called "transcyclometallation" (TCM) reactions.[28] This process describes the substitution of one cyclometallated ligand without the formation of significant and detectable amounts of purely inorganic compounds (dissociated metal salts). TCM reactions were initially investigated with bidentate coordinating ligands,[29] but the concept has subsequently been extended to tridentate-binding pincer ligands. This is an useful strategy for the synthesis of PCP type complexes as it can be seen in the Scheme below.[30] An excellent palladium source for transcyclometallation is the palladacycle shown in Scheme 1.6 reported by Cope and co-workers,[31] which is commercially available.



Scheme 1.6. Pincer complexes obtained by transcyclometallation.

[28] a) M. Albrecht, P. Dani, M. Lutz, A. L. Spek, G. van Koten *J. Am. Chem. Soc*. **2000**, *122*, 11822; b) H. A. Younus, W. Su, N. Ahmad, S. Chen, F. Verpoort *Adv. Synth. Catal.* **2015**, *357*, 283.

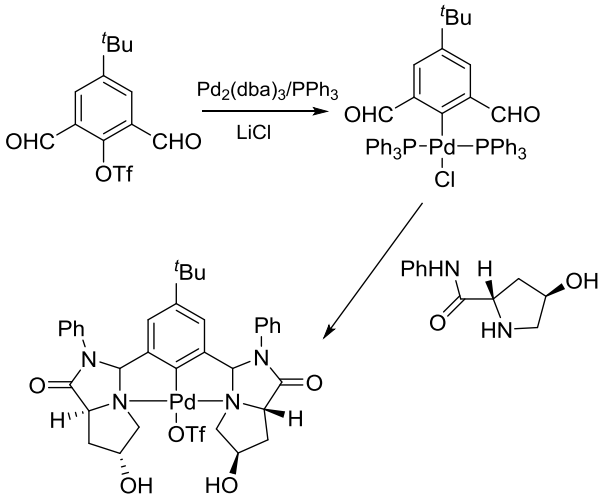
[29] J. Dupont, N. Beydoun, M. Pfeffer *J. Chem. Soc. Dalton Trans.* **1989**, 1715.

[30] a) O. A. Wallner, K. J. Szabó *Org. Lett.* **2004**, *6*, 2997; b) G. van Koten *Organometallic Chem.* **2013**, *40*, 1.

[31] A. C. Cope, E. C. Friedich *J. Am. Chem. Soc.* **1968**, *90*, 909.

Ligand introduction route

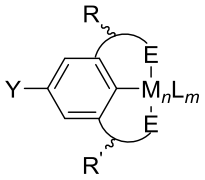
According to previously described methods, the last step of the synthesis is the introduction of palladium. Although these methods usually provide easy access to pincer complexes, they can be sometimes sensitive to the steric bulk of the substituents in the side arms. Uozumi and coworkers[32] described an interesting alternative to the metal introduction route, which circumvents the problems caused by bulky substituents in the side arms. The key step of their strategy is the introduction of the palladium atom in an early stage of the synthesis, therefore, this method is called a "ligand introduction route". A representative example of this methodology is the synthesis of chiral NCN complex represented in Scheme 1.7.



Scheme 1.7. Synthesis of pincer complexes by the "ligand introduction route".

[32] a) T. Kimura, Y. Uozumi *Organometallics* **2006**, *25*, 4883; b) T. Kimura, Y. Uozumi *Organometallics* **2008**, *27*, 5159.

Complexes containing biscyclometallated pincer ligands offer particularly attractive possibilities for catalytic applications, since the tailoring of catalytic properties is readily achieved as it can be seen in Figure 1.3. First of all, the tridentate-binding mode and the covalent M-C σ-bond stabilize the catalytically active site. This stabilization is assumed to prevent the metal dissociating from the ligand (leaching), and hence circumvents a problem common to most catalysts containing exclusively heteroatom-coordinated metals.[33] Besides, the electronic properties of the metal center are highly sensitive towards modifications in the donor array (substitution patterns and hybridization of the donor atom E). Electronic fine-tuning through variation of the aromatic substituent Y represents an additional option in some cases. Finally, the steric requirements around the catalytic site may be modified to discriminate against some substrates or to create a chiral pocket for asymmetric catalysis. Due to all the characteristics mentioned, a broad range of powerful catalysts containing pincer ligands have been employed.[34]



1.4. Cross-coupling reactions

Cross-coupling reactions catalyzed by transition metals have become key transformations in organic synthesis as effective methodologies for the

[33] a) J. T. Singleton *Tetrahedron* **2003**, *59*, 1837; b) *Organometallic PincerChemistry*, (Eds.: G. van Koten, D. Milstein), Springer-Verlag, Heidelberg, **2013.**

[34] a) M. E. van der Boom, D. Misltein *Chem. Rev*. **2003**, *103*, 1759; b) S. Xu, E. H. Kim, A.r Wei and E. Negishi *Sci. Technol. Adv. Mater*. **2014**, *15*, 1.

formation of C-C or C-heteroatom bonds. This strategy has been applied in the synthesis of a broad range of organic compounds, including natural products and those involved in supramolecular chemistry, as well as in materials science.[35]

Among the transition metals, palladium is one of the most widely used, due to its great tolerance against a wide variety of functional groups in this field. [36] Its use spread in the late 60's and early 70's. By the time, reactions catalyzed by palladium became popular, among others, the Mizoroki-Heck reaction which involves the coupling of aryl or alkenyl halides or triflates with alkenes[37] or Sonogashira-Hagihara reaction which couples alkynes and aryl or alkenyl halides employing salts of Cu(I) as co-catalysts.[38] The coupling between aryl halides or triflates with organometallic reagents catalyzed by palladium also became important. These reactions have a specific name depending on the metal used to perform transmetallation with palladium, such as, Kumada reaction if the metal is Mg,[39] Negishi reaction

[35] a) *Metal-catalyzed Cross-coupling Reactions, 2nd ed.*, (Eds.: A. de Meijere, F. Diedercich), Wiley-VCH, Weinheim, **2004**; b) C. Bolm *J. Org. Chem.* **2012**, *77*, 5221.

[36] a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Eds.: E. I. Negishi, A. de Meijere), Wiley-VCH, Weinheim, **2002**; b) T. J. Colacot *Platinum Metals Rev.*, **2011**, *55*, 84.

[37] a) R. F. Heck *J. Am. Chem. Soc.* **1968**, *90*, 5518; b) T. Mizoroki, K. Mori, A. Ozaki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; c) I. P. Beletskaya, A. V. Cheprakov *RSC Catal. Ser.* **2015**, *21*, 355.

[38] a) K. Sonogashira, Y. Kohda, N, Hagihara *Tetrahedron Lett.* **1975**, 4467; b) K. Sonogashira *J. Organomet. Chem*. **2002**, *653*, 46; c) M. Schilz, H. Plenio *J. Org. Chem.* **2012**, *77*, 2798.

[39] a) M. Kumada *Pure Appl. Chem*. **1980**, *52*, 669; b) M. M. Heravi, P. Hajiabbasi *Monatsh. Chem.* **2012**, *143*, 1575.

when Zn is used,[40] Migita-Stille with Sn,[41] Hiyama if for Si[42] or Suzuki-Miyaura in the case of the B[43] among others.

1.4.1. Suzuki-Miyaura reaction

The coupling between aryl halides and organoboronic acids is one of the most widely used synthetic transformations in the formation of carbon-carbon bonds, and especially in the formation on biaryl bonds or C_{Ar}-C_{Ar}. The stability and weak nucleophilic nature of organoboron compounds has made this reaction very practical. It tolerates a wide range of functional groups and it is highly chemoselective. Furthermore, boron compounds are generally non-toxic and the reaction can be run under very mild conditions.[44]

In 1979 Suzuki and co-workers found out that organoboron compounds in the presence of a base can be used as coupling partners in palladium-catalyzed cross coupling with vinyl and aryl halides (Scheme 1.8).[45]

[40] a) E. I. Negishi, L. F. Valenti, M. Kobayashi *J. Am. Chem. Soc*. **1980**, *102*, 5223; b) Y.Yang, N. J. Oldenhius, S. L. Buchwald *Angew Chem Int Ed*. **2013**, *52*, 615.

[41] A) J. K. Stille *J. Am. Chem. Soc*. **1979**, *101*, 4992; b) C. Cordovilla, C. Bartolome, J. M. Martinez-Ilarduya, P. Espinet *ACS Catal.* **2015**, *5*, 3040.

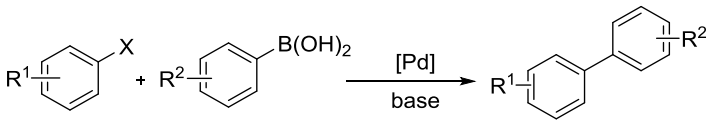
[42] a) T. Hiyama, Y. Hatanaka *Pure Appl. Chem*. **1994**, *66*, 1471; b) J. J. Li in *Name Reaction, 5th ed*., Springer, Switzerland, **2014**.

[43] a) A. Suzuki *J. Organomet. Chem.* **1999**, *576*, 147; b) F.-S. Han *Chem. Soc. Rev.* **2013**, *42*, 5270.

[44] a) A. Suzuki *Pure Appl. Chem.* **1991**, *63*, 419; b) N. Miyaura, A. Suzuki *Chem. Rev*. **1995**, *95*, 2457; c) A. J. J. Lennox, G. C. Lloyd-Jones *Chem. Soc. Rev*. **2014**, *43*, 412.

[45] a) N. Miyaura, K. Yamada, A. Suzuki *Tetrahedron Lett.* **1979**, *20*, 3437; b) N. Miyaura, A. Suzuki *J. Chem. Soc. Chem. Commun.* **1979**, 866.

Although this reaction is mostly known for the formation of biaryl compounds,[46] the transformation is not limited to the coupling between sp^2 carbons, as there are many examples in which both the halogenated compound or the boronic acid have alkyl groups (haloalkanes and alkylboron reagents).[44c, 47]



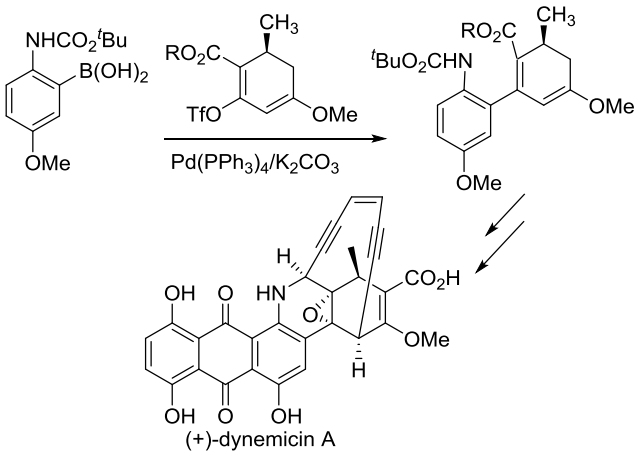
Scheme 1.8. General reaction for Suzuki cross-coupling.

This cross-coupling reaction has found applications in the fine chemical and pharmaceutical industries as key for the preparation of a large number of natural products and biologically active compounds of complex molecular structures. For example, an efficient synthesis of the natural potent antitumor agent (+)-dynemicin A which involves a Suzuki coupling in one of the carbon-carbon bond forming steps (Scheme 1.9) was reported by Myers and co-workers.[48]

[46] a) L. Liu, Y. Zhang, Y. Wang *J. Org. Chem.* **2005**, *70*, 6122; b) F. Zeng, Z. Yu *J. Org. Chem.* **2006**, *71*, 5274; c) A. Suzuki *Heterocycles* **2010**, *80*, 15.

[47] a) G. W. Kabalka, R. M. Pagni, C. M. Hair *Org. Lett.* **1999**, *1*, 1423; b) I. Kondolff, H. Doucet, M. Santelli *Tetrahedron* **2004**, *60*, 3813; c) S. M. Nobre, A. L. Monteiro *Tetrahedron Lett.* **2004**, *45*, 8225; d) G. A. Molander, M. D. Elia *J. Org. Chem.* **2006**, *71*, 9198; e) *Adv. Chem. Eng. Sci.* **2013**, *3*, 19.

[48] a) A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, D. J. Madar *J. Am. Chem. Soc.* **1997**, *119*, 6072; for a report on the biological activity of dynemicin, see: b) C. W. Liew, A. Sharff, M. Kotaka, R. Kong, H. Sun, I. Qureshi, G. Bricogne, Z.-X. Liang, J. Lescar *J. Mol. Bio.* **2010**, *404*, 291.



Scheme 1.9. Synthesis of the antitumor agent (+)-dynemicin A.

The Suzuki reaction was also used to prepare the antiviral bromoindole alkaloid dragmacidin F. At the cross coupling stage, as several sensitive functional groups were present in the molecule (Figure 1.9), mild reagents such as an organoboron reagent were required.[49]

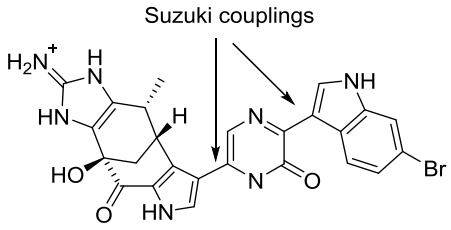


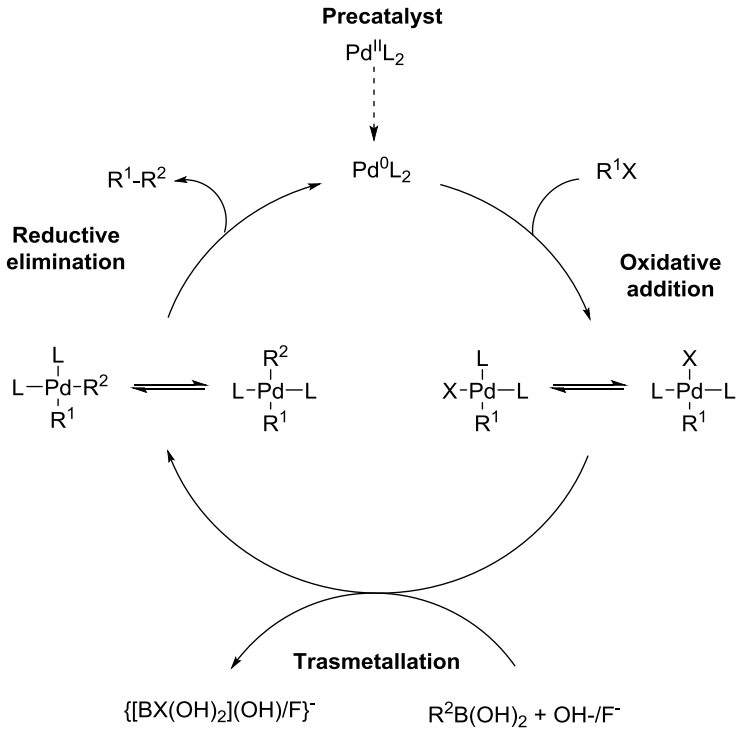
Figure 1.9. Antiviral bromoindole alkaloid dragmacidin F.

[49] N. K. Garg, D. D. Caspi, B. M. Stoltz *J. Am. Chem. Soc.* **2004**, *126*, 9552.

The properties of such boron compounds (high selectivity in cross-coupling reactions, stability, non-toxic nature, and tolerance to other functional groups) provide to Suzuki coupling advantage over other cross-coupling processes. Furthermore, it is stated that compounds where any C-B bond is present, are suitable as cross-coupling reagents.[44b]

The catalytic pathway proposed for Suzuki reaction is outlined in Scheme 1.10. The mechanism involves oxidative addition of the halide to the Pd(0) complex to give a Pd(II) species. Then, by the action of the base which activates the boronic acid , the organic group is transferred to palladium by transmetallation to give a stable 16 e^- complex. In the final step the R and R^1 groups are coupled to give a new carbon-carbon single bond and R-R^1 is released from palladium by a reductive elimination. In this process Pd(II) is reduced to Pd(0). The transmetallation of organoboron reagent to transfer the organic group requieres the coordination of a base or a fluoride anion to the boron atom, so the use of a basic medium accelerates significantly the transmetallation step.[50]

[50] a) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki *J. Am. Chem. Soc*. **1985**, *107*, 912; b) C. Amatore, G. Le Duc, A Jutan *Chem. Eur. J.* **2013**, *19*, 10082.



Scheme 1.10. General catalytic cycle for Suzuki reactions.

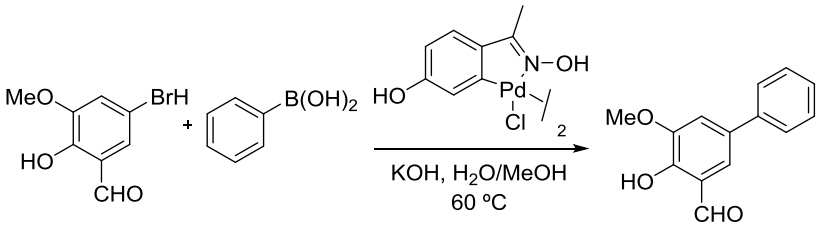
The most used electrophilic reagents are aryl halides or triflates, their reactivities are indicated as follows: Ar-I > Ar-Br > Ar-OTf >> Ar-Cl. In spite of the interest of chloroarenes due to their low cost and availability, the oxidative addition of the aryl chloride upon Pd is too slow.[51] Therefore, such reagents are not so often used as aryl bromides.

Different bases have been used, such as carbonates, phosphates, hydroxides, alkoxides, etc. The most common solvents in Suzuki coupling are dioxane,

[51] a) A. F. Littke, G. C. Fu *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; b) *Science of Synthesis*: *Cross-Coupling and Heck-Type reaction* (Ed.: G. A. Molander), Thieme, Stuttgart, **2012**.

DMF, MeOH, PhMe and THF. Regarding to the catalysts used, besides to sources of Pd(0), such as $Pd(PPh_3)_4$, the catalyst is often added as a complex of Pd(II). The most employed precursors to generated *in situ* Pd(0) complex are $Pd(OAc)_2$ and the mixture of $PdCl_2$-phosphine.[52]

One of the disadvantages of using phosphines as ligands is the formation of byproducts. In order to avoid this, more elaborated catalysts have been developed, including those of palladacycle nature. In 1995 Herrmann and co-workers used for the first time a palladacycle as catalyst in Mizoroki-Heck and Suzuki-Miyaura reactions.[53] Since their discovery, the palladacyles have been widely used in Suzuki cross-coupling reactions, due to their high catalytic activity for biaryl coupling reactions under mild reaction conditions. For instance, as it is shown in Scheme 1.11, Nájera and co-workers carried out Suzuki coupling employing the palladacycle developed by them.[54]



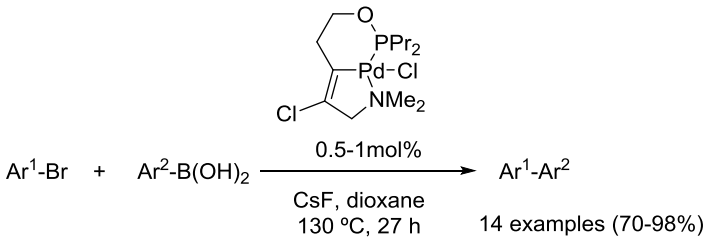
Scheme 1.11. Suzuki cross-coupling using a palladacycle.

[52] a) C. M. So, C. P. Lau, F. Y. Kwong *Org. Lett.* **2007**, *9*, 2795; b) S. S.h Gujral, S. Khatri, P. Riyal *Indo Global Journal of Pharmaceutical Sciences* **2012**; *2*, 351.

[53] M. Beller, H. Fischer, W. A. Herrman, K. Ofele, C. Brossmer *Angew. Chem. Int. Ed.* **1995**, *34*, 3009.

[54] a) D. A. Alonso, C. Nájera, M. C. Pacheco *Org. Lett.* **2000**, *2*, 1823; b) D. A. Alonso, C. Nájera, M. C. Pacheco *J. Org. Chem.* **2002**, *670*, 5588; see also: R. Ratti *Can. Chem. Trans.* **2014**, *2*, 467.

On the other hand, pincer complexes have also demonstrated to be effective catalysts in Suzuki reactions under relatively mild reaction conditions and in many cases with low catalyst loadings. In this way, in 2006 Dupont and co-workers successfully performed Suzuki coupling (Scheme 1.12) using 0.5 to 1 mol% of catalyst and dioxane as solvent with a non-symmetrical PCN palladium pincer as the catalyst.[55]



Scheme 1.12. Suzuki cross-coupling using a PCN pincer.

1.5. Background of the research group

During the last years our research group has focused mainly on metal catalysis, especially on the synthesis of new pincer type palladacycles and the study of their activity as catalysts in several cross-coupling reactions. Thereby, we have developed a variety of palladium pincer complexes as displayed in Figure 1.10,[56] obtaining excellent results as homogeneous catalysts or pre-catalysts for cross-coupling and in oxidation reactions.[57]

[55] G. R. Rosa, C. H. Rosa, F. Rominger, J. Dupont, A. L. Monteiro *Inorg. Chim. Acta* **2006**, *359*, 1947.

[56] a) F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez *Synlett* **2005**, 3116; b) F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez *Tetrahedron Lett.* **2006**, *47*, 3233; c) F.

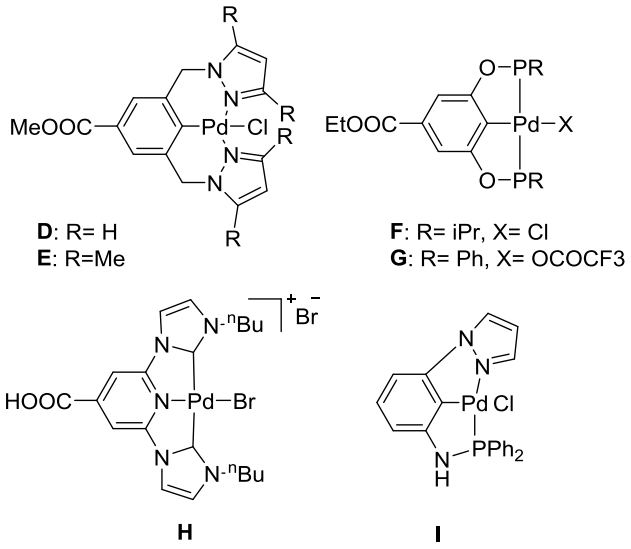


Figure 1.10. A selection of palladium pincer complexes developed by our group.

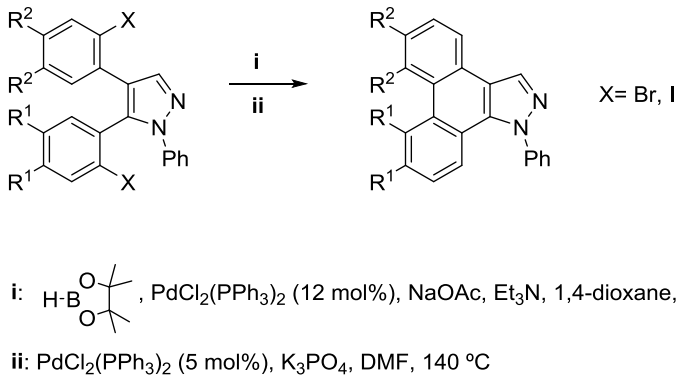
Complexes **D** and **E**, were tested in cross-coupling reactions such as Mizoroki-Heck, Suzuki-Miyaura and Sonogashira, providing excellent results regardless of the electronic nature of the substrates.[56a] These pincers were particularly effective in Suzuki cross-coupling, where quantitative yields were obtained with low catalyst loadings. In the latter coupling is also noteworthy the use of water as solvent. The PCP complexes **F** and **G** not only were effective in those cross-coupling reactions, but also catalyzed α-arylation reactions of ketones.[56b] The pincer **H** allowed to carry out Suzuki

Churruca, R. SanMartin, B. Inés, I. Tellitu, E. Domínguez *Adv. Synth. Catal.* **2006**, *348*, 1836; d) B. Inés, R. SanMartin, F. Churruca, E. Domínguez, M. K. Urtiaga, M. I. Arriortua *Organometallics* **2008**, *27*, 2833.

[57] G. Urgoitia, R. SanMartin, M. T. Herrero, E. Domínguez *Green Chem*. **2011**, *13*, 2161.

coupling reactions in aqueous media using small quantities of catalyst (the amount of it was reduced in one case to 10^{-7} mol% Pd). This complex was also employed in oxidation reactions, obtaining excellent yields in almost all the cases.[56c,57] As it can be seen, although most of the pincers are symmetric, the group also developed a non-symmetrical one, the PCN **I**, which was also tested in cross-coupling reactions, with excellent results.[56d]

Investigation on Suzuki cross-couplings in the presence of commercially available Pd sources led us to relevant results, as in the synthesis of the phenanthro[9,10-*d*]pyrazoles depicted in Scheme 1.13.

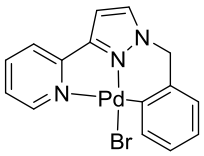


Scheme 1.13. General conditions for the formation of phenanthro[9,10-*d*]pyrazoles *via* Suzuki cross-coupling.

This biaryl coupling reaction was carried out by the so-called Miyaura's variant of the traditional Suzuki cross-coupling, a sequential procedure which allowed the pre-formation of the arylboronate and subsequent intramolecular coupling with the haloarene moiety. Nevertheless, it should

be pointed out that a relatively high amount of the commercially available palladium source was required in this case.[58]

Considering our background in Suzuki and other cross-coupling reactions, the number of pincer-type palladacycles already synthesized and applied to different organic transformations and the shortage of non-symmetrical palladium pincers designed, we decided to prepare a new non-symmetrical NNC pincer **1** in order to explore it as a suitable catalyst for Suzuki coupling (Figure 1.11).



1

Figure 1.11. NNC palladium pincer complex.

Once synthesized and after verifying its thermal and chemical stability, the catalytic activity of the new pincer complex **1** would be evaluated. As an initial study, the biaryl coupling of boronic acids with aryl halides, would be tested as a model reaction to prove the catalytic activity of the new NNC pincer.

In addition, we also decided to test other new palladacycles in order to achieve either an even more efficient catalytic system or more sustainable reaction conditions for such a relevant organic transformation. This was possible thanks to the collaboration with Dr. Josep Giner's research group

[58] R. Olivera, R. SanMartin, I. Tellitu, E. Domínguez *Tetrahedron* **2002**, *58*, 3021.

from *Institut de Ciència de Materials de Barcelona* (ICMAB-CSIC). This collaborative work was based on the evaluation of the catalytic activity of the new *o*-carborane-based NBN palladium pincer complex **8** shown in Figure 1.12.

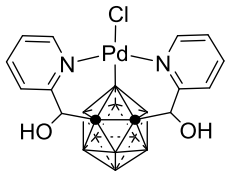


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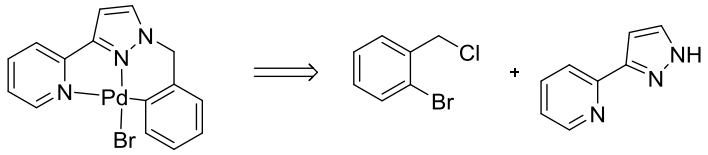
Figure 1.12. New *o*-carborane-based NBN palladium pincer prepared by Giner and co-workers.

2. AIMS AND OBJECTIVES

Taking into account the issues mentioned before, the aims of this work will be to carry out the synthesis of pincer type palladacyclic complex **1** and its application in Suzuki cross-coupling reactions for C-C bonds formation.

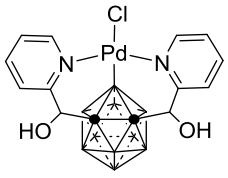
As shown in the retrosynthetic scheme below, palladium pincer complex **1** would be prepared from commercially available 2-bromobenzyl chloride **2** and 2-(1*H*-pyrazol-3-yl) pyridine **3**. The key step in the scheduled sequence would be the metal insertion by an oxidative addition process.



1 **2** **3**

The use of the pincer complex **1** as a suitable palladium source for Suzuki biaryl coupling reactions will be subsequently explored.

In addition, the evaluation of the catalytic activity of a carborane based palladium pincer complex as a catalyst or precatalyst for Suzuki cross-coupling reactions will be also performed.



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Priority will be given to environmentally friendly reaction media.

3. RESULTS AND DISCUSSION

3.1. Synthesis and characterization of NNC palladium complex

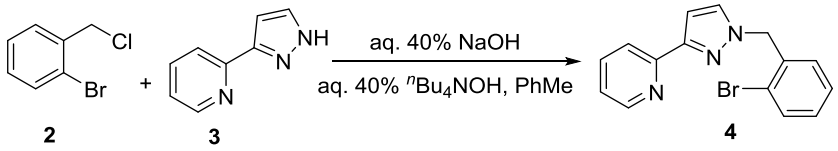
As it has been described, our group has developed several routes to obtain different palladium pincer complexes, most of them symmetric. Therefore, our initial aim was to synthesize a non-symmetrical palladium complex in an effective way.

For this purpose, first we carried out the synthesis of the benzylated intermediate **4**. A modification of the optimized conditions for the alkylation of pyrazoles reported independently by the groups of Mukherjee and Bu was tested.[59,60] In both cases, a biphasic system (H_2O/PhMe) and a phase transfer catalyst ($^nBu_4NOH$) was employed. The only difference between the assays was the temperature and the reaction time as it can be seen in Table 1.1. It can be concluded from the results obtained by our modification (entry 3) that the reaction needed prolonged heating (48 h) to reach an excellent yield.

[59] J. Mukherjee, R. Mukherjee *Dalton Trans.* **2006**, *13*, 1611.

[60] X.-S. Shi, C.-S. Liu, J.-S. Li, Y. Guo, J.-N. Zhou, X.-H. Bu *J. Mol. Struct.* **2005,** *754*, 71.

Table 1.1. Synthesis of benzyl derivative **4**. Optimization assays.



2 **3** **4**

	T/t	(%)
1	120 ºC (8 h)→ 25 ºC (12 h)	66
2	120 ºC (24 h)	72
3	120 ºC (48 h)	95

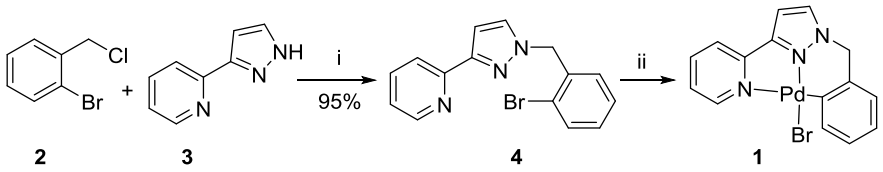
[a]Isolated yield.

Once intermediate **4** was prepared, the second step of the sequence was the insertion of palladium, which was carried out by an oxidative addition process. In the first assays $Pd_2(dba)_3$ was used as the palladium source, in toluene at room temperature and 60 ºC during 48 hours (Table 2.1, entries 1-2). In none of the trials was obtained the desired product. Therefore, we decided to change the reaction conditions, both the source of Pd(0) and the solvent. Thus, in the next assays the *ortho*-bromo derivative **4** was reacted with $Pd(dba)_2$ in tetrahydrofurane in a similar way as described by Xia and co-workers for the insertion of palladium.[61] Different temperatures and reaction times were tried in order to optimize the process, obtaining in this way a good yield for **1** (Table 1.2, entry 3). Although longer reaction times

[61] J. Yorke, J. Sanford, A. Decken, A. Xia *Inorg. Chim. Acta* **2010**, *363*, 961.

were necessary to obtain similar yields, this oxidative addition + coordination process was also attained at room temperature (Table 1.2, entry 6).

Table 1.2. Oxidative addition assays for the synthesis of NNC complex **1**.



2 **3** **4** **1**

i: aq. NaOH 40%, aq. ^{n}BuNOH 40%, PhMe, 120 ºC, 48 h

	(ii)	**1** (%)[a]
1	$Pd_2(dba)_3$, PhMe, 60 ºC, 48 h	-
2	$Pd_2(dba)_3$, PhMe, r.t., 48 h	-
3	$Pd(dba)_2$, THF, 120 ºC, 8 h	88
4	$Pd(dba)_2$, THF, r.t., 48 h	42
5	$Pd(dba)_2$, THF, 80 ºC, 8 h	65
6	$Pd(dba)_2$, THF, r.t., 5 days	82

[a]Isolated yield.

Thus, the synthesis of the metal complex **1** was achieved in just two steps and with an overall yield of 83%.

In order to confirm the structure of the new complex **1**, different spectroscopic and spectrometric techniques were used, such as proton and 13-carbon nuclear magnetic resonance and mass spectrometry. The most evident differences between compounds **4** and **1** were observed in nuclear magnetic resonance experiments. The C-Br signal disappeared in ^{13}C NMR

once the insertion of the metal occurred and ^{1}H NMR signals were slightly shifted further downfield.

The structure of palladacycle **1** was determined by single crystal X-ray diffractrometry of a monocrystalline solid crystallized by a diffusion method (acetone/petrol ether).

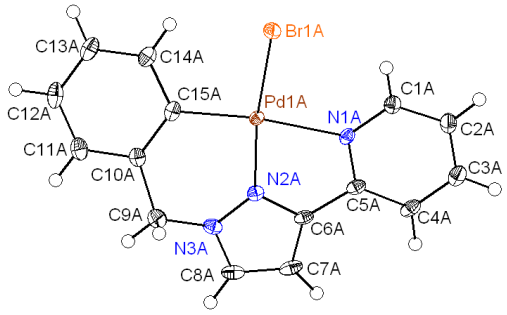
As shown in Figure 1.13, C15-Pd, N1-Pd and N2-Pd bond distances are in agreement with those expected (by comparison with other Pd(II) complexes described in the literature)[62] from target complex **1** after the metal insertion by oxidative addition/coordination (2.00, 2.18 and 1.97 Å respectively). However, the observed distortion from square planar geometry should be pointed out, probably due to the uncommon combination of 5- and 6-membered rings in the metal coordination sphere.[63] Whereas the 5-membered ring containing pyridine, pyrazole heterocyclic moieties and Pd(II) core is almost flat, the planarity of the adjacent 6-membered ring is far from ideal, as the meaningful N3-N2-Pd-C15 and C9-C10-C15-Pd (6.4 and 9.2º respectively) torsion angles clearly reflect.[64] Such distortion can be also visualized by observation of both bond angles C15-Pd-N1 and N2-Pd-Br, which instead of 180º, are 164.9 and 169.9º respectively. Figure 1.12 discloses the ORTEP representation of both complexes (A and B) that

[62] M. Broering, C. Kleeberg, S. Koehler *Inorg. Chem.* **2008**, *47*, 6404.

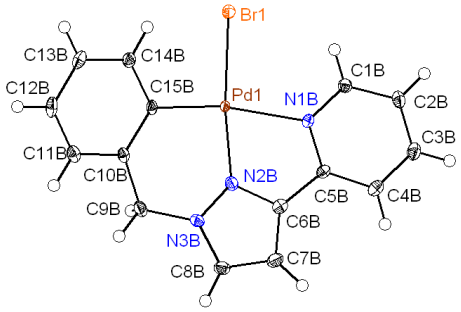
[63] Z. Wang, M. R. Eberhard, C. M. Jensen, S. Matsukawa, Y. Yamamoto *J. Organomet. Chem.* **2003**, *681*, 189.

[64] The bond distances, angles and torsion angles have been chosen from those of molecule/complex A, which are close to those of B.

comprise the asymmetric unit, and the observed bond distances, angles and torsion angles are summarized in Tables 1.3-1.5.



Molecule A



Molecule B

Figure 1.13. Molecular structure of NNC pincer complex **1**. ORTEP representation of both A and B molecules comprising the asymmetric unit of **1** are displayed. Thermal ellipsoids are given at the 50% probability level.

Table 1.3. Selected bond-distances (Å).

Complex A		Complex B	
Atoms	Dist.(Å)	Atoms	Dist.(Å)
Pd1A-N2A	1.971(3)	Pd1-Br1	2.4225(3)
Pd1A-Br1A	2.4412(3)	Pd1-N1B	2.173(2)
Pd1A-N1A	2.179(2)	Pd1-N2B	1.968(2)
Pd1A-C15A	2.005(3)	Pd1-C15B	2.005(3)
N1A-C1A	1.338(4)	N1B-C1B	1.334(3)
N1A-C5A	1.362(4)	N1B-C5B	1.365(3)
N2A-N3A	1.334(4)	N2B-C6B	1.347(3)
N2A-C6A	1.340(3)	N2B-N3B	1.329(3)
N3A-C8A	1.351(4)	N3B-C9B	1.465(3)
N3A-C9A	1.463(4)	N3B-C8B	1.353(4)

Table 1.4. Selected bond-angles (º).

Complex A		Complex B	
Átoms	Ang.(°)	Átoms	Ang.(°)
Br1A-Pd1A-C15A	97.45(8)	Br1-Pd1-C15B	97.42(7)
Br1A-Pd1A-N1A	95.46(7)	Br1-Pd1-N1B	94.60(5)
Br1A-Pd1A-N2A	169.96(7)	Br1-Pd1-N2B	171.54(6)
C1A-C2A-C3A	118.7(3)	C1B-C2B-C3B	118.9(3)
C1A-N1A-C5A	118.5(2)	C1B-N1B-C5B	118.5(2)
C2A-C3A-C4A	119.2(3)	C2B-C3B-C4B	119.6(3)
C3A-C4A-C5A	119.2(3)	C3B-C4B-C5B	118.4(2)
C4A-C5A-C6A	123.9(3)	C4B-C5B-C6B	123.6(2)
C5A-C6A-C7A	135.6(3)	C5B-C6B-C7B	135.7(2)
C6A-C7A-C8A	105.0(2)	C6B-C7B-C8B	105.5(2)
C9A-C10A-C15A	124.8(2)	C9B-C10B-C15B	125.0(2)
N1A-C1A-C2A	122.4(3)	N1B-C1B-C2B	122.3(2)
N1A-C5A-C4A	121.9(3)	N1B-C5B-C4B	122.4(2)
N1A-C5A-C6A	114.2(2)	N1B-C5B-C6B	114.0(2)
N1A-Pd1A-C15A	164.94(11)	N1B-Pd1-C15B	165.58(9)

Tabla 1.5. Selected torsion angles (º).

Complex A		Complex B	
Átoms	Ang.(°)	Átoms	Ang.(°)
Br1A-Pd1A-C15A-C10A	-161.3(2)	Br1-Pd1-C15B-C10B	164.8(2)
Br1A-Pd1A-C15A-C14A	28.2(2)	Br1-Pd1-C15B-C14B	-21.5(2)
Br1A-Pd1A-N1A-C1A	-5.9(2)	Br1-Pd1-N1B-C1B	2.8(2)
Br1A-Pd1A-N1A-C5A	173.8(17)	Br1-Pd1-N1B-C5B	175.5(16)
C1A-C2A-C3A-C4A	1.5(4)	C1B-C2B-C3B-C4B	-0.6(4)
C1A-N1A-C5A-C4A	3.7(4)	C1B-N1B-C5B-C4B	-0.8(4)
C1A-N1A-C5A-C6A	-178.0(2)	C1B-N1B-C5B-C6B	179.2(2)
C2A-C3A-C4A-C5A	-0.9(4)	C2B-C3B-C4B-C5B	0.0(4)
C3A-C4A-C5A-C6A	-179.9(2)	C3B-C4B-C5B-C6B	-179.3(2)
C9A-C10A-C15A-Pd1A	9.2(4)	C9B-C10B-C15B-Pd1	-9.4(4)
C15A-Pd1A-N2A-N3A	-6.4(2)	C15B-Pd1-N2B-N3B	8.9(2)

In this monoclinic crystal (spacial group $P2_1/n$), an asymmetric crystal unit can be found, comprised by two crystallographically independent molecules of **1** and an acetone molecule from the crystallization process. Finally, with regard to crystal packing, it can be represented as chains along b axis formed by Br···H-C bonds. Further interaction with oxygen atoms from acetone molecules create parallel layers along plane [101]. Moreover, π-stacking involving electron clouds of aromatic rings can be also observed in Figure 1.14, and the determined values for the aforementioned interactions are displayed in Table 1.6.

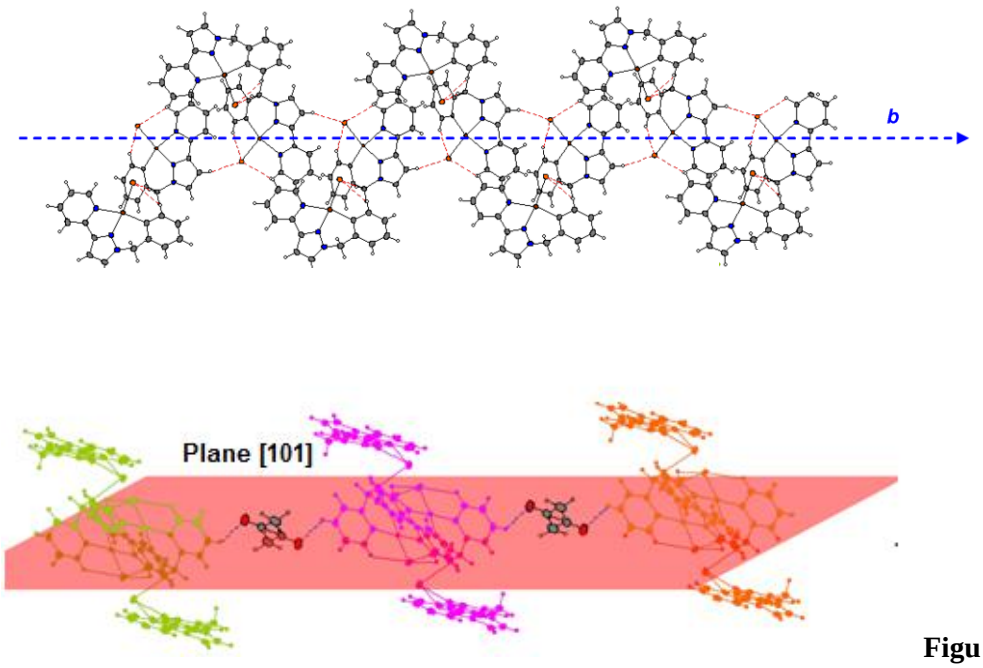


Figure 1.14. Interactions present in the crystal structure of **1**.

Table 1.6. Possible hydrogen-bonds (Å, º).

D—H···A	***D—H***	***H···A***	***D···A***	***D—H···A***
C1B-H1B···Br1	0.9500	2.8800	3.478(3)	122.00
C9B-H9BB···Br1Ai	0.9900	2.7900	3.780(3)	174.00
C7B-H7B···Br1ii	0.9500	2.8000	3.721(3)	164.00
C12B-H12B···O1Diii	0.9500	2.5100	3.229(7)	132.00
C14A-H14A···Br1A	0.9500	2.7200	3.343(3)	123.00
C14B-H14B···Br1	0.9500	2.6800	3.310(3)	125.00

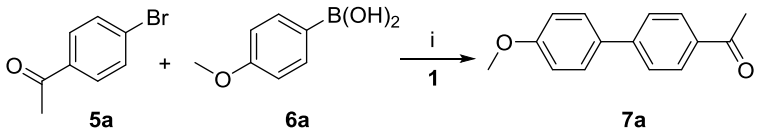
Symmetry operations: (i)= 1-x,1-y,1-z; (ii)= 3/2-x,-1/2+y,3/2-z; (iii)= -1/2+x,3/2-y,1/2+z.

3.2. Catalytic activity of palladium pincer NNC

After completing the first aim of the research, the synthesis of a new non-symmetrical pincer type palladium complex NNC, we studied its catalytic properties in the cross coupling reaction between aryl halides and aryl boronic acids (Suzuki-Miyaura).

As discussed in the introduction, there are several examples of the use of pincer-type palladacycles in Suzuki coupling reactions.[55] With such precedents, and those from our own group, we decided to explore the catalytic properties of the NNC complex in the Suzuki reaction. For this purpose, 4-bromoacetophenone **5a** and 4-methoxyphenylboronic acid **6a** were used as model substrates. These compounds were reacted under different reaction condition in the presence of pincer **1** as the only source of palladium and ligand. We used aqueous media in the reaction and also to use catalyst amounts below the usual values reported when using commercial sources of palladium. The results of our assays are summarized in Table 1.7.

Table 1.7. Summary of reaction conditions assayed for the Suzuki coupling in the presence of **1**.



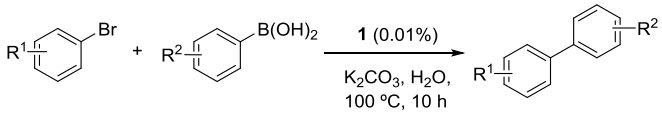
5a **6a** **7a**

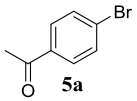
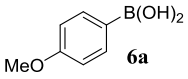
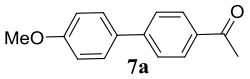
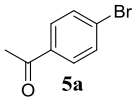
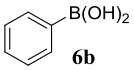
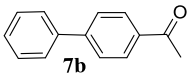
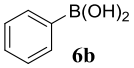
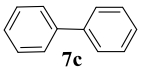
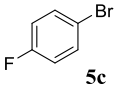
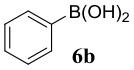
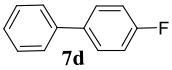
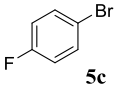
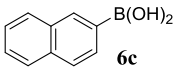
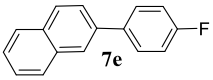
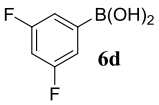
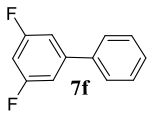
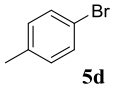
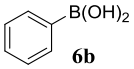
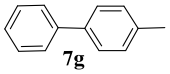
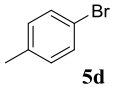
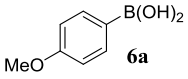
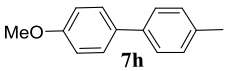
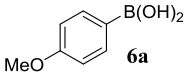
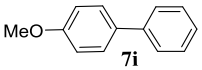
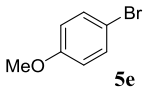
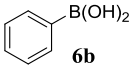
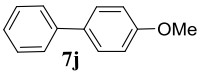
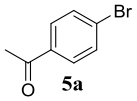
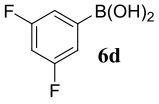
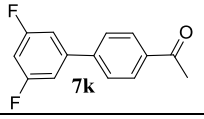
	(i)[a]	(%)[b]
1	K_2CO_3, H_2O, 100 ºC	84
2	Cs_2CO_3, H_2O, 100 ºC	60
3	KOH, H_2O, 100 ºC	63
4	K_2CO_3, EtOH, 60 ºC	66
5	K_2CO_3, MeOH, 60 ºC	82
6	K_2CO_3, H_2O, 110 ºC, 10 h	>99
7	K_2CO_3, H_2O, 110 ºC	80
8	K_2CO_3, H_2O, 100 ºC, 10 h	>99
9[c]	K_2CO_3, H_2O, 100 ºC, 10 h	-

[a] **5a** (1 equiv.), **6a** (1.5 equiv.), base (2 equiv.), **1** (0.01 mol%), solvent (1 ml per mmol of substrate), 2 hours of reaction (except where indicated). [b] Isolated yield. [c] Reaction performed in absence of **1**.

Different bases (entries 1-3) were tested initially, and in view of the results, we tried to optimize the reaction conditions by varying both temperature and solvent (Table 1.7, entries 4-5). Finally, different assays were performed to find out the best combination of reaction time and temperature (entries 6-8), concluding that heating to 100 ºC for 10 hours led to the product with the best yield (entry 8). These optimized conditions were applied to a number of aryl bromides **5** and boronic acids **6** to provide the corresponding biaryls **7,** as displayed in Table 1.8. It should be mentioned that the coupling was not observe in the absence of the pincer complex (Table 1.7, entry 9).

Table 1.8. Suzuki cross-coupling scope.



	ArBr (**5**)	$Ar^1B(OH)_2$ (**6**)	Ar-Ar^1 (**7**)	(%)[a]
1	 **5a**	 **6a**	 **7a**	>99
2	 **5a**	 **6b**	 **7b**	>99
3	 **5b**	 **6b**	 **7c**	81
4	 **5c**	 **6b**	 **7d**	98
5	 **5c**	 **6c**	 **7e**	96
6	 **5b**	 **6d**	 **7f**	66
7	 **5d**	 **6b**	 **7g**	82
8	 **5d**	 **6a**	 **7h**	73
9	 **5b**	 **6a**	 **7i**	73
10	 **5e**	 **6b**	 **7j**	66
11	 **5a**	 **6d**	 **7k**	53

[a] Isolated yield.

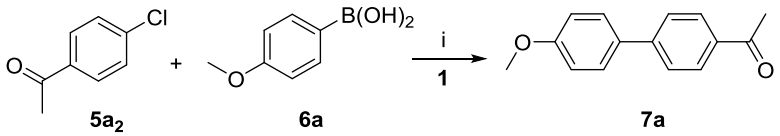
Taking into account the obtained results, we can conclude that the presence of electron-withdrawing groups in the aryl bromide eased the reaction, providing the corresponding biaryl in good yields in most of the cases. On the other hand, when substrates had electron-donating groups in *para* position or no substituent, the coupling product was obtained in lower yields. This could happen because the oxidative addition step is usually more difficult with electron-rich haloarenes.[65] Besides, the reaction is favored when boronic acid had no subtituents at the aryl ring (phenyl, 2-napthyl) as in entries 2-5 and 7. In contrast, the yield of the transformation decreased in presence of boronic derivatives 3,5-difluorosubstituted.

Then, we decided to carry out the cross-coupling reaction using aryl chlorides aiming to improve the scope of the reaction. As mentioned before, chloroarenes are so interesting due to their low cost and availability.[51] Thereby, we tried the optimized conditions with **5a$_2$** and **6a** as model substrates. Unfortunately, as it can be seen in Table 1.9 (entry 1), they did not work with this kind of haloarene. At this point, we decided to add a phase transfer agent to the reaction media to enhance the reactivity of the reaction in water.[66] The addition of a tetraalkylammonium salt had a positive effect in the reaction outcome, especially when combined with a higher concentration (Table 1.9, entry 3 *vs* entries 1-2) and higher amount of catalyst. With the purpose of increasing the yield we changed both temperature and reaction time (entries 4-6), observing that longer reaction

[65] K. H. Shaughnessy, R. B. DeVasher *Curr. Org. Chem.* **2005**, *9*, 585.
[66] M.-J. Jin, D.-H. Lee *Angew. Chem. Int. Ed.* **2010**, *49*, 1119.

times were required to improve the result. We also observed that it was possible to decrease the catalyst loading to the initial 0.01 mol% with just a slight variation in the yield (entry 7). Unfortunately, all attempts to explore substrates other than 4-chloroacetophenone and phenylboronic acid failed.[67]

Table 1.9. Optimization assays for aryl chlorides.



5a₂ **6a** **7a**

	(i)[a]	Additive	(%)[b]
1	K_2CO_3, H_2O, 100 ºC, 10 h	---	20
2	K_2CO_3, H_2O, 100 ºC, 10 h	TBAB	40
3[c]	K_2CO_3, H_2O, 100 ºC, 10 h	TBAB	72
4[c]	K_2CO_3, H_2O, 120 ºC, 10 h	TBAB	65
5[c]	K_2CO_3, H_2O, 80 ºC, 36 h	TBAB	74
6[c]	K_2CO_3, H_2O, 100 ºC, 48 h	TBAB	80
7	K_2CO_3, H_2O, 100 ºC, 48 h	TBAB	76

[a] 5**a₂** (1 equiv.), **6a** (1.5 equiv.), K_2CO_3 (2 equiv.), **1** (0.01 mol%),additive (1 equiv.), H_2O (1 ml per mmol of substrate). [b] Isolated yield. [c] 0.5 ml H_2O per mmol of substrate and 0.5 mol % **1**.

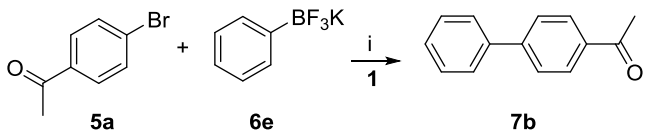
An extension of the reaction scope to aryltrifluoroborates was attempted. In fact, the last years have witnessed an increase in the use of such boron derivatives as more convenient coupling partners.[68] Potassium

[67] Chloroarne, p-methylchlorobenzene and phenyl boronic acid **6b** were tested with negative results.

[68] G. A. Molander, B. Canturk *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.

phenyltrifluoroborate and 4-bromoacetophenone were chosen as model substrates, and in view of the excellent results obtained by the procedure optimized for arylboronic acids (Table 1.10, entry 1) we decided to decrease the catalyst amount and to assay other solvent conditions (entries 2-6). Excellent yields were obtained even when 10^{-5} mol% was employed (87%, entry 5).

Table 1.10. Optimization assays for potassium trifluoroborates.



5a **6e** **7b**

	(i)[a]	**1** (x mol %)	(%)[b]
1	K_2CO_3, H_2O	10^{-2}	>99
2	K_2CO_3, EtOH:H_2O (9:1)	10^{-2}	---
3	K_2CO_3, H_2O	10^{-3}	>99
4[c]	K_2CO_3, H_2O	10^{-4}	>99
5[c]	K_2CO_3, H_2O	10^{-5}	87
6[c]	K_2CO_3, H_2O	10^{-6}	65

[a] 5**a** (1 equiv.), **6e** (1.5 equiv.), K_2CO_3 (2 equiv.), solvent (1 ml per mmol of substrate), 10 h, 100 ºC. [b] Isolated yield.

Nevertheless, when the optimized conditions displayed in Table 1.10, entry 5, were applied to other bromoarenes, the boroxine shown in Figure 1.15 was detected on all cases instead of the expected biaryl compound. It is already known that trifluoroborates hydrolyze to form the corresponding boronic acid when they are heated in aqueous or protic media.[69] In addition,

[69] A. J. J. Lennox, G. C. Lloyd-Jones *J. Am. Chem. Soc.* **2012**, *134*, 7431.

boronic acids are in equilibrium with the trimeric anhydride called boroxine, which is an entropically favoured process. Although boroxines are known to work in the same way as boronic acids[44b] do in Suzuki-Miyaura reaction, we were unable to obtain the desired coupling product. Several assays were tried introducing the isolated boroxine as substrate, even so only starting materials were observed after the reaction.

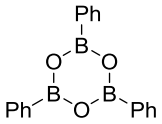


Figure 1.15. Phenyl boroxine.

3.3. Synthesis and characterization of carborane-based NBN pincer complexes

As part of our ongoing collaboration with the Institut de Ciència de Materials de Barcelona (ICMAB-CSIC), we decided to carry out a preliminary study on the catalytic properties of a recently prepared carborane-based palladium pincer complex. Although *meta*-carborane pincer complexes have been already used as convenient metal sources for a number of organic transformations,[70] no report on the catalytic behaviour of any *ortho*-carborane-based palladium pincer complex has been described so far. All *closo*-carborane-pincer complexes reported up to now are based in the *meta*-carborane isomer, that is, one of the three possible isomers of

[70] M. E. El-Zaria, H. Arii, H. Nakamura *Inorg. Chem.* **2011**, *50*, 4149.

carborane (*ortho*-, *meta*- and *para*- *closo*-$C_2B_{10}H_{10}$; Figure 1.16). Electron density of the vertexes is strongly affected by the different electronegativities between carbon and boron atoms and by their arrangement in the three isomers. Both calculations and chemical reactivity reveal that B(3 or 6) in *o*-carborane is more positive than the related B(2 or 3) in *m*-carborane and B atoms in *p*-carborane are practically neutral.[71,72] In other words, the boron atoms attached to both carbon atoms of the cluster feature a more electron-withdrawing character in the *o*-carborane than in the *m*-carborane isomers.

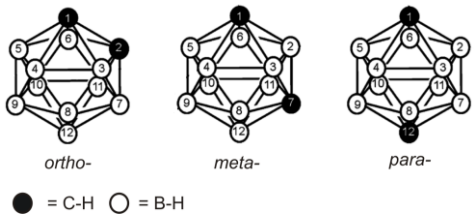


Figure 1.16. Graphical representation of the caborane isomers with vertex numbering.

The effect above mentioned is known to transmit to the substitutents at boron and therefore it should also affect the metal centers in carboranyl based EBE complexes. Providing that this effect is significant, it could

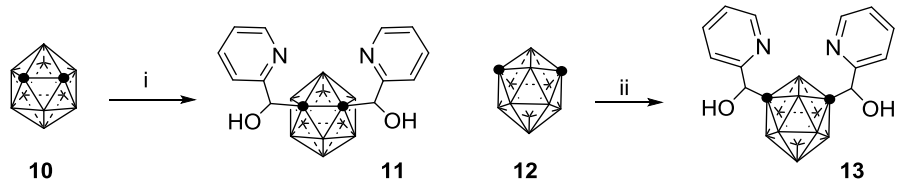
[71] a) R. N. Grimes in *Carboranes 2nd ed*., Elsevier, **2011**; b) M. Scholz, E. Hey-Hawkins *Chem. Rev.* **2011**, *111*, 7035; c) I. T. Chizhevsky *Coord. Chem. Rev.* **2007**, *251*, 1590; d) F. Teixidor, C. Viñas in *Science of Synthesis*, Thieme, Stuttgart, **2005**; e) Z. Xie *Acc. Chem. Res.* **2003**, *36*, 1; f) J. F. Valliant, K. J. Guenther, A. S. King, P. Morel, P. Schaffer, O. O. Sogbein, K. Stephensen *Coord. Chem. Rev.* **2002**, *232*, 173; g) M. F. Hawthorne, Z.-P. Zheng *Acc. Chem. Res.* **1997**, *30*, 267; h) J. Plešek *Chem. Rev.* **1992**, *92*, 269; i) V. I. Bregadze *Chem. Rev.* **1992**, *92*, 209.

[72] K. Hermansson, M. Wójcik, S. Sjöberg *Inorg. Chem.* **1999**, *38*, 6039.

provide an exclusive control of electronic properties (such as *trans* influence) over the steric ones by simply selecting the desired carborane isomer for a given carboranyl based ligand and its corresponding EBE complex. Such control in electronic tuning without altering the steric factors is an exclusive feature of carborane based ligands.[73]

Moreover, we sought to gain a better understanding on the *ortho- vs meta*-carborane influence on catalytic properties, so *meta*-carborane analogue was also included in the scheduled catalytic evaluation. In regard to the synthesis of the aforementioned palladium NBN complexes, the first step was the access to carborane ligands **11** and **13**, as shown in Scheme 1.15. In this context, following their previous report on carborane-based bis-*o*-methylpyridyl alcohols,[74d] a new bis-pyridylmethyl alcohol **11** derived from the *o*-carborane cluster was prepared and a new related *m*-carborane **13** analogue was also synthesized. Thus, *o*-carborane **10** and *m*-carborane **12** were treated with ^{n}BuLi at 0 ºC in diethyl ether to generate the correponding dilithiated intermediates, which were immediately reacted with 2-pyridinecarboxaldehyde at low temperatures (-84 ºC for **10** and -63 ºC for **12)** to afford the desired ligands **11** and **13** in reasonable yields (57% and 79% respectively).

[73] a) A. M. Spokoyny, C. W. Machan, D. J. Clingerman, M. S. Rosen, M. J. Wiester, R. D. Kennedy, C. L. Stern, A. A. Sarjeant, C. A. Mirkin *Nature Chem.* **2011**, *3*, 590; b) T. Teixidor, G. Barberà, A. Vaca, R. Kivekäs, R. Sillanpää, J. Oliva, C. Viñas *J. Am. Chem. Soc.* **2005**, *127*, 10158.



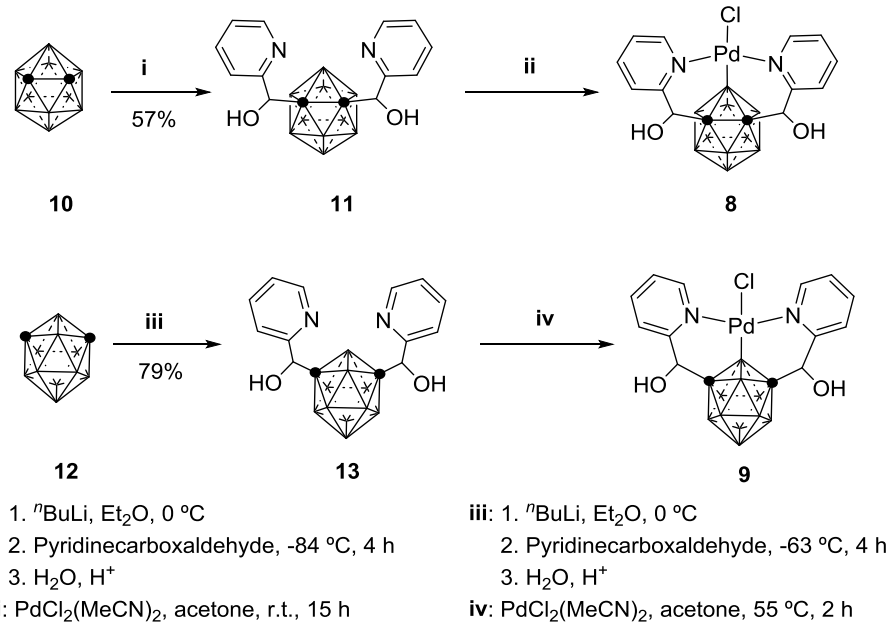
i: 1. ^{n}BuLi, Et_2O, 0 ºC
2. pyridinecarboxaldehyde, -84 ºC, 4 h
3. H_2O, H^+

ii: 1. ^{n}BuLi, Et_2O, 0 ºC
2. pyridinecarboxaldehyde, -63 ºC, 4 h
3. H_2O, H^+

Scheme 1.14. Carborane-based ligands **11** and **13**.

The latter carbinol ligands **11** and **13** were fully characterized by standard spectroscopic and analytical techniques and the data correlated well with that of related alcohols.[74] Due to the presence of two chiral centers, a mixture of both diastereoiseomers, a *meso* compound (*RS;* OH groups in a *syn* orientation) and a racemic compound (mixture of *SS* and *RR*; OH groups in an *anti* orientation) was employed in the next metallation step. For that, the synthesized **11** and **13** carborane ligands were reacted with $[PdCl_2(MeCN)_2]$ in acetone (25 ºC, 15 hours for **10**, and 55 ºC, 2 hours for **12)** to afford new pincer complexes **8** and **9** in 71% and 76% yield respectively. The complexes precipitated from the reaction media as air stable pale yellow solids. Both of them were soluble in very polar solvents such as DMF or DMSO (being **8** slightly more soluble than **9**).

[74] a) V. Terrasson, J. G. Planas, D. Prim, C. Viñas, F. Teixidor, M. E. Light, M. B. Hursthouse *J. Org. Chem.* **2008**, *73*, 9140; b) V. Terrasson, Y. García, P. Farràs, F. Teixidor, C. Viñas, J. G. Planas, D. Prim, M. E. Light, M. B. Hursthouse *CrystEngComm*. **2010**, *12*, 4109; c) F. Di Salvo, J. G. Planas, B. Camargo, Y. Garcia, F. Teixidor, C. Viñas, M. E. Light, M. B. Hursthouse *CrystEngComm*, **2011**, *13*, 5788; d) F. Di Salvo, C. Paterakis, M. T. Tsang, C. Viñas, F. Teixidor, J. G. Planas, M. E. Light, M. B. Hursthouse, D. Choquesillo-Lazarte *Cryst. Growth Des.* **2013,** *13*, 1473.



Scheme 1.15. Synthesis of NBN pincer complexes.

All spectroscopic and analytical data were consistent with the proposed molecular structures and are in agreement with the solid-state structures determined by single crystal X-ray diffraction methods (Figure 1.16).

The molecular structures for compounds **8** and **9** were unequivocally established by single crystal X-ray diffraction (Figure 1.17). Whereas the *o*-carborane derivative **8** crystallized in the triclinic P-1 space group, the *m*-carborane compound **9** crystallized in the monoclinic $P2_1/c$ space group. Carborane moieties show typical icosahedrons geometry with very similar bond distances and angles, and also similar to those in other *o*- or *m*-carboranyl alcohols.[74]

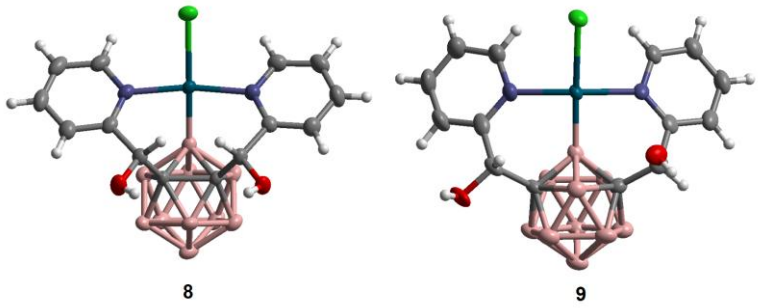


Figure 1.17. Molecular structures of **8** and **9**,thermal ellipsoids set at 90% and 80% probability, respectively, and H atoms are represented as fixed-size spheres of 0.18Å (B-H atoms are omitted for clarity). Color code: B pink; C grey; H white; O red; N blue; Cl green; Pd prussian blue. Only one stereoisomer is represented in those structures with disorder of OH groups.

The Pd(II) metal atoms display a strongly distorted square planar coordination: for complex **8**, maximum distances from the least-squares plane are +0.163 Å for B(6), and –0.167/–0.165 for N(20)/N(28); and for complex **9**, corresponding distances are +0.267 Å for B(2), and –0.256/–0.260 for N(20)/N(28). In all complexes the two pyridine rings are in a *trans* fashion and a chloride atom is *trans* to the boron atom coordinated to Pd(II). Molecular structures for the complexes show unambiguously B–H activation of the carborane cages. Activation takes place in the B–H bonds close to the carborane carbon atoms, B(3/6)H in **8** or B(2/3)H in **9** (Figure 1.16). A comparison of selected bond distances and angles is shown in Table 1.11.

Table 1.11. Comparison of selected distances (Å) and angles (º) for **8** and **9**.

	8	**9**
Bond-distances		
Pd-Cl	2.5063 (8)	2.4915 (5)
Pd-B	1.974 (4)	2.021 (2)
Pd-N(a)	2.088 (3)	2.0557 (17)
Pd-N(b)	2.087 (3)	2.0564 (18)
Cc(a)-B	1.704 (5)	1.718 (3)
Cc(b)-B	1.706 (5)	1.723 (3)
Bond-angles		
Cl-Pd-B	170.98 (10)	175.14 (7)
N-Pd-N	161.55 (10)	166.76 (7)

The structures of compounds **8** and **9** display exceptionally long Pd–Cl distances in the solid state, suggesting a strong *trans* influence of the carborane moieties (Table 1.11). Such long Pd–Cl distances are sensibly longer than similar motifs in aryl-based pincers,[75] and are comparable with

[75] Selected examples of $NC_{aryl}N$-Pincer palladium: (pyrido[2',3':5,6]naphtho[2,3-h]quinolin-14-yl)PdCl, Pd–Cl 2.4304(17) Å (K. J. H. Young, X. Bu, W. C. Kaska *J. Organomet. Chem.* **2011**, *696*, 3992); (2-(pyridin-2-yl)-6-((pyridin-2-yl)sulfanyl)phenyl)PdCl, Pd–Cl 2.4191(6) Å (M. Hirotsu, Y. Tsukahara, I. Kinoshita *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1058); ((5*S*,7*S*)-2,6-bis(6,6-dimethyl-5,6,7,8-tetrahydro-5,7-methanoquinolin-2-yl)phenyl)PdCl, Pd–Cl 2.451(1) Å (B. Soro, S. Stoccoro, G. Minghetti, A. Zucca, M. A. Cinellu, M. anassero, S. Gladiali *Inorg. Chim. Acta* **2006**, *359*, 1879); (2,6-bis(2-pyridyl)phenyl)PdCl, Pd–Cl 2.427(1) Å (B. Soro, S. Stoccoro, G. Minghetti, A. Zucca, M. A. Cinellu, S. Gladiali, M. Manassero, M. Sansoni *Organometallics* **2005**, *24*, 53); (4-bromo-2,6-bis(7-azaindolyl)phenyl)PdCl, Pd–Cl 2.3867(16) Å (D. Song, Q. Wu, A. Hook, I. Kozin, S. Wang *Organometallics* **2001**, *20*, 4689).

that for related alkyl-based pincer Pd complexes.[76] The Pd–B distances (1.97-2.02 Å) are also short and are consistent with a Pd–B σ bond.[77]

3.4. Catalytic activity of carborane-based palladium pincer

As mentioned before, we established a collaboration with Dr. Giner and co-workers in order to evaluate the suitability of uncommon complexes, such as the new carboranyl NBN Pd pincer **8** as a palladium source. The catalytic profile of complex **8** was examined in Suzuki-Miyaura cross-coupling reaction. At this point, the screening of the reaction conditions was performed using two common substrates, 4-methoxyphenylboronic **6a** acid and 4-bromoacetophenone **5a**, employing **8** as palladium source. As it can be seen in Table 1.12, we realized that aqueous mixtures of solvents (THF, DMF, MeOH, THF/H_2O, MeOH/H_2O) despite being more suitable to solubilize carborane-based Pd pincer **8**, gave worse results than water as reaction media (entry 9-10 *vs* 1-8). The addition of TBAB (known for being a great stabilizing agent for palladium nanoparticles)[66] did not improve the conversion using MeOH or THF as solvents in comparison with the results obtained in water (entries 2 and 5 *vs* 9-10). Besides, different bases were also assayed in combination with the above solvents, affording the best results with the employment of Et_3N or K_2CO_3 in water (entries 9-10).

[76] Selected examples of $NC_{alkyl}N$-Pincer palladium: (3,5-^{t}Bu$_2$pz)$_2$PdCl(Me), Pd–Cl 2.5165(9) Å (K. Li, J. Darkwa, I. A. Guzei, S. F. Mapolie *J. Organomet. Chem.* **2002**, *660*, 108); (N-N')(η^2-olefin)PdCl(Me), Pd–Cl 2.492(1) Å (V. G. Albano, C. Casterllari *Organometallics* **1990**, *9*, 1269).

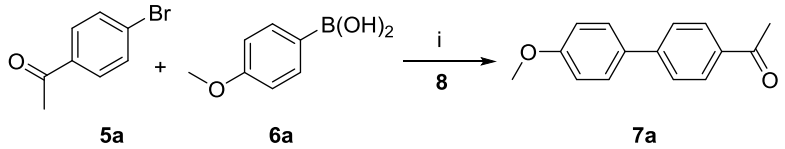
[77] A. M. Spokoyny, M. G. Reuter, C. L. Sterm, M. A. Ratner, T. Seideman, C. A. Mirkin *J. Am. Chem. Soc.* **2009**, *131*, 9482.

Taking into account the results achieved, we decided to further decrease the catalyst amount down to 10^{-4} mol%. The decrease was applied to all the conditions where the desired coupling product was obtained, since it has been reported that some pincer-type complexes show better catalytic activity in fewer quantities.[78.] After several trials (entries 11-16), although the conversions did not drastically decrease, only the same result was obtained with such low catalyst loading in entry 16, turning out to be the optimized conditions.

Besides, we should mention that the coupling did not occur in the absence of the pincer complex (Table 1.12, entry 17). ICP-MS analysis of all the reagents employed (aryl halide, boronic acid, potassium carbonate) revealed that the palladium contents in the reaction mixture were around 10^{-5} mol%. These facts reveal that the possibility of a coupling catalyzed by residual palladium traces from the reagents could be ruled out.

78 G. de Vries *Dalton Trans.* **2006**, 42.

Table 1.12. Optimization assays.



5a **6a** **7a**

	(i)[a]	(%)[b]
1	KOH (2.5 equiv.), THF, 40 ºC, 10 h	-
2	K_2CO_3 (2 equiv.), TBAB (1 equiv.), THF, 40 ºC, 12 h	10
3	K_3PO_4 (2 equiv.), DMF, 80 ºC, 10 h	5
4	K_2CO_3 (2 equiv.), MeOH:H_2O (3:1), 70 ºC, 12 h	-
5	K_2CO_3 (2.5 equiv.), TBAB (1 equiv.), MeOH, 70 ºC, 10 h	68
6	K_2CO_3 (2 equiv.), MeOH, 70 ºC, 10 h	66
7	Cs_2CO_3 (2.5 equiv.), H_2O, 100 ºC, 12 h	7
8	K_2CO_3 (2.5 equiv.), THF:H_2O (9:1), 80 ºC, 10 h	88
9	Et_3N (2 equiv.), H_2O, 80 ºC, 12 h	>99
10	K_2CO_3 (2 equiv.), H_2O, 110 ºC, 10 h	>99
11[c]	K_2CO_3 (2.5 equiv.), TBAB (1 equiv.), MeOH, 70 ºC, 10 h	62
12[c]	K_2CO_3 (2.5 equiv.), TBAB (1 equiv.), MeOH, 100 ºC, 10 h	63
13[c]	K_2CO_3 (2 equiv.), MeOH, 70 ºC, 10 h	60
14[c]	K_2CO_3 (2.5 equiv.), THF:H_2O (9:1), 80 ºC, 10h	84
15[c]	Et_3N (2 equiv.), H_2O, 80 ºC, 12 h	95
16[c]	K_2CO_3 (2 equiv.), H_2O, 110 ºC, 10 h	>99
17[d]	K_2CO_3 (2 equiv.), H_2O, 110 ºC, 10 h	-

[a] **5a** (1.5 equiv.), **6a** (1.5 equiv.), base (2-3 equiv.), **8** (10^{-2} mol%), solvent (1 ml per mmol of substrate), additive (when indicated). [b] Conversion rate measured by GC-MS. [c] **8** (10^{-4} mol%). [d] Reaction performed in the absence of **1**.

We decided to apply the optimized reaction conditions (K_2CO_3, H_2O, 110 ^oC, 10 h, 10^{-4} mol%) to a range of substrates using **8** and **9** as catalysts or precatalysts (Table 1.13). In view of the results displayed in Table 1.13 we can conclude that not only arylboronic acids can be effectively coupled with aryl bromides but also potassium phenyltrifluoroborate (Table 1.13, entries 3, 5, 7 and 10). In addition, benzyl bromide can be also used as a coupling partner (entries 11-14), and both electron-withdrawing and -donating groups can be incorporated in the substrates. It is noteworthy the fact that both complexes are selective against halide nature, since in presence of substrates containing bromide and chloride substituents only the coupling product at the brominated position was obtained (*e.g.* entries 6-10). Moreover, by-products were not observed, as apart from the coupling products only unreacted halides were detected in the crude reaction mixtures. On the other hand, it can be said that complex **8** showed a better catalytic profile than **9** with some exceptions (entries 4, 11 and 13). Although **9** failed to provide the corresponding biaryl compound with acceptable yields in some cases (entries 6 and 8), we observed that it provided better results than **8** when benzyl halides were employed.

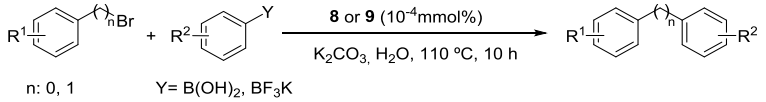
The TON values ranged from 770,000 to 990,000 for **8**, thus showing a very high catalytic activity. This is an important achievement since it rivals with previous Suzuki couplings performed with extremely low amounts of palladium catalysts, even with pincer complexes. Last but not least, it is worth noting that water is used as a convenient and sustainable solvent.

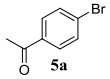
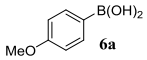
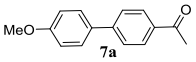
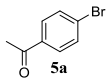
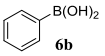
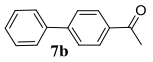
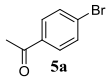
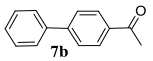
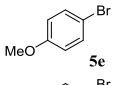
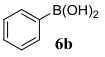
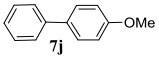
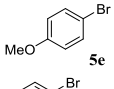
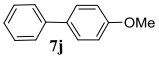
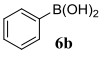
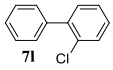
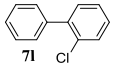
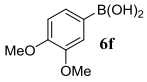
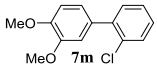
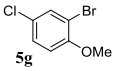
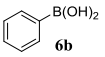
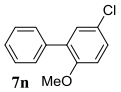
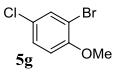
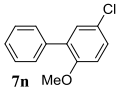
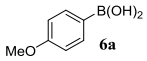
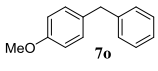
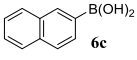
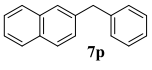
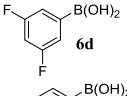
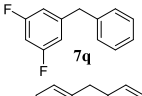
The low catalytic loading employed prevented an analysis of the palladium species generated after the coupling reaction, including that related to possible changes in the structure of the carborane moiety.

However, no palladium black or mirror was observed, even when the catalyst amount was increased at 10^{-2} mol% level (Table 1.13 entry 10), which is to some extent indicative of the integrity of the metal complex under the reaction conditions. Although no detailed mechanistic studies have been carried out for the present Suzuki coupling reactions, it occurs to us that the catalytic activity of complexes **8** and **9** might be related to a steady release of palladium nanoparticles or to the partial hemilability of such complexes under the optimized reaction conditions.[79]

[79] For a discussion on the role of pincer complexes in Suzuki coupling carried out in aqueous media, see: B. Inés, R. SanMartin, M. J. Moure, E. Domínguez *Adv. Synth. Catal.* **2009**, *351*, 2124.

Table 1.13. Summary of coupled products.



	ArBr	$Ar^1B(OH)_2$	Ar-Ar^1	**8** (%)[a]	**9** (%)[a]
1	 **5a**	 **6a**	 **7a**	99	60
2	 **5a**	 **6b**	 **7b**	99	85
3[b]	 **5a**	 **6e**	 **7b**	99	93
4	 **5e**	 **6b**	 **7j**	84	90
5[b]	 **5e**	 **6e**	 **7j**	92	60
6	 **5f**	 **6b**	 **7l**	91	5
7[b]	 **5f**	 **6e**	 **7l**	97	69
8	 **5f**	 **6f**	 **7m**	77	20
9	 **5g**	 **6b**	 **7n**	66	56
10[b]	 **5g**	 **6e**	 **7n**	61	54
11	 **5h**	 **6a**	 **7o**	82	99
12	 **5h**	 **6c**	 **7p**	99	99
13	 **5h**	 **6d**	 **7q**	87	95
14	**5h**	**6f**	**7r**	99	99

[a]Isolated yields. [b] 2.5 equiv. of base were used.

In summary, we have synthesized a new non-symmetric palladium pincer NNC (**1**). Besides, it has been applied to Suzuki cross-coupling reaction in aqueous media, achieving good results in almost all the cases. In addition, palladium pincer complexes **8** and **9** from our collaborative work with the *Institut de Ciència de Materials de Barcelona* have turned out to be good catalysts or precatalysts in Suzuki couplings. These reactions have been carried out in water, with remarkably low amounts of catalyst loadings, and showing a good functional group tolerance.

4. EXPERIMENTAL PROCEDURES

4.1. General methods and materials

All reagents were purchased and used as received except when indicated. All solvents used in reactions were dried and purified according to standard procedures.[80] All air- or moisture-sensitive reactions were performed under argon atmosphere. The glassware was oven dried (140 ºC) overnight and purged with argon prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H, 75.4 MHz for ^{13}C and 96 MHz for ^{11}B) at 20 ºC. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.00 for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz). In occasional cases $BF_3 \cdot OEt_2$ is used as an external standard for ^{11}B NMR. Melting points were determined in a capillary tube on a Gallenkamp instrument and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230-400 mesh ASTM). IR spectra were recorded using an ATR on a JASCO FT/IR4100 in the interval between 400 and 400 cm^{-1} with 4 cm^{-1} resolution, and only noteworthy absorptions are reported in cm^{-1}. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory

[80] a) W. L. F. Armarego, C. Chai in *Purification of Laboratory Chemicals, 5th ed.*, Elsevier Science, **2009**; b) B. G. Williams, M. S. Lawton *Org. Chem.* **2010**, *75*, 8351.

evaporator. ICP-MS measurements were carried out on a Thermo Elemental X7 Series ICP-MS equipped with an ASX-520 autosampler. MS spectra were recorded on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions. HRMS were recorded using a Micromass GCT spectrometer by electronic impact (EI) or electrospray ionization (ESI). Occasionally, the mass spectra were recorded in the positive or negative ion mode using a BrukerBiflex MALDI-TOF-MS [N_2 laser; λ_{exc} 337 nm (0.5 ns pulses); voltage ion source 20.00 kV (Uis1) and 17.50 kV (Uis2)] with 3,5-dimethoxy-4-hydroxycinnamic acid as matrix.

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Cu kα radiation (λ= 1.54184 A) and Atlas CCD detector. Measurement was carried out at 100(2) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crysalis software package.[81] The structure was solved using Olex2[82] and refined by full-matrix least-squares with SHELXL-97.[83] Final geometrical calculations were carried out with Mercury[84] and PLATON[85] as integrated in WinGX.[86]

[81] CrysAlisPro, Agilent Technologies, Version 1.171.37.31 (release 14-01-2014 CrysAlis171 .NET) (compiled Jan 14 2014,18:38:05).

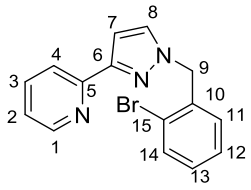
[82] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann *J. Appl. Cryst.* **2009**, *42*, 339.

[83] G. M. Sheldrick *Acta Crystallogr*. **2008**, *64*, 112.

[84] C. F. Macrae *J. Appl. Cryst.* **2008**, *41*, 466.

4.2. Synthesis of the palladium pincer NNC

2-[1-(2-Bromobenzyl)-1*H*-pyrazol-3-yl]pyridine, 4.



In a round bottom flask 2-bromobenzyl chloride **2** (0.29 ml, 2.28 mmol), 2-(1*H*-pyrazol-3-yl)pyridine **3** (333 mg, 2.23 mmol), 3.5 ml of a 40% aqueous solution of NaOH, and 165 µl of a 40% aqueous solution of $^{n}Bu_4OH$ were dissolved in 27 ml of toluene at room temperature under argon atmosphere. The mixture was heated to 120 ºC for 48 hours. After cooling the reaction mixture was washed with H_2O (3 x 5 ml) and the aqueous layer was extracted with diethyl ether (3 x 5 ml). The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by flahs column chromatography using hexanes:EtOAc (6:4) as eluent to afford pure product **4** as a yellow powder (682 mg, 95%).

m.p. 62-65 °C (hexanes/EtOAc).

^{1}H NMR ($CDCl_3$) δ 8.61 (d, *J* = 4.7 Hz, 1H, H-1), 7.93 (d, *J* = 7.9 Hz, 1H, H-4), 7.66 (td, *J* = 7.8, 1.7 Hz, 1H, H-3), 7.55 (d, *J* = 7.8 Hz, 1H, H_{arom}),

[85] A. L. Spek *J. Appl. Cryst*. **2003**, *36*, 7.

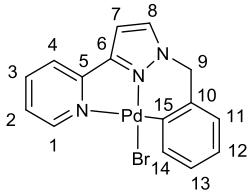
[86] L. J. Farrugia *J. Appl. Cryst*. **1999**, *32*, 837.

7.47 (d, *J* = 2.3 Hz, 1H, H-8), 7.28-7.06 (m, 3H, H_{arom}), 6.93 (d, *J* = 2.4 Hz, 2H, H_{arom}), 5.46 (s, 2H, H-9).

^{13}C NMR ($CDCl_3$) δ 151.9 (qC_{arom}), 151.8 (qC_{arom}), 149.2 (C-1), 136.3 (C-3), 135.8 (qC_{arom}), 132.5, 131.3, 129.2, 129.0 (C_{arom}), 127.6 (C-8), 122.4 (CBr), 122.0 (C-2), 119.8 (C-4), 104.6 (C-7), 55.7 (C-9).

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{12}N_3Br$: 131.0215; found: 313.0209.

[2-[1-[(Phenil-κC2)-methyl]-1*H*-pyrazol-3-yl-κN2]-pyridine-κN-palladium(II) bromide, 1.



In a round bottom flask pyrazol **1** (200 mg, 0.63 mmol) was dissolved in 15 ml of THF under argon atmosphere and was then added to previously dried $Pd(dba)_2$ (400 mg, 0.69 mmol). The reaction mixture was heated to 120 ºC for 8 hours. After cooling it was filtered through a plug of celite. The filtrate was evaporated under reduced pressure and the crude was purified by flash chromatography with a gradient starting at hexanes:EtOAc (1:1) and ending at 100% EtOAc. Complex **1** was obtained as an orange powder (191 mg, 88%).

m.p. 142-144 ºC (hexanes:EtOAc).

^{1}H NMR ($CDCl_3$) δ 9.1 (d, *J* = 5.3 Hz, 1H, H-1), 8.41 (d, *J* = 2.8 Hz, 1H, H-4), 7.83 (td, *J* = 9.3, 1.6 Hz, 1H, H-3), 7.65 (d, *J* = 5.1 Hz, 2H, H_{arom}),

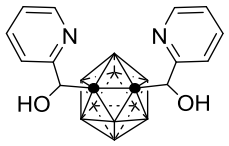
7.32 (m, 1H, H_{arom}), 7.00-6.89 (m, 3H, H_{arom}), 6.71 (d, *J* = 5.3 Hz, 1H, H-7), 5.31 (s, 2H, H-9).

^{13}C-NMR ($CDCl_3$) δ 151.2 (qC_{arom}), 150.8 (qC_{arom}), 149.2 (C-1), 143.1 (C-4), 138.9 (qC_{arom}), 135.6 (qC_{arom}), 132.4 (C-15), 131.5, 127.3, 127.0, 124.6, 124.5 (C_{arom}), 120.4 (C-3), 104.9 (C-7), 60.6 (C-9).

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{12}N_3Pd$: 340.00665; found: 340.00613.

4.3. Synthesis of carborane-based NBN palladium pincers

Bis-[2-pyridyl-(hydroxy)methyl]-1,2-dicarba-closo-dodecaborane, 11.[87]



^{n}BuLi (1.75 mL, 1.6 M in hexane, 2.8 mmol) was added dropwise to a solution of *o*-carborane **10** (201.4 mg, 1.4 mmol) in diethyl ether (10 mL) at 0 °C (ice/water bath) under nitrogen atmosphere. The mixture was stirred for 30 min at 0 ºC and for a further 1.5 h at room temperature to give a clear pale yellow suspension. The flask was then cooled to −84 °C, where upon a solution of 2-pyridinecarboxaldehyde (0.27 mL, 2.8 mmol) in diethyl ether (1 mL) was added. The resulting pale-yellow solution was stirred at −84 °C, and the reaction was monitored by TLC. When the reaction had reached

[87] F. Di Salvo, C. Paterakis, M. T. Tsang, C. Viñas, F. Teixidor, J. G. Planas, M. E. Light, M. B. Hursthouse, D. Choquesillo-Lazarte; *Cryst. Growth Des.* **2013,** *13*, 1473**.**

completion (after about 4 h), a saturated aqueous solution of NH_4Cl (10 mL) was added at −84 °C, and then the mixture was taken out of the cooling bath and allowed to warm naturally to room temperature while stirring. The aqueous phase was then extracted with Et_2O (3 × 20 mL), and the organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The resultant dark yellow oil was washed with n-pentane (2 × 10 mL). Fresh n-pentane was added and the mixture was treated with ultrasound for c.a. 15 min, and the slightly colored pentane supernatant was removed afterwards. The same procedure was repeated until a light yellow solid was obtained (4−5 times). After the solvent was removed, the yellow solid was dried under vacuum affording pure **11** (361.8 mg, 72%). NMR experiments confirmed the presence of the two different diastereoisomers *anti*-**11** and *syn*-**11** in a 44:56 proportion.

^{1}H-NMR ($CDCl_3$) δ (mixture) 8.63-8.58 (m, 2H, C_5H_4N *syn*- and *anti*-isomers), 7.96-7.89 (m, 2H, C_5H_4N *syn*- and *anti*-isomers), 7.66 (apparent t, *J* = 8.3 Hz, 2H, C_5H_4N *syn*- and *anti*-isomers), 7.46-7.41 (m, 2H, C_5H_4N *syn*- and *anti*-isomers), 6.34 (bs, 1H, O*H* *anti*-isomer), 6.19 (bs, 1H, O*H* *syn*-isomer), 5.98 (bs, 1H, C*H*OH *syn*-isomer), 5.75 (bs, 1H, C*H*OH *anti*-isomer).

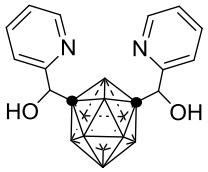
^{13}C NMR ($CDCl_3$) δ (mixture) 159.5 and 159.4, 149.1 and 149.0, 138.0, and 137.9 (C_5H_4N *syn*- plus *anti*-isomers), 124.9 (C_5H_4N *syn*- plus *anti*-isomers), 123.6 and 123.4 (C_5H_4N *syn*- plus *anti*-isomers), 86.37 and 86.24 ($C_{cluster}$ *syn*- plus *anti*-isomers), 74.3 (*C*HOH *syn*-isomer), 73.53 (*C*HOH *anti*-isomer).

^{11}B NMR ($CDCl_3$) δ -2.9 (d, $J_{B,H}$ = 145, 2B), -10 a -11 (m, 8B).

IR (ATR) υ_{max} 3197 (OH), 2599, 2573 (BH) cm^{-1}.

MALDI-TOF m/z: $[M + H]^+$ 359.27.

Bis-[2-pyridyl (hydroxy)methyl]-1,2-dicarba-meta-dodecaborane, 13.[87]



^{n}BuLi (1.86 mL, 1.48 M in hexane, 2.76 mmol) was added dropwise to a solution of *m*-carborane **12** (201.4 mg, 1.4 mmol) in THF (10 mL) at 0 °C (ice/water bath) under nitrogen atmosphere. The mixture was stirred for 30 min at 0 ºC and for a further 1.5 h at room temperature to give a clear, pale yellow suspension. The flask was then cooled to −63 °C, where upon a solution of the 2-pyridinecarboxaldehyde (0.27 mL, 2.8 mmol) in THF (1 mL) was added. The resulting pale-yellow solution was stirred at -63 °C, and the reaction was monitored by TLC. When the reaction had reached completion (after about 4 h), a saturated aqueous solution of NH_4Cl (10 mL) was added at -63 °C, and then the mixture was taken out of the cooling bath and allowed to warm naturally to room temperature while stirring. The aqueous phase was then extracted with Et_2O (3 × 20 mL), and the organic phases were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The resultant dark yellow oil was washed with n-pentane (2 × 10 mL). Fresh n-pentane was added and the mixture was treated with

ultrasound for c.a. 15 min, and the slightly colored pentane supernatant was removed afterwards. The same procedure was repeated until a light yellow solid was obtained (4-5 times). After the solvent was removed, the yellow solid was dried under vacuum affording pure **13** (369.6 mg, 79%). NMR experiments confirmed the presence of the two different diastereoisomers *anti*-**13** and *syn*-**13**.

^{1}H NMR (Acetone-d_6) δ 8.51 (d, *J* = 3.0 Hz, 1H, C_5H_4N), 7.81 (td, *J* = 9.0, 3.0 Hz, 1H, C_5H_4N), 7.42 (d, *J* = 6.0 Hz, 1H, C_5H_4N), 7.36 (td, *J* = 6.0, 3.0 Hz, 1H, C_5H_4N), 5.40 (d, *J* = 6.0 Hz, 1H, OH), 4.96 (d, *J* = 6.0 Hz, 1H, CHOH).

^{13}C NMR (Acetone-d_6) δ 160.2 (C_5H_4N), 149.0 (C_5H_4N), 137.4 (C_5H_4N), 124.4 (C_5H_4N), 122.8 (C_5H_4N), 82.4 ($C_{cluster}$), 75.3 (CHOH).

^{1}H {^{11}B} NMR (Acetone-d_6) δ Only signals due to B-H protons are given: 2.73 (bs, 2H), 2.19 (bs, 2H), 2.15 (bs, 3H), 1.88 (bs, 3H).

^{11}B-NMR (Acetone-d_6) -5.34 (bs, 2B), -10.61 (bs, 6B), -12.98 (bs, 2B).

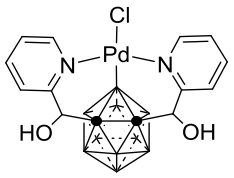
^{1}H NMR (DMSO-d_6) 8.45 (d, *J* = 5.0 Hz, 2H, C_5H_4N), 7.80 (t, *J* = 7.4, 1.5 Hz, 2H, C_5H_4N), 7.35 (d, *J* = 8.0 Hz, 2H, C_5H_4N), 7.30 (dd, *J* = 7.5, 4.7 Hz, 2H, C_5H_4N), 6.50 (d, *J* = 5.7 Hz, 2H, OH), 4.80 (d, *J* = 5.3 Hz, 2H, C*H*OH).

^{1}H{^{11}B}NMR (DMSO-d_6) Only signals due to B-H protons are given: 2.60 (bs, 2H), 2.06 (bs, 6H), 1.79 (bs, 2H).

^{11}B-NMR (DMSO-d_6) -5.13 (bs, 2B), -10.66 (bs, 6B).

General procedure for the synthesis complexes of 8 and 9. $PdCl_2(MeCN)_2$ (61 mg, 0.28 mmol) and the corresponding ligand **11** or **13** (100 mg, 0.28 mmol) were dissolved in acetone (10 mL) in a capped vial. The reaction mixture was stirred under air at room temperature for 15 h. Then a yellowish precipitate was collected by centrifugation (6000 r.m.p, 10 mins), washed with acetone (3 x 3 mL) to remove excess of starting materials, and dried under vacuum to provide pure the desired product.

***Palladium complex* 8.**



The general procedure was followed to obtained pure **8** as a pale yellow solid (100 mg, 71%).

^{1}H NMR (DMSO-d_6) δ 8.92 (d, *J* = 4.9 Hz, 2H, C_5H_4N), 8.14 (t, *J* = 7.6 Hz, 2H, C_5H_4N), 7.90 (d, *J* = 7.3 Hz, 2H, NC_5H_4), 7.55 (t, *J* = 6.7 Hz, 2H, C_5H_4N), 7.45 (bs, 2H, CHO*H*), 6.09 (bs, 2H, C*H*OH).

^{13}C NMR (DMSO-D_6) δ 161.0, 153.4, 139.5, 124.5, 123.52 (C_5H_4N), 89.9 (C*H*OH), 72.4 ($CHB_{10}H_9$).

^{1}H{^{11}B} NMR (DMSO-d_6): Only signals due to B-H protons are given δ 2.75 (bs, 1H), 2.17 (bs, 3H), 1.86 (bs, 3H), 0.39 (bs, 2H).

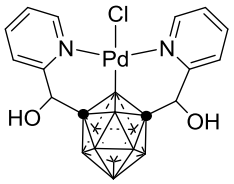
^{11}B NMR (DMSO-d_6) δ +10 to -20 (br m).

Elemental analysis calculated for $C_{14}B_{10}H_{21}N_2O_2ClPd•H_2O$ C 32.50%, H 4.48%, N 5.42%; found C 32.52%, H 4.20%, N 5.42%.

MALDI-TOF m/z: $[M\text{-}Cl\text{-}H]^+$ 462.45.

IR (ATR) υ_{max} 3344, 3316 (OH), 2617, 2594, 2567, 2553 (BH) cm^{-1}.

Palladium complex, 9.



The general procedure was followed, heating the mixture at 55 ºC for 2 hours obtaining pure **9** (100.6 mg, 76%).

^{1}H NMR (DMSO-d_6) δ 10.02, 9.91, 9.82, 9.68 (d, *J* = 5.7 Hz, 2H, C_5H_3N for four diasteromers), 8.10-7.49 (m, 6H, C_5H_3N), 7.08, 7.07, 6.91, 6.83 (d, *J* = 5.9 Hz, 2H, OH for four diasteromers), 5.14 (d, *J* = 5.9 Hz, 1H, C*H*OH for *anti*- or *syn*- isomer), 4.96 (d, *J* = 5.3 Hz, 1H, C*H*OH for *syn*- or *anti*-isomer).

^{13}C NMR (DMSO-d_6) δ 162.2, 161.2, 161.0, 157.8, 155.8, 154.7, 139.7, 139.5, 139.4, 127.3, 124.2, 123.6, 122.9, 122.6 (C_5H_4N), 76.1, 75.7, 75.4, 74.5, 73.9, 73.7 (C*H*OH, $CHB_{10}H_9$).

^{11}B NMR (DMSO-d_6) δ -11.4 (br m).

Elemental analysis calculated for $C_{14}B_{10}H_{21}N_2O_2ClPd$•DMF C 35.67%, H 4.93%, N 7.34 %; found C 35.76%, H 5.08%, N 7.10%.

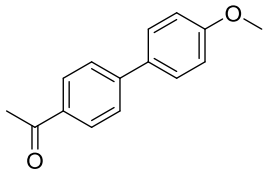
MALDI-TOF m/z: $[M\text{-}Cl\text{-}H]^+$ 462.49.

IR (ATR) υ_{max} 3412, 3178 (OH), 2603 (BH) cm^{-1}.

4.4. General procedures for Suzuki cross-coupling

General procedure for Suzuki coupling with arylboronic acids and aryl bromides in the presence of 1. A screw-capped tube equipped with a magnetic stirrer bar was charged with the aryl bromide (1 mmol), arylboronic acid (1.5 mmol), potassium carbonate (2.0 mmol) and **1** (10^{-2} mol %) and distilled water (1 mL) at room temperature. This mixture was heated to 100 ºC for 10 h under stirring, allowed to cool and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexanes:EtOAc as eluent. By this procedure the following biaryls were prepared:

4-Acetyl-4'-methoxybiphenyl, 7a.[88]



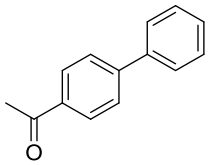
The general procedure for cross-coupling was followed, and compound **7a** was obtained as a white powder (223.7 mg, 99%).

^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.65 (d, *J* = 8.5 Hz. 2H, H_{arom}), 7.58 (d, *J* = 9.0 Hz, 2H, H_{arom}), 7.00 (d, *J* = 8.5 Hz, 2H, H_{arom}), 3.87 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3).

[88] Q-X. Liu, W. Zhang, X-J. Zhao, Z-X. Zhao, M-C. Shi, X-G. Wang *Eur. J. Org. Chem*. **2013**, 1253.

^{13}C NMR ($CDCl_3$) δ 197.7 (CO), 159.9 (qC_{arom}-O), 145.3 (qC_{arom}), 135.2 (qC_{arom}), 132.2, 128.9, 128.3, 126.6, 114.4 (C_{arom}), 55.3 ($COCH_3$), 26.6 (CH_3).

4-Acetylbiphenyl, 7b.[88,89]



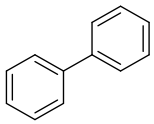
The general procedure for cross-coupling was followed, and compound **7b** was obtained as a white powder (194.0 mg, 99%).

^{1}H NMR ($CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H, H_{arom}), 7.69 (d, *J* = 4.0 Hz, 2H, H_{arom}), 7.63 (t, *J* = 4.5 Hz, 2H, H_{arom}), 7.48 (t, *J* = 7.5 Hz, 2H, H_{arom}), 7.40 (t, *J* = 7.0 Hz, 1H, H_{arom}), 2.64 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$) δ 197.7 (CO), 145.7 (qC_{arom}), 139.8 (qC_{arom}), 135.8 (qC_{arom}), 128.9, 128.8, 128.2, 127.2, 127.1 (C_{arom}), 26.7 ($COCH_3$).

[89] L. Liu, Y. Dong, B. Pang, J. Ma *J. Org. Chem.* **2014**, *79*, 7193.

1,1'-Biphenyl, 7c.[88,90]

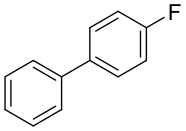


The general procedure for cross-coupling was followed, and compound **7c** was obtained as a white powder (124.8 mg, 81%).

^{1}H NMR ($CDCl_3$) δ 7.59 (dd, *J* = 7.5, 1.4 Hz, 2H, H_{arom}), 7.43 (t, *J* = 7.5 Hz, 4H, H_{arom}), 7.34 (dd, *J* = 7.5, 1.4 Hz, 4H, H_{arom})

^{13}C NMR ($CDCl_3$) 141.4 (qC_{arom}), 128.9 (qC_{arom}), 127.4, 127.3 (C_{arom}).

4-Fluoro-1,1'-biphenyl, 7d.[88,91]



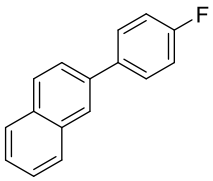
The general procedure for cross-coupling was followed, and compound **7d** was obtained as a white powder (124.8 mg, 98).

^{1}H NMR ($CDCl_3$) δ 7.57-7.53 (4H, m, H_{arom}), 7.44 (2H, t, *J* = 7.6 Hz, H_{arom}), 7.35 (1H, t, *J* = 7.2 Hz, H_{arom}), 7.13 (2H, t, *J* = 8.8 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$) δ 161.8 (d, J_{C-F} = 244.6 Hz, CF), 140.2 (qC_{arom}), 136.5 (d, J_{C-F} = 3.3 Hz, qC_{arom}), 128.8, 128.6, 127.2, 127.0 (C_{arom}), 115.5 (d, J_{C-F} = 21.1 Hz, C_{arom}).

[90] Z. Zhou, M.Liu, X. Wu, H. Yu, G. Xu, Y. Xi *Appl. Organometal. Chem*. **2013**, *27*, 562.
[91] Q. Wu, L. Wu, L. Zhang, H. Fu, X. Zheng, H. Chen, R. Li *Tetrahedron* **2014**, *70*, 3471.

2-(4-Fluorophenyl)naphthalene, 7e.[92]

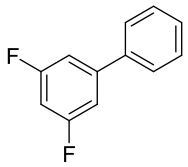


The general procedure for cross-coupling was followed, and compound **7e** was obtained as a white powder (213.2 mg, 96%).

^{1}H NMR ($CDCl_3$) δ 7.92-7.83 (m, 3H, H_{arom}), 7.53-7.38 (m, 6H, H_{arom}), 7.20-7.16 (m, 2H, H_{arom}).

^{13}C-NMR ($CDCl_3$) δ 162.3 (d, J_{C-F} = 244.6 Hz, CF), 139.2 (qC_{arom}), 136.7 (d, J_{C-F} = 3.3 Hz, qC_{arom}), 133.8, 131.7 (C_{arom}), 131.6 (d, J_{C-F} = 7.9 Hz, C_{arom}), 128.3, 127.8, 127.0, 126.1, 125.83, 125.76, 125.3 (C_{arom}), 115.2 (d, J_{C-F} = 21.1 Hz, C_{arom}).

3,5-Difluoro-1,1'-biphenyl, 7f.[93]



The general procedure for cross-coupling was followed, and compound **7f** was obtained as a yellow oil (125.4 mg, 66%).

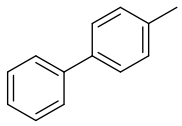
[92] Z-Y. Wang, G-Q. Chen, L-X. Shao *J. Org. Chem.* **2012**, *77*, 6608.

[93] A. S. Demir, H. Findik, N. Saygili, N. T. Subasi *Tetrahedron* **2010**, *66*, 1308.

^{1}H NMR ($CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 2H, H_{arom}), 7.47 (t, *J* = 7.2 Hz, 2H, H_{arom}), 7.41 (t, *J* = 7.2 Hz, 2H, H_{arom}), 7.14 (dd, *J* = 8.8, 2.4 Hz, 2H, H_{arom}), 6.76 (tt, *J* = 8.8, 2.0 Hz, 1H, H_{arom}).

^{13}C NMR ($CDCl_3$) 163.5 (dd, $J_{C–F}$ = 247.1 Hz, CF), 144.6 (t, $J_{C–F}$ = 10 Hz, qC_{arom}), 139.2 (qC_{arom}), 129.2, 128.6, 127.1 (C_{arom}), 110.1 (dd, $J_{C–F}$ = 18.6 Hz, C_{arom}), 102.5 (t, $J_{C–F}$ = 100 Hz, C_{arom}).

4-Methyl-1,1'-biphenyl, 7g.[88,90]

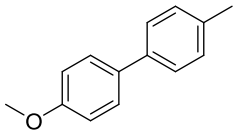


The general procedure for cross-coupling was followed, and compound **7g** was obtained as a white powder (137.8 mg, 82%).

^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 2H, H_{arom}), 7.49 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.43 (d, *J* = 7.5 Hz, 2H, H_{arom}), 7.32 (t, *J* = 7.3 Hz, 1H, H_{arom}), 7.25 (d, *J* = 7.5 Hz, 2H, H_{arom}), 2.39 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) 141.3 (qC_{arom}), 138.5 (qC_{arom}), 130.7 (qC_{arom}), 129.6, 129.2, 128.8, 127.2, 127.1 (C_{arom}), 21.2 (CH_3).

4-Methoxy-4'-methyl-1,1'-biphenyl, 7h.[94]

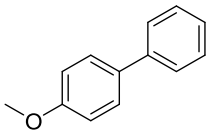


The general procedure for cross-coupling was followed, and compound **7h** was obtained as a white powder (144.6 mg, 73%).

^{1}H NMR ($CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H, H_{arom}), 7.22 (d, *J* = 8.0 Hz, 2H, H_{arom}), 6.97 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.51 (d, *J* = 8.0 Hz, 2H, H_{arom}), 3.85 (s, 3H, OC*H*$_3$), 2.38 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) 159.1 (qC_{arom}-O), 138.2 (qC_{arom}), 136.5 (qC_{arom}), 129.6 (qC_{arom}), 128.1, 127.7, 126.7, 114.3 (C_{arom}), 55.5 (OCH_3), 21.2 (CH_3).

4-Methoxy-1,1'-biphenyl, 7i.[88,90]



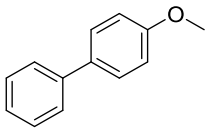
The general procedure for cross-coupling was followed, and compound **7i** was obtained as a white powder (134.4 mg, 73%).

^{1}H NMR ($CDCl_3$) δ 7.56-7.52 (m, 4H, H_{arom}), 7.50-7.35 (m, 2H, H_{arom}), 7.30 (t, *J* = 7.5 Hz, 1H, H_{arom}), 7.00 (d, *J* = 8.5 Hz, 2H, H_{arom}), 3.85 (s, 3H, CH_3).

[94] L. Goswami, P. Gogoi, J. Gogoi, A. Borah, M. R. Das, R. C. Boruah *Tetrahedron Lett,* **2014**, *55*, 5539.

^{13}C NMR ($CDCl_3$) 159.0 (qC_{arom}-O), 140.7 (qC_{arom}), 133.7 (qC_{arom}), 128.6, 128.0, 126.6, 126.5, 114.1(C_{arom}), 55.3 (OCH_3).

4-Methoxy-1,1'-biphenyl, 7j.[88,90]

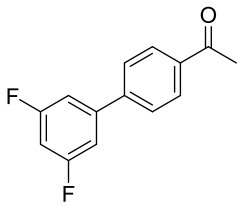


The general procedure for cross-coupling was followed, and compound **7j** was obtained as a white powder (121.5 mg, 66%).

^{1}H NMR ($CDCl_3$) δ 7.56-7.52 (m, 4H, H_{arom}), 7.50-7.35 (m, 2H, H_{arom}), 7.30 (t, *J* = 7.5 Hz, 1H, H_{arom}), 7.00 (d, *J* = 8.5 Hz, 2H, H_{arom}), 3.85 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) 159.0 (qC_{arom}-O), 140.7 (qC_{arom}), 133.7 (qC_{arom}), 128.6, 128.0, 126.6, 126.5, 114.1(C_{arom}), 55.3 (OCH_3).

1-(3',5'-Difluoro-[1,1'-biphenyl]-4-yl)ethan-1-one, 7k.[90]



The general procedure for cross-coupling was followed, and compound **7k** was obtained as a white powder (123.0 mg, 53%).

^{1}H NMR ($CDCl_3$) δ 8.03 (d, 2H, *J* = 8.0 Hz, H_{arom}), 7.62 (d, 2H, *J* = 8.0 Hz, H_{arom}), 7.11-6.96 (m, 2H, H_{arom}), 6.82-6.69 (m, 2H, H_{arom}), 2.64 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$) 197.4 (CO), 164.6 (dd, $J_{C\text{-}F}$ = 247.0 Hz, CF), 143.4 (t, J_{C-F} = 12.3 Hz, qC_{arom}), 136.8 (qC_{arom}), 135.6 (qC_{arom}), 129.0, 127.2 (C_{arom}), 110.2 (dd, J_{C-F} = 18.6 Hz, C_{arom}), 103.4 (t, J_{C-F} = 100 Hz, C_{arom}), 26.6 ($CO\mathit{C}H_3$).

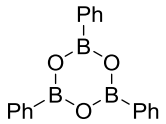
General procedure for Suzuki coupling with arylboronic acids and aryl chlorides in the presence of 1. A screw-capped tube equipped with a magnetic stirrer bar was charged with the aryl chloride (1 mmol), arylboronic acid (1.5 mmol), potassium carbonate (2.0 mmol), tetrabutylammonium bromide (1 mmol), **1** (10^{-2} mol %) and distilled water (1 mL) at room temperature. This mixture was heated to 100 ºC for 48 h under stirring, allowed to cool and extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexanes:EtOAc as eluent. By this procedure the following biaryls were prepared:

4-Acetyl-4'-methoxybiphenyl, 7a. The general procedure for cross-coupling was followed, and compound **1** was obtained as a white powder (171.8 mg, 76%).

4-Acetylbiphenyl, 7b. The general procedure for cross-coupling was followed, and compound **1** was obtained as a white powder (137.3 mg, 70%).

Suzuki coupling between potassium phenyltrifluoroborate and aryl 4-bromoacetophenone in the presence of 1. A screw-capped tube equipped with a magnetic stirrer bar was charged with 4-bromoacetophenone (199.0 mg, 1 mmol), potassium phenyltrifluoroborate (276.0 mg, 1.5 mmol), potassium carbonate (276.4 mg, 2.0 mmol) and **1** (10^{-4} mol%) and distilled water (1 mL) at room temperature. This mixture was heated to 110 ºC for 10 hours under stirring, allowed to cool and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexane:EtOAc (7:3) as eluent, providing 4-acetylbiphenyl **7b** as a white powder (168.6 mg, 86%).

2,4,6-Triphenylboroxin, 14.[95]



^{1}H NMR ($CDCl_3$) δ 7.77-7.75 (m, 6H, H_{arom}), 7.36-7.34 (m, 9H, H_{arom}).

^{13}C NMR ($CDCl_3$) δ 133.4 (C_{arom}), 131.5 (qC_{arom}), 128.7 (C_{arom}).

[95] Y. Huang, T. Hayashi *J. Am. Chemi. Soc.* **2015**, *137*, 7556.

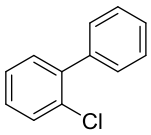
General procedure for Suzuki coupling with arylboronic acids in the presence of 8. A screw-capped tube equipped with a magnetic stirrer bar was charged with the aryl- or benzyl bromide **5** (1 mmol), arylboronic acid **6** (1.5 mmol), potassium carbonate (2.0 mmol), **8** (10^{-4} mol %) and distilled water (1 mL) at room temperature. This mixture was heated to 110 ºC for 10 h under stirring, allowed to cool and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexanes:EtOAc as eluent. By this procedure the following biaryls and diarylmethanes were prepared:

4-Acetyl-4'-methoxybiphenyl, 7a. The general procedure for cross-coupling was followed, and compound **7a** was obtained as a white powder (223.7 mg, 99%).

4-Acetylbiphenyl, 7b. The general procedure for cross-coupling was followed, and compound **7b** was obtained as a white powder (194.0 mg, 99%).

4-Methoxy-1,1'-biphenyl, 7j. The general procedure for cross-coupling was followed, and compound **7j** was obtained as a white powder (154.6 mg, 84%).

2-Chlorobiphenyl, 7l.[96]

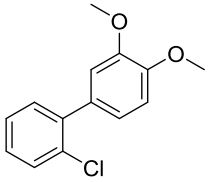


The general procedure for cross-coupling was followed, and compound **7l** was obtained as a white powder (171.1 mg, 91%).

^{1}H NMR ($CDCl_3$) δ 7.48-7.38 (m, 6H, H_{arom}), 7.36-7.26 (m, 3H, H_{arom}).

^{13}C NMR ($CDCl_3$) δ 140.5 (qC_{arom}), 139.4 (qC_{arom}), 132.5 (CCl), 131.4, 129.9, 129.4, 128.5, 128.0, 127.6, 126.8 (C_{arom}).

2-Chloro-3',4'-dimethoxy-1,1'-biphenyl, 7m.[97]



The general procedure for cross-coupling was followed, and compound **7m** was obtained as a white powder (190.9 mg, 77%).

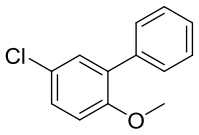
^{1}H NMR ($CDCl_3$) δ 7.52-7.39 (m, 4H, H_{arom}), 7.12 (dd, J = 8.2, 2.2 Hz, 1H, H_{arom}), 7.08 (d, J = 2.0 Hz, 1H, H_{arom}), 6.94 (d, J = 8.4 Hz, 1H, H_{arom}), 3.89 (s, 3H, CH_3), 3.87 (s, 3H, CH_3).

[96] N. Marzari, A. A. Mostofi, J. R. Yates, I. Souza, D. Vanderbilt *Rev. Mod. Phys.* **2012**, *84*, 1419.

[97] M. R. McLean, U. Bauer, A. R. Amaro, L. W. Robertson *Chem. Res. Toxicol.* **1996,** *9*, 158.

^{13}C NMR ($CDCl_3$) δ 148.6 (qC_{arom}-O), 148.4 (qC_{arom}-O), 140.3 (qC_{arom}), 132.6 (qC_{arom}), 132.1 (CCl), 131.4, 130.0, 128.3, 126.8, 121.8, 112.9, 110.8 (C_{arom}), 56.0 (CH_3), 55.9 (CH_3).

5-Chloro-2-methoxy-1,1'-biphenyl, 7n.[98]

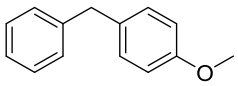


The general procedure for cross-coupling was followed, and compound **7n** was obtained as a white powder (190.9 mg, 66%).

^{1}H NMR ($CDCl_3$) δ 7.52-7.42 (m, 2H, H_{arom}), 7.37-7.23 (m, 5H, H_{arom}), 6.92 (d, *J* = 8.4 Hz, 1H, H_{arom}), 3.81 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 155.9 (qC_{arom}-O), 137.1 (qC_{arom}), 132.4 (qC_{arom}), 130.4, 129.4, 128.1, 128.0, 127.4 (C_{arom}), 125.7 (CCl), 112.5, 55.9 (CH_3).

1-Benzyl-4-methoxybenzene, 7o.[99]



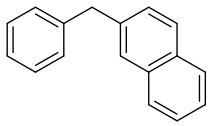
The general procedure for cross-coupling was followed, and compound **7o** was obtained as a white powder (162.4 mg, 82%).

[98] J. L. Bolligera, C. M. Frecha *Adv. Synth. Catal*. **2010**, *352*, 1075.
[99] G. A. Molander, M. D. Elia *J. Org. Chem.* **2006**, *71*, 9198.

^{1}H NMR ($CDCl_3$) δ 7.32 (t, *J* = 7.3 Hz, 2H, H_{arom}), 7.29-7.24 (m, 3H, H_{arom}), 7.18 (d, *J* = 8.5 Hz, 2H, H_{arom}), 6.86 (d, *J* = 8.5 Hz, 2H, H_{arom}), 3.96 (s, 2H, CH_2), 3.81 (s, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ 158.1 (qC_{arom}-O), 141.7 (qC_{arom}), 133.4 (qC_{arom}), 130.0, 129.0, 128.6, 126.1, 114.0 (C_{arom}), 55.4 (CH_3), 41.2 (CH_2).

1-Benzylnaphthalene, 7p.[100]



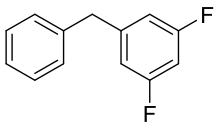
The general procedure for cross-coupling was followed, and compound **7p** was obtained as a white powder (215.8 mg, 99%).

^{1}H NMR ($CDCl_3$) δ 8.12-8.05 (m, 1H, H_{arom}), 7.99-7.97 (m, 1H, H_{arom}), 7.85 (d, *J* = 8.4 Hz, 1H, H_{arom}), 7.56-7.47 (m, 3H, H_{arom}), 7.40-7.32 (m, 3H, H_{arom}), 7.31-7.24 (m, 3H, H_{arom}), 4.53 (s, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 140.8 (qC_{arom}), 136.8 (qC_{arom}), 134.1 (qC_{arom}), 132.3 (qC_{arom}), 128.9, 128.8, 128.6, 127.5, 127.5, 126.2, 126.1, 125.7, 124.4 (C_{arom}), 39.2 (CH_2).

[100] M. McLaughlin *Org. Lett*. **2005**, *7*, 4875.

1-Benzyl-3,5-difluorobenzene, 7q.[101]

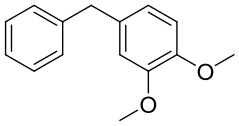


The general procedure for cross-coupling was followed, and compound **7q** was obtained as a white powder (177.5 mg, 87%).

^{1}H NMR ($CDCl_3$) δ 7.33 (tt, *J* = 8.2, 1.6 Hz, 2H, H_{arom}), 7.25 (tt, *J* = 6.2, 1.4 Hz, 1H, H_{arom}), 7.20-7.17 (m, 2H, H_{arom}), 6.74-6.68 (m, 2H, H_{arom}), 6.65 (tt, *J* = 9.0, 2.3 Hz, 1H, H_{arom}), 3.96 (s, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 163.0 (dd, J_{C-F} = 248.0, 12.9 Hz, CF), 145.0 (t, J_{C-F} = 8.9 Hz, qC_{arom}), 139.4 (qC_{arom}), 128.9, 128.7, 126.6 (C_{arom}), 111.6 (dd, J_{C-F} = 18.4, 6.5 Hz, C_{arom}), 101.6 (t, J_{C-F} = 25.4 Hz, C_{arom}), 41.6 (t, J_{C-F} = 1.9 Hz, CH_2).

4-Benzyl-1,2-dimethoxybenzene, 7r.[102]



The general procedure for cross-coupling was followed, and compound **7r** was obtained as a white powder (225.7 mg, 99%).

[101] M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal, R. J. K. Taylor *Org. Lett.* **2007**, *9*, 5397.

[102] T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukazawa *J. Org. Chem.* **1997**, *62*, 6997.

^{1}H NMR ($CDCl_3$) δ 7.34-7.20 (m, 5H, H_{arom}), 6.83-6.74 (m, 3H, H_{arom}), 3.96 (s, 2H, CH_2), 3.87 (s, 3H, CH_3), 3.84 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 148.8 (qC_{arom}-O), 147.3 (qC_{arom}-O), 141.2 (qC_{arom}), 133.5 (qC_{arom}), 128.6, 128.3, 125.9, 120.8, 120.7, 112.2, 111.2, 111.1 (C_{arom}), 55.8 (OCH_3), 55.7 (OCH_3), 41.4 (CH_2).

General procedure for Suzuki coupling with potassium phenyltrifluoroborate in the presence of 8. A screw-capped tube equipped with a magnetic stirrer bar was charged with the aryl bromide **5** (1 mmol), potassium phenyltrifluoroborate **6e** (1.5 mmol), potassium carbonate (2.0 mmol), **8** (10^{-4} mol %) and distilled water (1 mL) at room temperature. This mixture was heated to 110 ºC for 10 h under stirring, allowed to cool and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexanes:EtOAc as eluent. By this procedure the following biaryls were prepared:

4-Acetylbiphenyl, 7b. The general procedure for cross-coupling was followed, and compound **7b** was obtained as a white powder (223.7 mg, 99%).

4-Methoxybiphenyl, 7j. The general procedure for cross-coupling was followed, and compound **7j** was obtained as a white powder (169.3 mg, 92%).

2-Chlorobiphenyl, 7l. The general procedure for cross-coupling was followed, and compound **7l** was obtained as a white powder (182.4 mg, 97%).

5-Chloro-2-methoxy-1,1'-biphenyl, 7n. The general procedure for cross-coupling was followed, and compound **7n** was obtained as a white powder (133.0 mg, 61%).

General procedure for Suzuki coupling with arylboronic acids in the presence of 9. A screw-capped tube equipped with a magnetic stirrer bar was charged with the aryl- or benzyl bromide **5** (1 mmol), arylboronic acid **6** (1.5 mmol), potassium carbonate (2.0 mmol), **9** (10^{-4} mol%) and distilled water (1 mL) at room temperature. This mixture was heated to 110 ºC for 10 h under stirring, allowed to cool and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexanes:EtOAc as eluent. By this procedure the following biaryls and diarylmethanes were prepared:

4-Acetyl-4'-methoxybiphenyl, 7a. The general procedure for cross-coupling was followed, and compound **7a** was obtained as a white powder (135.6 mg, 60%).

4-Acetylbiphenyl, 7b. The general procedure for cross-coupling was followed, and compound **7b** was obtained as a white powder (166.6 mg, 85%).

4-Methoxybiphenyl, 7j. The general procedure for cross-coupling was followed, and compound **7j** was obtained as a white powder (165.6 mg, 90%).

2-Chlorobiphenyl, 7l. The general procedure for cross-coupling was followed, and compound **7l** was obtained as a white powder (9.4 mg, 5%).

2-Chloro-3',4'-dimethoxy-1,1'-biphenyl, 7m. The general procedure for cross-coupling was followed, and compound **7m** was obtained as a white powder (49.6 mg, 20%).

5-Chloro-2-methoxy-1,1'-biphenyl, 7n. The general procedure for cross-coupling was followed, and compound **7n** was obtained as a white powder (122.1 mg, 56%).

1-Benzyl-4-methoxybenzene, 7o. The general procedure for cross-coupling was followed, and compound **7o** was obtained as a white powder (196.0 mg, 99%).

1-Benzylnaphthalene, 7p. The general procedure for cross-coupling was followed, and compound **7p** was obtained as a white powder (215.8 mg, 99%).

1-Benzyl-3,5-difluorobenzene, 7q. The general procedure for cross-coupling was followed, and compound **7q** was obtained as a white powder (193.8 mg, 95%).

4-Benzyl-1,2-dimethoxybenzene, 7r. The general procedure for cross-coupling was followed, and compound **7r** was obtained as a white powder (225.7 mg, 99%).

General procedure for Suzuki coupling with potassium phenyltrifluoroborate in the presence of 9. A screw-capped tube equipped with a magnetic stirrer bar was charged with the aryl bromide **5** (1 mmol), potassium phenyltrifluoroborate **6e** (1.5 mmol), potassium carbonate (2.0 mmol), **9** (10^{-4} mmol) and distilled water (1 mL) at room temperature. This mixture was heated to 110ºC for 10h under stirring, allowed to cool and extracted with diethyl ether (4 x 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue which was purified by flash column chromatography using hexanes:EtOAc as eluent. By this procedure the following biaryls were prepared:

4-Acetylbiphenyl, 7b. The general procedure for cross-coupling was followed, and compound **1** was obtained as a white powder (182.3 mg, 93%).

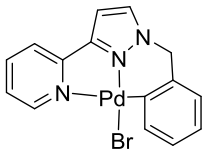
4-Methoxybiphenyl, 7j. The general procedure for cross-coupling was followed, and compound **1** was obtained as a white powder (110.4 mg, 60%).

2-Chlorobiphenyl, 7l. The general procedure for cross-coupling was followed, and compound **1** was obtained as a white powder (114.7 mg, 69%).

5-Chloro-2-methoxy-1,1'-biphenyl, 7n. The general procedure for cross-coupling was followed, and compound **1** was obtained as a white powder (117.7 mg, 54%).

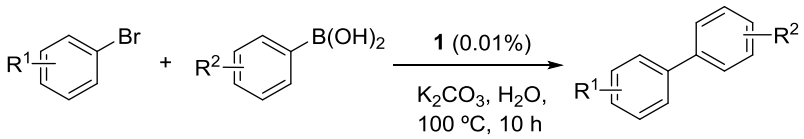
5. CONCLUSIONS

- A synthetic strategy based on an initial nucleophilic substitution followed by an oxidative palladation results highly convenient (89% overall yield) for the preparation of a new palladium pincer complex **1**, a non-symmetrical NNC-type fully identified by X-Ray diffractometry.

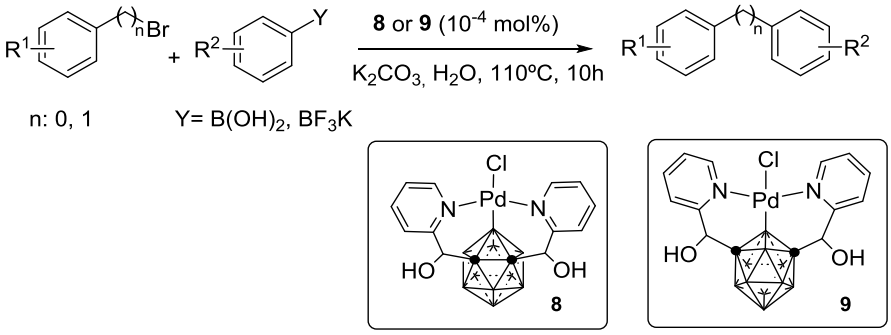


1

- Biaryl compounds can be easily obtained by reaction between arylboronic acids and aryl bromides in the presence of low amounts (10^{-2} mol%) of NNC palladium pincer complex. As an additional advantages to the low catalyst loading requiered, the reaction is conducted in aqueous media.



- Suzuki cross-coupling can be performed with high tolerance to a variety of functional groups employing even lower amounts of carborane-based pincer complexes **8** and **9** in aqueous media.



- Better catalytic profile has been seen for **8** than **9**. In addition both palladacycles showed an exceptional catalytic activity in the field of the couploing with organoboron reagents.

II

Palladium-catalyzed intramolecular direct arylation

1. INTRODUCTION

1.1. Aryl-Aryl bond formation

The biaryl structural motif is a predominant feature in many pharmaceutically relevant and biologically active compounds. As a result, for over a century organic chemists have sought to develop new and more efficient aryl-aryl bond-forming methods.[1] As a pharmacophore core, it is found in many medicinally important compounds such as antibiotics, anti-inflammatories, and anti-hypertensives, as well as other compounds currently employed in therapeutical treatments against cancer, fungi or infertility (Figure 2.1).[2]

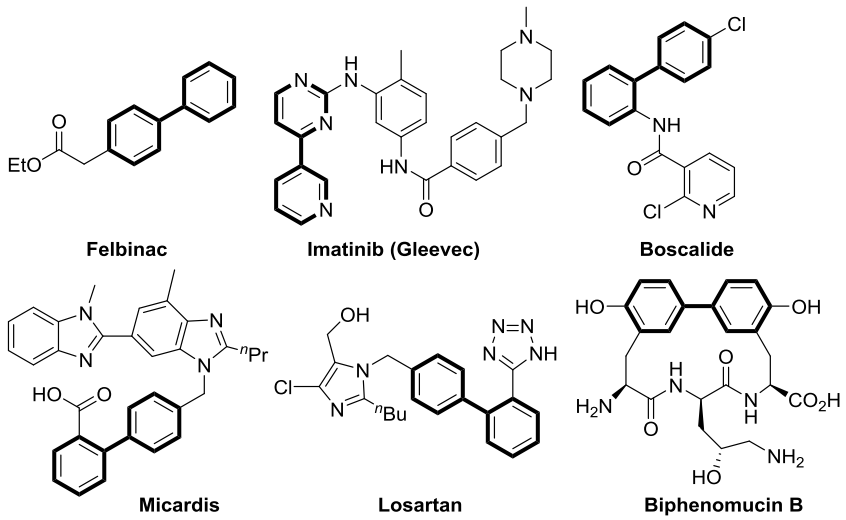


Figure 2.1. Examples of important biaryl-containing compounds.

[1] a)F. Ullmann, J. Bielecki *Chem. Ber.* **1901**, *34*, 2174; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire *Chem. Rev*. **2002**, *102*, 135; c) S.-L. You, J.-B. Xia *Top Curr Chem* **2010**, *292*, 165.

[2] a) D. A. Horton, G. T. Bourne, M. L. Smythe *Chem. Rev.* **2003**, *103*, 893; b) C. Han J. Zhang, M. Zheng, Y. Xiao, Y. Li, G. Liu *Mol Divers*. **2011**, *15*, 857.

The biaryl motif is also an integral part of important agrochemicals, liquid crystal displays and has been incorporated into molecular switches and motors.[3]

Over the past century, several methods have been developed for the synthesis of biaryl compounds.[4] Among these are the Ullmann-type coupling,[1,5] the Scholl reaction,[6] the Gomberg–Bachmann reaction,[7] and recently transition metal catalyzed cross-coupling reactions.[8] In the last decades, the main application of palladium-catalyzed cross-coupling reactions has been the synthesis of biaryls due to the high yields and excellent selectivities obtained. In these cross-coupling reactions, both coupling partners need to be pre-activated compared to simple arenes. Typically, one partner is an organometallic compound, and the other is an aryl halide or pseudohalide (Scheme 2.1).[8a]

[3] a) P. Steenwinkel, D. M. Grove, N. Veldman, A. L. Spek, G. van Koten *Organometallics* **1998**, *17*, 5647; b) C.-H. Wang, N.-N. Ma, X.-X. Sun, S.-L. Sun, Y.-Q. Qiu, P.-J. Liu *J. Phys. Chem. A* **2012**, *116*, 10496; c) Q.-Q. Wang, R. A. Begum, V. W. Day, K. Bowman-James *Inorg. Chem.* **2012**, *51*, 760; d) A. Dorazco-González *Organometallics* **2014**, *33*, 868.

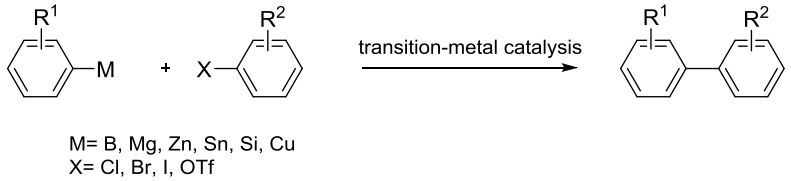
[4] a) D. Alberico, M. E. Scott, M. Lautens *Chem. Rev*. **2007**, *107*, 174; b) *Comprehensive Organic Synthesis, 2nd ed*., (Eds.: P. Knochel, G. A. Molander), Elsevier, Italy, **2014**, Ch. 3.

[5] a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire *Chem. Rev*. **2002**, *102*, 1359; b) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan *Chem. Soc. Rev.* **2014**, *43*, 3525.

[6] a) P. Kovacic, M. B. Jones *Chem. Rev*. **1987**, *87*, 357; b) M. Grzybowski, K. Skonieczny, H. Butenschçn,D. T. Gryko *Angew. Chem. Int. Ed*. **2013**, *52*, 9900.

[7] a) M. Gomberg, W. E. Bachmann *J. Org. Chem. Soc.* **1924**, *46*, 2339; b) G.Pratsch, T. Wallaschkowski, M. R. Heinrich *Chem. Eur. J.* **2012**, *18*, 11555.

[8] a) *Metal-catalyzed Cross-coupling Reactions, 2nd ed.*, (Eds.: A. de Meijere, F. Diedercich), Wiley-VCH, Weinheim, **2004**; b) C. Bolm *J. Org. Chem.* **2012**, *77*, 5221.



Scheme 2.1. Biaryl synthesis *via* traditional cross-coupling reactions.

Several efficient transition metal-catalyzed reactions, such as Suzuki–Miyaura,[9] Kumada,[10] Stille,[11] and Negishi couplings,[12] have been developed to afford biaryls in high yields from these pre-activated coupling partners. Among these, Suzuki–Miyaura coupling between boronic acids and halides in the presence of a palladium catalyst is the most widely used method in both academic and industrial laboratories. Nevertheless, in addition to high yield and selectivity, modern organic chemistry adds more criteria for a more sustainable catalytic reaction, such as robustness of catalyst, mild reaction conditions, availability of starting materials, atom economy and a low environmental impact. In this regard, the above-mentioned cross-coupling reactions still have many fundamental drawbacks. Preparation of both coupling partners often requires additional synthetic operations starting from simple aromatic compounds, generating waste from reagents, solvents,

[9] a) N. Miyaura, A. Suzuki *Chem. Rev.* **1995**, *95*, 2457; b) F.-S. Han *Chem. Soc. Rev.* **2013**, *42*, 5270.

[10] a) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada *J. Org. Chem. Soc.* **1972**, *94*, 9268; b) M. M. Heravi, P. Hajiabbasi *Monatsh. Chem.* **2012**, *143*, 1575.

[11] a) D. Milstein, J. K. Stille *J. Org. Chem. Soc.* **1978**, *100*, 3636; b) C. Cordovilla, C. Bartolome, J. M. Martinez-Ilarduya, P. Espinet *ACS Catal.* **2015**, *5*, 3040.

[12] a) S. Baba, E. Negishi *J. Org. Chem. Soc.* **1976**, *98*, 6729; b) Y.Yang, N. J. Oldenhius, S. L. Buchwald *Angew Chem Int Ed*. **2013**, *52*, 615.

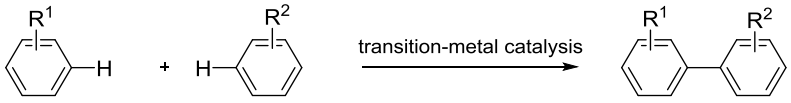
and purifications. Moreover, a stoichiometric amount of metal waste is produced to generate those arene-activating groups, a waste that cannot be ignored upon completion of the cross-coupling reaction. In order to tackle the undesirable issues of traditional aryl-aryl bond formation methods, new procedures have been developed. In this context, modern methods, preferred by most of the pharmaceutical industries, are based on the C–H bond activation of either one or both aromatic coupling moieties.[13]

A quite obvious solution to this problem is to replace both partners of the cross-coupling reaction with simple arenes by the cleavage of C–H bond during the coupling reaction (Scheme 2.2). Double C–H activation methodology is superior to the traditional transition metal-catalyzed cross-coupling, due to the increase of the efficiency of the reaction without requiring pre-activation of substrates; thus showing relatively greener and atom economical approach.[14] Nevertheless, coupling *via* double C–H activation comes up against a major challenge, since the process is thermodynamically disfavored due to the strength of C–H bond (for example, the homocoupling of benzene to give biphenyl and dihydrogen is thermodynamically disfavoured by 13.8 kJ mol^{-1}).[15]

[13] a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang *Green Chem.* **2007**, *9*, 411; b) K. Fagnou *Top. Curr. Chem.* **2010**, *292*, 35; c) L.-C. Campeau, K. Fagnou *Chem. Commun*. **2006**, 1253; d) J. A. Ashenhurst *Chem. Soc. Rev.* **2010**, *39*, 540; e) G. P. McGlacken, L. M. Bateman *Chem. Soc. Rev.* **2009**, *38*, 2447; e) I. Hussain, T. Singh *Adv. Synth. Catal.* **2014**, *356*, 1661.

[14] a) B. M. Trost *Science* **1991**, *254*, 1471; b) K. Okamoto, J. Zhang, J. B. Housekeeper, S. R. Marder, C. K. Luscombe *Macromolecules* **2013**, *46*, 8059.

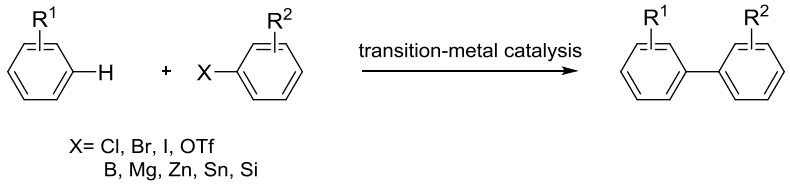
[15] R. Dasgupta, B. R. Maiti *Ind. Eng. Chem. Proc. Des. Dev.* **1986**, *25*, 381.



Scheme 2.2. Aryl-aryl bond formation through double C-H activation.

Moreover, despite of the promising features, there remain more difficulties added to the previously mentioned challenge. To date, all the reported processes have a relatively low turnover number. On the other hand, some of the reactions are even reported with sub-stoichiometric palladium catalyst but they are still at the proof stage. In addition to the low reactivity, regioselectivity is another big challenge for the intermolecular oxidative coupling of two arenes. Although this can be partially solved by using a directing group with the proximal control or the use of substrates with a preferential position towards electrophilic attack, a general strategy to control the regioselectivity with respect to both the coupling partners is still highly desirable but unknown. Moreover, the use of an excess of metal salts as the oxidant leaves the reaction with heavy wastes and difficulties at the work up. In other words, biaryl coupling *via* double C–H activation still has a long way to go to reach the practicality required for industrial application.[13a]

One solution which addresses the thermodynamic issue as well as the need for stoichiometric activating agents on both coupling partners lies on using a pre-activated aryl substrate as one coupling partner and a simple arene as the other (Scheme 2.3).



Scheme 2.3. Aryl-aryl bond formation *via* direct arylation.

While the coupling of an aryl halide or pseudohalide with an organometallic reagent is commonly referred to as a cross-coupling reaction, several terms such as C–H (bond) activation, C–H (bond) functionalization, cross-dehalogenative coupling, and catalytic direct arylation have been used to describe the corresponding coupling of an aryl halide or pseudohalide with a simple arene.[13c]Although the former two terms are more prevalent in the literature, direct arylation has been elected, which is defined as the direct coupling of a non-activated aryl C–H bond with an activated arene.[16]

1.2. Direct arylation

Direct arylation reactions have emerged as an attractive alternative to traditional cross-coupling methods.[17] These reactions substitute one of the preactivated coupling partners with a simple arene. In most cases, the more

[16] For a discussion on the use of the term C-H bond activation, see: a) B. Sezen, D. Sames in *Handbook of C-H Transformations*; (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; b) J.-P. Corbet, G. Mignani *Chem. Rev.* **2006**, *106*, 2651; c) *C-H Bond Activation in Organic Synthesis* (Ed.: J. J. Li), CRC press, **2014**.

[17] a) R. R. Schrock, R. T. DePue, J. Feldman, C. J. Schaverien, J. C. Dewan, A. H. Liu *J. Am. Chem. Soc.* **1988**, *110*, 1423; b) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan *J. Am. Chem. Soc.* **1990**, *112*, 3875; c) D. J. Schipper, Keith Fagnou *Chem. Mater.* **2011**, *23*, 1594.

difficult to prepare organometallic component is replaced, which also reduces the metal waste generated in the overall process. In the past few years, the field of direct arylation has undergone rapid growth and continues to garner worldwide attention.[18]

1.2.1. Reaction conditions

Although a variety of transition metals have been used for the formation of aryl-aryl bonds, second-row transition metals in low oxidation states (Rh, Ru, Pd) have emerged as the preferred catalysts in direct arylation reactions. In some cases, the high reactivity of the transition-metal complexes employed in direct arylation reactions has allowed the use of low catalyst loadings (as low as 0.1 mol%), making them industrially attractive.[19]

In combination with the metal sources, the use of a ligand is often required. The ligands employed in this reaction depend on the nature of the aryl halide. For more reactive aryl iodides, moderately electron-rich monodentate phosphines such as PPh_3 are typically used. The same phosphines have also been successfully utilized for aryl bromides, although in some systems far superior yields have been obtained using more sterically bulky and electron-rich trialkylphosphine or Buchwald's

[18] a) M. Norberg, L, Sanchez, R. E. Maleczka *Cur. Opin. Drug Discov. Devel.* **2008**, *11*, 853; b) A. Sharma, D. Vacchani and E. Van der Eycken, *Chem. Eur. J.* **2013**, *19*, 1158.

[19] a) D. Alberico, M. E. Scott, M. Lautens *Chem. Rev.* **2007**, *107*, 174; b) A. R. Martin, A. Chartoire, A. M. Z. Slawin, S. P. Nolan *Beilstein J. Org. Chem.* **2012**, *8*, 1637, c) L. Yabo W. Jingran, H. Mengmeng, W. Zhiwei, W. Yusheng, W. Yangjie *J. Org. Chem.* **2014**,*79*, 2890.

biphenylphosphines.[20] The use of aryl chlorides in a palladium-catalyzed direct arylation reaction has also been reported. However, as in other cross-coupling reactions,[21] the low reactivity of the C–Cl bond to oxidative addition required the use of electron-rich and sterically-hindered trialkylphosphines, Buchwald's biphenyl phosphines, or N-heterocyclic carbene ligands to achieve synthetically useful yields of the direct arylation product. It should also be noted that ligand-free conditions (Jeffery's conditions) have also been successfully used in this context.[22]

While base is generally required in direct arylation reactions,[23] in most cases the exact role of the base remains unclear. Some recent evidence, however, suggests that in some systems the base may be intimately involved in the formation of the diarylpalladium(II) species (and not simply as a bystander whose role is to regenerate the active catalyst).[13a,24] Typically, inorganic bases such as K_2CO_3, Cs_2CO_3, KOAc, ^{t}BuOK, and CsOPiv are used. In particular, cesium carbonate and cesium pivalate have proven to be very

[20] a) J. P. Wolfe, S. L. Buchwald *Angew. Chem. Int. Ed.* **1999**, *38*, 2413; b) J. P. Wolfe, S. L. Buchwald *Angew. Chem. Int. Ed.* **1999**, *38*, 3415; c) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald *J. Am. Chem. Soc.* **1999**, *121*, 9550; d) R. B. Bedford, S. J. Durrant, M. Montgomery *Angew. Chem. Int. Ed.* **2015**, *54*, 8787.

[21] a) A. F. Littke, G. C. Fu *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; b) P. V. Kumar, W.-S. Lin, J.-S. Shen, D. Nandi, H. M. Lee *Organometallics* **2011**, *30*, 5160.

[22] a) L. Basolo, E. M. Beccalli, E. Borsini, G. Broggini *Tetrahedron* **2009**, *65*, 3486; b) S. Hayashi, Y.a Kojima, T. Koizumi *Polym. Chem*. **2015**, *6*, 881.

[23] H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou *J. Org. Chem.* **2010**, *75*, 8180.

[24] a) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou *J. Am. Chem. Soc.* **2006**, *128*, 581; b) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren *J. Am. Chem. Soc.* **2006**, *128*, 1066.

effective in many cases due to the increased solubility in organic solvents. While polar, aprotic solvents such as DMF, DMA, CH_3CN, NMP and DMSO are commonly used, non-polar solvents such as toluene and xylene have also been employed successfully. In addition, temperatures higher than 100 °C are typically used, and in most cases heating for several hours to days is necessary.[25]

1.2.2. Mechanism

There are several possible mechanisms by which the above reactions take place. The initial oxidative addition of the transition metal to the aryl halide has often been proposed as the initial step. At this point mechanisms diverge in different pathways, as it can be seen in Scheme 2.4. An electrophilic aromatic (S_EAr) type might occur,[26,] or a concerted S_E3,[27] a σ-bond metathesis,'[28] a Heck-type (or carbometallation) process either through a formal *anti* β-hydride elimination or *via* isomerization followed by a *syn* β-hydride elimination[28b,29] or a C-H bond oxidative addition.[29a,30]

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[25] A. B. Khemnar, B. M. Bhanage *RSC Adv.* **2014**, *4*, 8939.

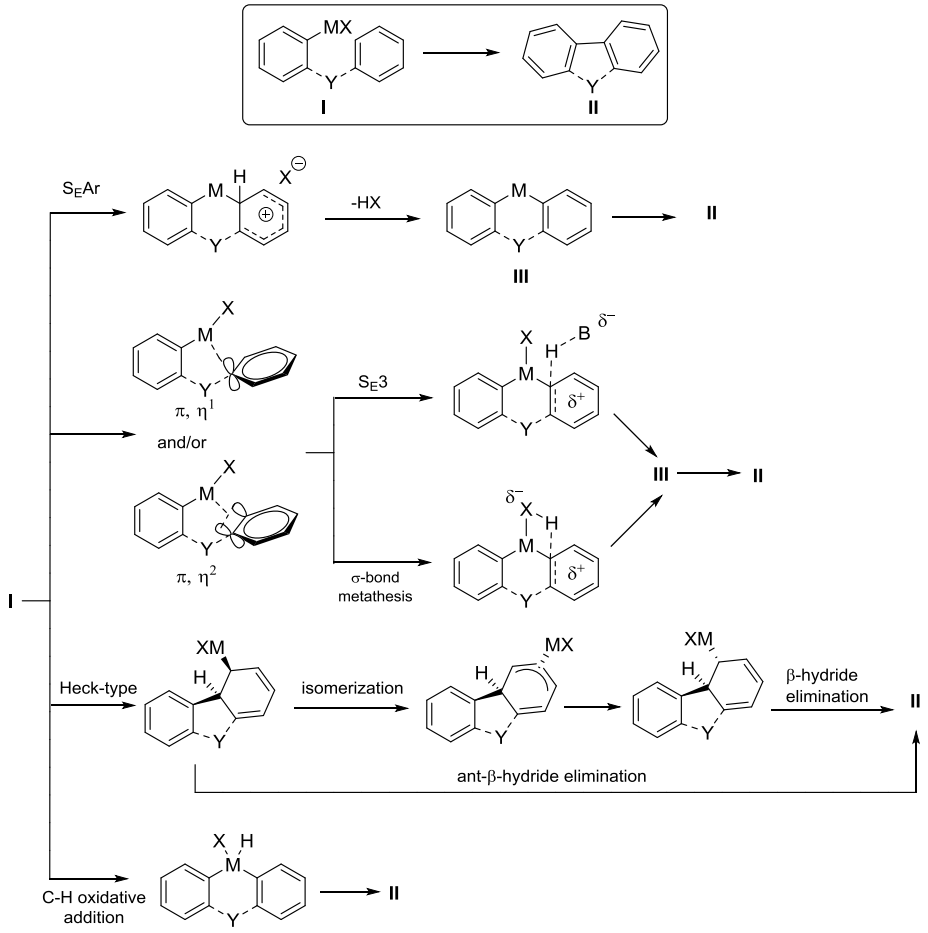
[26]a) B. Martín-Matute, C. Mateo, D. J. Cárdenas, A. M. Echavarren *Chem. Eur. J.* **2001**, *7*, 2341; b) C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, V. Gevorgyan *Org. Lett.* **2004**, *6*, 1159; c) B. S. Lane, M. A, Brown, D. Sames *J. Am. Chem. Soc.* **2005**, *127*, 8050; d)

[27] H. Zollinger *Adv. Phys. Org. Chem.* **1964**, *2*, 162.

[28] a) E. J. Hennessy, S. L. Buchwald *J. Am. Chem. Soc.* **2003**, *125*, 12084; b) A. J. Mota, A. Dedieu, C. Bour, J. Suffert *J. Am. Chem. Soc.* **2005**, *127*, 7171; c) D. L. Davies, S. A. Donald, S. A. Macgregor *J. Am. Chem. Soc.* **2005**, *127*, 13754.

[29] a) C. C. Hughes, D. Trauner *Angew. Chem. Int. Ed.* **2002**, *41*, 1569; b) M. Toyota, A. Ilangovan, R. Okamoto, T. Masaki, M. Arakawa, M. Ihara *Org. Lett.* **2002**, *4*, 4293.

[30] a) M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock *J. Am. Chem. Soc.* **2003**, *125*, 11506; b) E. Capito, J. M. Brown, A. Ricci *Chem. Commun.* **2005**, 1854.

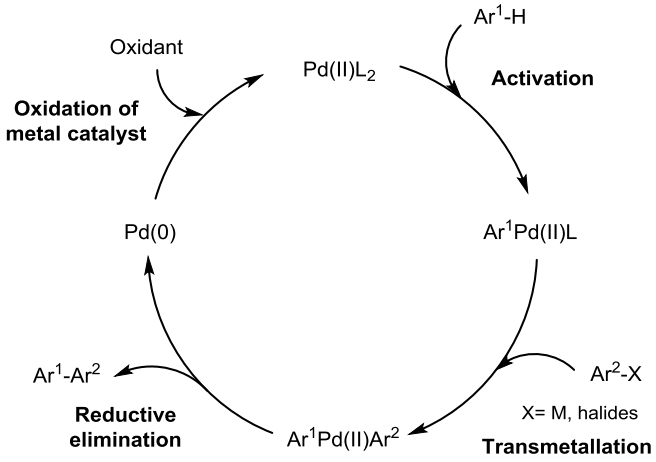


Scheme 2.4. Possible key C-C bond-forming steps in intramolecular direct arylations.

While several investigations have been carried out allowing better insight into particular systems, it is clear that working mechanisms heavily depend on the substrates, metal, solvent and ligands used. For example, in Ru-

catalyzed arylations the oxidative addition to C-H bond is suspected to be the first mechanistic step.[31]

There is another alternative mechanistic pathway in which the first step is the above explained activation instead of the oxidative addition. This catalytic cycle (Scheme 2.5) involves: i) activation step, simple arenes react with Pd(II) salts by losing H^+, leading to palladacylce complex $Ar^1Pd(II)L$; ii) transmetallation between $Ar^1Pd(II)L$ and Ar^2X generating $Ar^1Pd(II)Ar^2$; iii) reductive elimination of $Ar^1Pd(II)Ar^2$ releasing Pd(0) and Ar^1-Ar^2 and iv) regeneration of the catalyst where an oxidant is required to convert Pd(0) to Pd(II) for completion of catalytic cycle. [32]



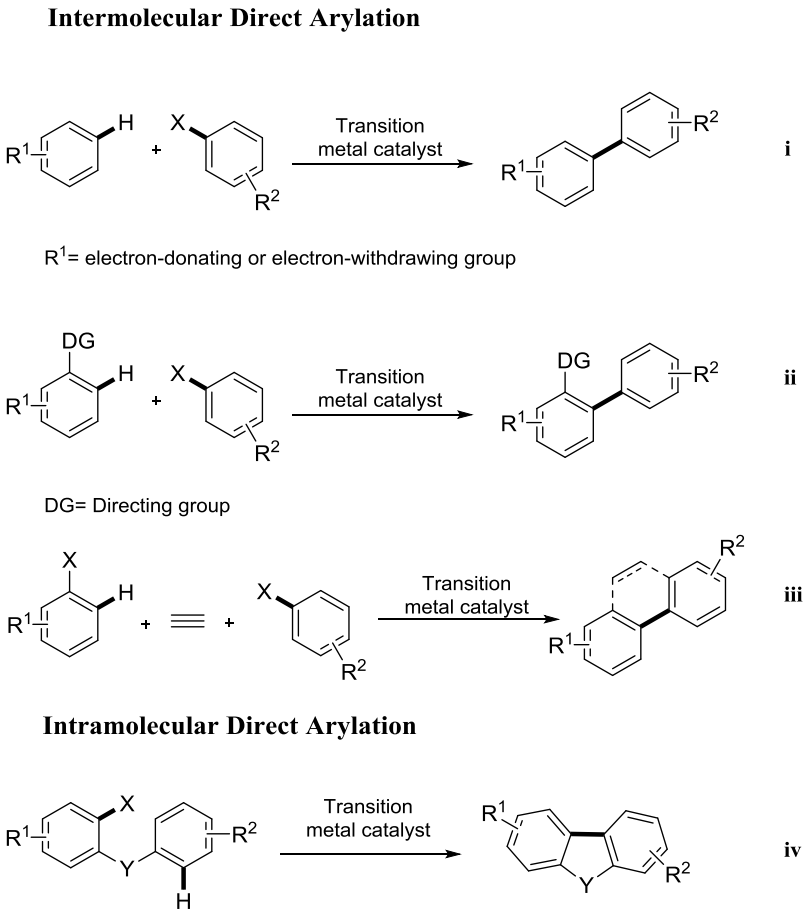
Scheme 2.5. General catalytic cycle for direct arylation.

[31] a) L. Ackermann, R. Vicente, H. K. Potukuchi, V. Pirovano *Org. Lett.* **2010**, *12*, 5032; b) E. F. Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand *J. Am. Chem. Soc*. **2011**, *133*, 10161; c) H. Zhang *J. Org. Chem.* **2014**, *756*, 47.

[32] a) L.-C. Campeau, M. Bertrand-Laperie, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou *J. Am. Chem. Soc*. **2008**, *130*, 3276; b) L. Ackermann, R.Vicente, H. K. Potukuchi, V. Pirovano *Organic Lett.* 2010, *12*, 5032.

1.2.3. Regioselectivity

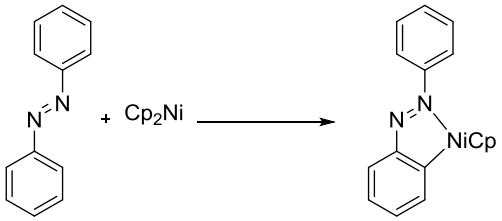
Intermolecular direct arylation reactions present quite a formidable task since boththe catalyst and reagents have a greater degree of freedom when reacting at the C–H bond. Two factors that influence the regioselectivity of the intermolecular direct arylation are: i) the electronics of the arene being functionalized and more commonly, ii) the directing group.



Scheme 2.6. Different types of direct arylation.

With regard to the former factor, the reaction occurs *ortho* or *para* to the electron-donating group *via* an electrophilic aromatic substitution process (Scheme 2.6, i). Directing group assistance may be also crucial for the reaction outcome. Typically, directing group-assisted reactions employ nitrogen- and oxygen-coordinating functional groups to direct the arylation (Scheme 2.6, ii) although in some cases external alkenes or alkynes in a cascade process have been used to create a "directing" alkyl- or alkenylmetal species *in situ* (Scheme 2.6, iii).

This concept of using a directing group to control the regioselectivity of the subsequent transition-metal insertion into a C–H bond was first reported by Kleinman and Dubeck over 50 years ago (Scheme 2.7).[33]



Scheme 2.7. First report using directing groups for regioselective C-H activation.

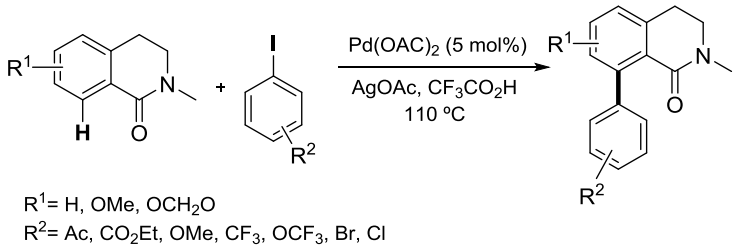
Since this initial report, the preparation and use of metallacycles not only as mechanistic tools but also as highly active precatalysts has been extensively reported.[34] Generally, these metallacycles are obtained through the use of a

[33] J. P. Kleinman, M. Dubeck *J. Am. Chem. Soc.* **1963**, *85*, 1544.

[34] a) W. A. Herrmann, V. P. Böhm, C.-P. Reisinger *J. Organomet. Chem.* **1999**, *576*, 23, b) J. Cámpora, P. Palma, E. Carmona *Coord. Chem. Rev.* **1999**, *193*, 207; c) I. P. Beletskaya, A. V. Cheprakov *Organomet. Chem.* **2004**, *689*, 4055; d) J. J. Mousseau, A. B. Charette *Acc Chem Res.* **2013**, *46*, 412.

coordinating group that aids in directing the subsequent transition-metal C–H bond insertion, usually resulting in the formation of either the kinetically or thermodynamically favored five- or six-membered metallacycle. It is this same approach that is often used to control the regioselectivity of the required C–H bond activation step in direct arylations.[35] In symmetrical substrates, mono- or bis-direct arylation typically proceeds *ortho* to the directing group *via* formation of a five- or six-membered metallacycle. In non-symmetrical substrates, sterics become the controlling factor, resulting in direct arylation occurring predominantly at the less hindered *ortho* position.[4a] More recently C–H acidity has become a very important aspect of regioselective C–H activation, with substitution not occurring at the position predicted by an S_EAr mechanism. Furthermore, in the C–H activation event, the most acidic proton is targeted even if it is the most sterically hindered.[5] A clear example of the employment of directing groups is the one reported by Kim and co-workers, in which they synthesized biologically interesting cross-coupling products (8-aryl-1,2,3,4-tetrahydroisoquinolones) through palladium-catalyzed *ortho*-arylation of dihydroisoquinolones with aryl iodides in moderate to high yields (50–86%) and high regioselectivities (Scheme 2.8).[36] In this case, the introduction of the aryl group at C-8 position was regioselectively directed by the carbonyl group present on quinolone in the presence of $Pd(OAc)_2$/AgOAc/CF_3COOH system.

[35] G. Rousseau, B. Breit *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.
[36] J. Kim, M. Jo, W. So, Z. No *Tetrahedron Lett.* **2009**, *50*, 1229.



Scheme 2.8. Pd-catalyzed *ortho*-arylation.

Of course, direct arylation reactions can take place in either an intermolecular or an intramolecular fashion (Scheme 2.6). Intramolecular direct arylation reactions employ tethers to limit the degree of freedom in a system, thereby controlling the regioselectivity of the reaction (Scheme 2.6, iv).

The value of intramolecular direct arylation reactions is evident from their application to the synthesis of several chemically important compounds, including natural products, ligands, chiral auxiliaries, and polycyclic aromatic hydrocarbons (PAHs).[37] However, in comparison with other more established arylation methods, direct arylation can be considered at its infancy. In fact, the emergence of moderately complex natural product targets using this methodology has been slow. Some examples include

[37] a) D. C. Hegan, Y. Lu, G. C. Stachelek, M. E. Crosby, R. S. Bindra, P. M. Glazer *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 2201; b) H. Aoyama, K. Sugita, M. Nakamura, A. Aoyama, M. T. A. Salim, M. Okamoto, M. Baba, Y. Hashimoto *Bioorg. Med. Chem*. **2011**, *19*, 2675; c) F. Moroni, A. Cozzi, A. Chiaguri, L. Formentini, E. Camaioni, D. E. Pellegrini-Giampietro, Y. Chen, S. Liang, M. M. Zaleska, C. Gonzales, A. Wood, R. Pellicciari *British J. Pharma*. **2012**, *165*, 1487.

defucogilocarcins M and E[38] and intermediates in the syntheses of dioncophylline A and mastigophorene B shown in Figure 2.2.[39,40]

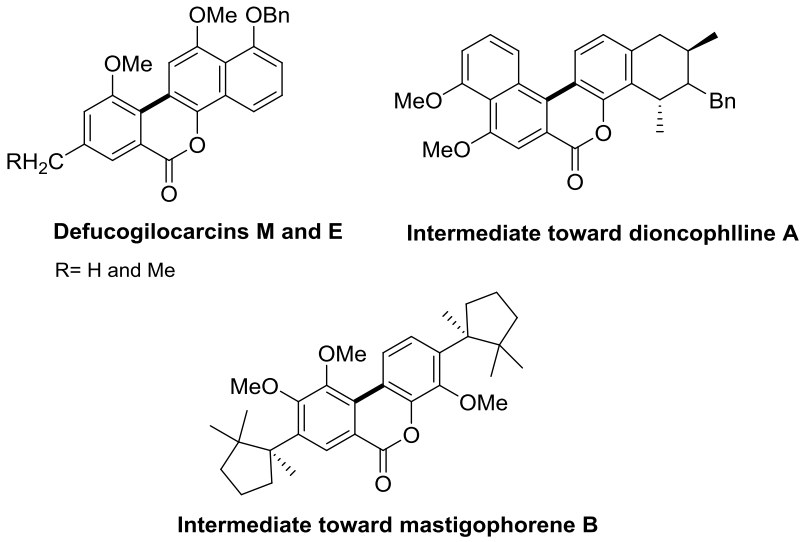


Figure 2.2. Several compounds obtained *via* intramolecular direct arylation.

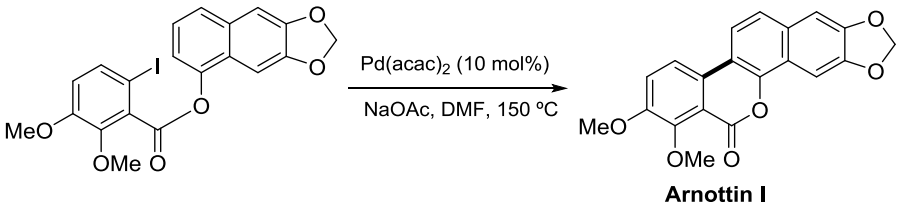
In that context, Harayama and co-workers reported the synthesis of the gilvocarcin-related arnottin I, where the key bond is formed *via* direct

[38] a) P. P. Deshpande, O. R. Martin *Tetrahedron Lett.* **1990**, *44*, 6313; b) *Handbook of C-H Transformations,1st ed.,* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**.

[39] a) G. Bringmann, R. Walter, R. Weirich *Angew. Chem. Int. Ed.* **1990**, *29*, 977; b) Y. Hemberge, G. Zhang, R. Brun, M. Kaiser, G. Bringmann *Chem.Eur. Joc*. **2015**, *21*, 14507.

[40] G. Bringmann, T. Pabst, P. Henschel, J. Kraus, K. Peters, E.-M. Peters, D. S. Rycroft, J. D. Connolly *J. Am. Chem. Soc.* **2000**, *122*, 9127.

arylation. The reaction was carried out employing $Pd(acac)_2$ (10 mol%) as catalyst, PPh_3, and NaOAc in DMF at 150 °C (Scheme 2.9).[41]

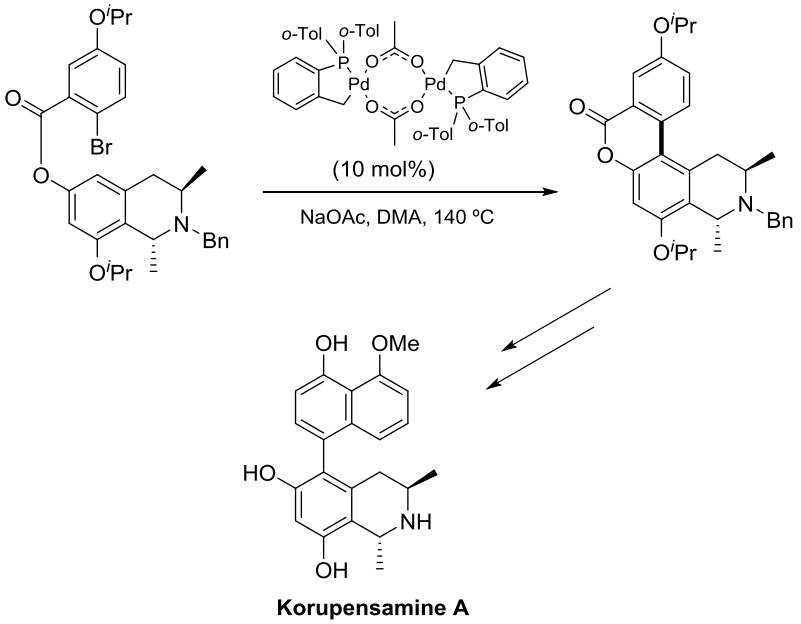


Scheme 2.9. Synthesis of arnottin I *via* direct arylation.

In another interesting example, Bringmann reported a stereoselective total synthesis of antimalarial korupensamines.[42] The key steps involved a regioselective intramolecular direct arylation (Scheme 2.10) to give a configurationally labile lactone-bridged biaryl, and the atropisomer-selective cleavage of the lactone with a variety of chiral and achiral hydride sources. Conditions employing Herrmann's catalyst resulted in a 74% yield of the required biaryl intermediate, while $Pd(OAc)_2$ and PPh_3 conditions afforded a much lower 26% yield. The coupling occurred exclusively at the 5´-position of the isoquinoline moiety regardless of the catalyst system used. This example shows that it is also possible to employ palladacycles in this transformation, obtaining better results than using commercial palladium sources.

[41] a) T. Harayama, H. Yasuda, T. Akiyama, Y. Takeuchi, H. Abe *Chem. Pharm. Bull.* **2000**, *48*, 861; b) M. J. Moschitto, D. R. Anthony, C. A. Lewis *J. Org. Chem.* **2015**, *80*, 3339.

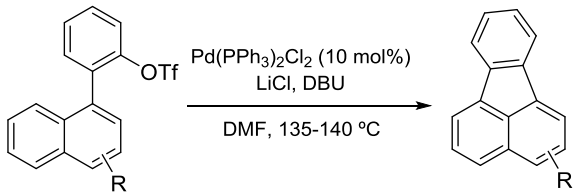
[42] G. Bringmann, M. Ochse, R. Götz *J. Org. Chem.* **2000**, *65*, 2069.



Scheme 2.10. Synthesis of korunpensamine A.

The synthesis of fullerene fragments, also referred to as bowl-shaped PAHs, has attracted considerable attention due to their potential use as starting materials for the synthesis of structurally divergent fullerenes. While flash vacuum pyrolysis (FVP) is a common method of constructing fullerene fragments, it suffers from modest yields, low functional group tolerance due to harsh reaction conditions, and difficulty in scale-up. Recently, the palladium-catalyzed intramolecular direct arylation has been applied to the synthesis of bowl-shaped fullerene fragments and other PAHs. This mild method not only allows for a high-yielding route to this class of PAHs, but also for the construction of a wide range of PAHs due to its wide functional

group tolerance.[43] It was first reported by Rice and co-workers, obtaining a large number of substituted and unsubstituted PAHs (Scheme 2.11).[44]



Scheme 2.11. Synthesis of PAHs *via* direct arylation.

1.3. Background of the research group

In view of that sustainable chemistry based on efficient waste effluent minimization procedures, the substitution of polluting processes that require stoichiometric amounts of metallic reagents by catalytic reactions has become a common trend in synthetic organic chemistry.[13] The above mentioned direct arylation reaction is a great alternative, since it is a short and atom efficient strategy forward to a relatively complex polycyclic systems.

In that context, our group has carried out different methologies to obtain polycyclic structures in an easy way, employing as key step direct arylation procedures. A meaningful example of our contributions to this field is the synthesis of a number of pyrazolo-fused heterocyclic systems

[43] a) A. M. Echavarren, B. Gómez-Lor, J. J. González, O. de Frutos *Synlett* **2003**, 585; b) B. Liu, F. Hu, B.-F. Shi *Adv. Synth. Catal.* **2014**, *356*, 2688.

[44] J. E. Rice, Z.-W. Cai, Z.-M. He, E. J. LaVoie *J. Org. Chem.* **1995**, *60*, 8101.

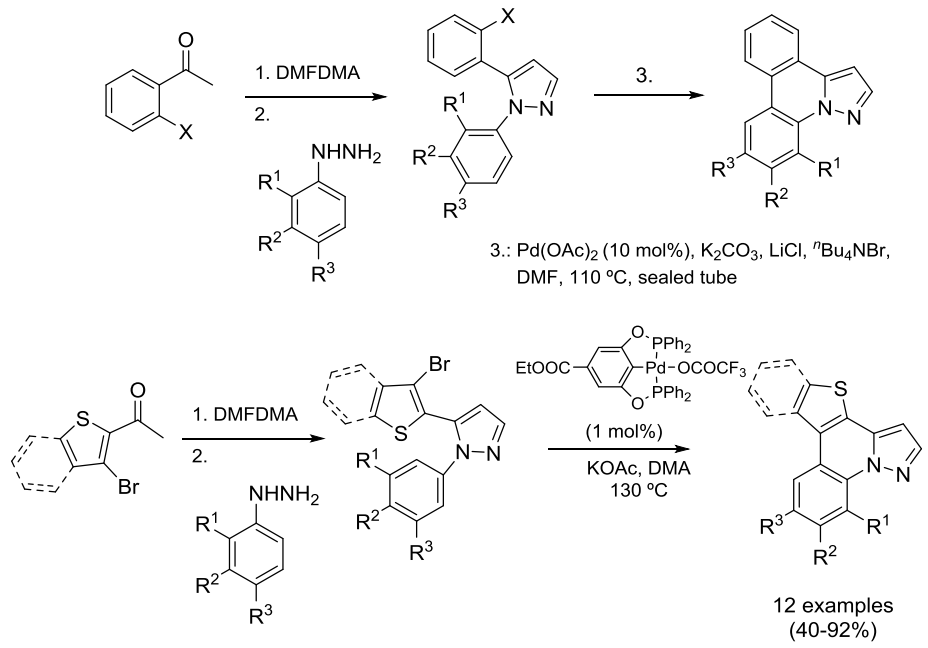
(pyrazolophenanthridines, pyrazolothienoquinolines, pyrazolobenzothienoquinolines) by a synthetic sequence involving an amine-exchange/heterocyclization tandem process on N,N-dimethylamino(hetero)arylpropenones followed by the intramolecular direct arylation step. In our initial reports, the latter arylation was performed under Jeffrey's ligand free conditions, thus avoiding the use of stoichiometric amounts of transmetallating agents and the isolation of metallated intermediates.[45]

In addition to that, in the last years the group has also prepared palladium pincer-type complexes and applied them as efficient catalysts or pre-catalyst to a variety of chemical transformations.[46] Therefore, it was considered to explore their potential in the construction of the pyrazolo(benzo) thienoquinoline framework. That way, a similar sequence was then performed (Scheme 2.12) using a PCP-type pincer complex as the palladium source. Good yields were obtained for the target tetra- and pentacyclic compounds and the catalyst amount significantly reduced (from 10 mol% to 1 mol%).[47]

[45] a) S. Hernández, R. SanMartin, I. Tellitu, E. Dominguez *Org. Lett.* **2003**, *5*, 1095; b) S. Hernández, I. Moreno, R. SanMartin, G. Gómez, M. T. Herrero, E. Dominguez *J. Org. Chem.* **2009**, *75*, 434.

[46] a) B. Inés, R. SanMartin, F. Churruca, E. Domínguez, M. K. Urtiaga, M. I. Arriortua *Organometallics* **2008**, *27*, 2833; b) G. Urgoitia, R. SanMartin, M. T. Herrero, E. Domínguez *Green Chem*. **2011**, *13*, 2161.

[47] F. Churruca, S. Hernández, M. Perea, R. SanMartin, E. Domínguez *Chem. Commun.* **2013**, *49*, 1413.



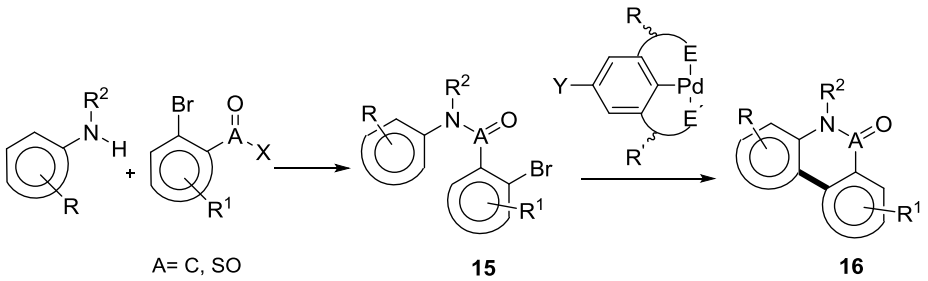
Scheme 2.12. Synthesis of pyrazolo-fused heterocyclic systems by a short sequence based on intramolecular direct arylation.

Considering our experience in direct arylation reactions, the possibility of affording this type of transformation employing palladacycles as catalysts [42,47] and the background of the research group in the use of these catalysts in a large number of transformations, including direct arylation, we decided to attempt a synthetic approach to several polycyclic structures with *o*-bromobenzanilides and benzosulfonamides as key intermediates. For that purpose, intramolecular direct arylation will be tested for the general access of phenanthridinones and related biaryl sultams in the presence of palladium pincer complexes. In addition, we also will try to perform this

transformation under lower catalyst loadings than the ones previously reported.

2. AIMS AND OBJECTIVES

Considering the issues mentioned before, our objectives are based in the preparation of polycyclic structures using *o*-bromobenzanilides and benzosulfonamides **15** as intermediates in the presence of pincer type palladacycles as catalysts or pre-catalysts. In addition, the decrease of palladium loading will be tried.



First of all, a set of structurally divergent *N*-(hetero)aryl-*o*-bromobenzanilides and benzosulfonamides **15** will be prepared by means of several protocols.

Palladium pincer compounds will be assayed as potential palladium sources for the palladium-catalyzed intramolecular direct coupling of model compounds.

The optimized reaction conditions will be applied to the above set of amides and sulfonamides in order to define the scope of the methodology.

3. RESULTS AND DISCUSSION

3.1. Synthesis of *N*-substituted *o*-bromobenzanilides and benzosulfonamides

Since the required amides and sulfonamides are not commercially available, several protocols were employed for their preparation. As it will be mentioned later, some initial arylation assays carried out simultaneously revealed that N-H derivatives were unsuitable for the target reaction and therefore *N*-alkyl and *N*-aryl amides and sulfonamides were synthesized.

Amides constitute one of the most important and ubiquitous of organic functional groups, found in natural products, both peptidic and nonpeptidic, pharmaceuticals, agrochemicals, materials, and polymers. The privileged nature of the amide functional group is evident from its occurrence in an estimated 25% of available drugs.[48] Most amide bond formations utilize the reaction of amines in the presence of acylating agents, such as acyl chlorides,[49] or the reaction of carboxylic acids with amines in the presence of coupling agents.[50]

However, although the synthesis of an amide is supposed to be easy, is not trivial since one methodology is not applicable to all type of reagents. It

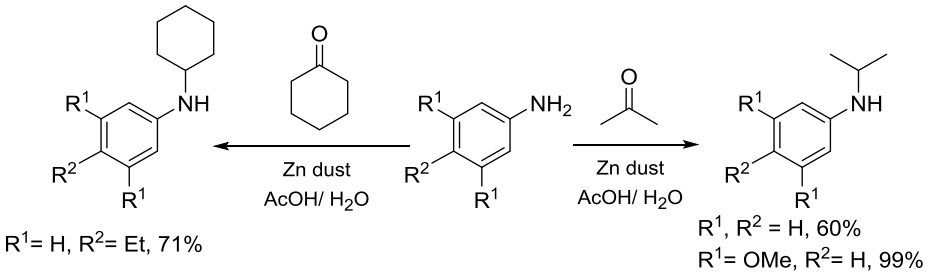
[48] a) A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski *J. Comb. Chem.* **1999**, *1*, 55; b) M. Baumann, I. R. Baxendale *Beilstein J. Org. Chem.* **2013**, *9*, 2265.

[49] a) C. A. G. N. Montalbetti, V. Falque *Tetrahedron* **2005**, *61*, 10827; b) M.M. Joullié, K. M. Lassen *Arkivoc* **2010**, 189.

[50] a) F. Albericio, J. M. Bofill, A. El-Faham, S. A. Kates *J. Org. Chem.* **1998**, *63*, 9678; b) R. T. Pon, S. Yu, Y. S. Sanghvi *Bioconjugate Chem.* **1999**, *10*, 105; c) S.-Y. Han, Y.-A. Kim *Tetrahedron* **2004**, *60*, 2447; d) J. Hachmann, M. Lebl *Biopolymers* **2006**, *84*, 340; e) E. Valeur, M. Bradley *Chem. Soc. Rev*. **2009**, *38*, 606; f) V. R. Pattabiraman, J. W. Bode *Nature* **2011**, *480*, 471.

depends strongly on the nature of the amine and carboxylic acid this methodology would change. This limitation, and the importance of the amides continued advances in protocols and reagents based upon these approaches.[51]

Our first step was to synthesize some *N*-substituted amines *via* a reductive amination[52] of the anilines and ketones (acetone and cyclohexanone) in the presence of activated zinc dust in $AcOH/H_2O$ mixture (Scheme 2.13).

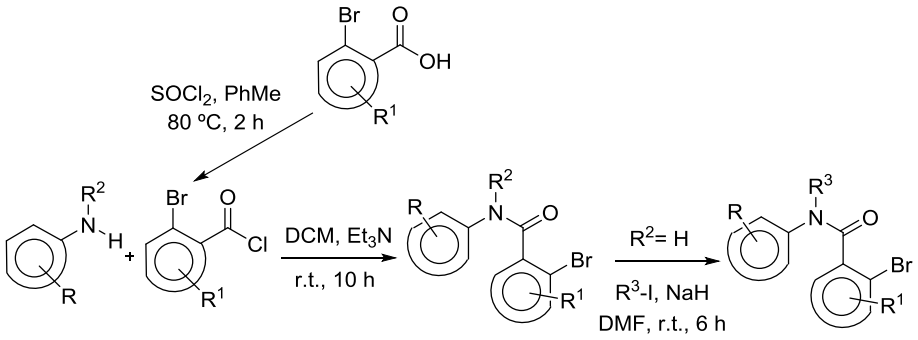


Scheme 2.13. Synthesis of *N*-alkylanilines by reductive amination.

As it has been stated, different methodologies were employed to obtain intermediate amides **15** (Scheme 2.14).

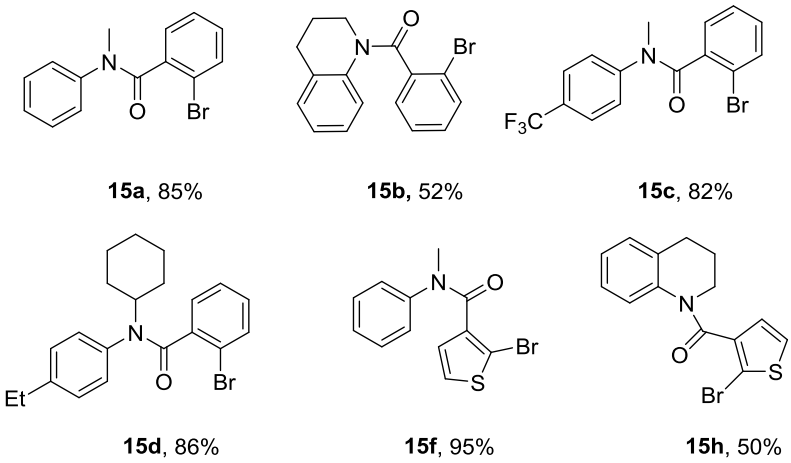
[51] A. El-Faham, F. Albericio *Chem. Rev.* **2011**, *111*, 6557.

[52] a) I. V. Micovic, M. D. Ivanovic, D. M. Piatak, V. D. Bojic *Synthesis* **1991**, 1043; b) G. B Giovenzana, D. Imperio, A. Penoni, G. Palmisano *Beilstein J Org Chem.* **2011**; *7*: 1095.



Scheme 2.14. Synthetic path to access amides **15**.

For the preparation of the first series of amides, several anilines were reacted with the *in situ* generated acyl chloride in DCM using Et_3N as base for 10 hours at room temperature. The latter was prepared by the reaction of the corresponding carboxylic acid in toluene with $SOCl_2$ at 80 ºC and used without further purification to obtain the amides displayed in Figure 2.3.

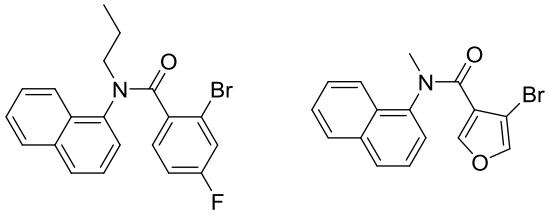


15a, 85% **15b,** 52% **15c**, 82%

15d, 86% **15f**, 95% **15h**, 50%

Figure 2.3. Intermediate amides prepared by reaction between aryloyl chlorides and *N*-alkyl amines.

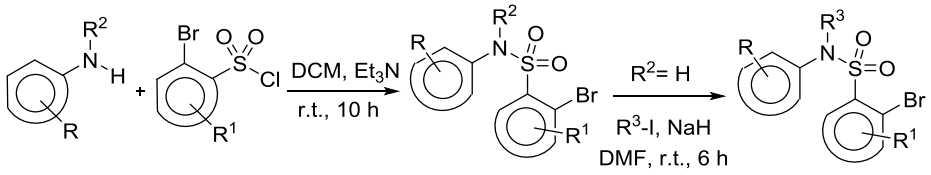
Amides **15e** and **15g** were prepared by initial amidation between α-naphthylamine and aryloyl chlorides followed by a *N*-alkylation (MeI or ^{n}PrI) step.



15e, 41% **15g**, 54%

Figure 2.4. Structure of amides **15e** and **15g** (overall yields displayed).

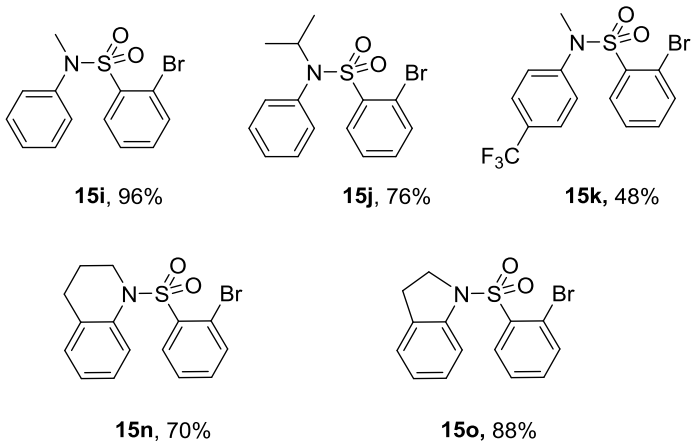
Another group of compounds chosen for the next arylation step was that of sulfonamides, already known for their antibacterial activity and some modern pharmatheutical applications.[53]



Scheme 2.15. Synthetic path to access sulfonamides **15**.

Commercially available *o*-bromobenzenesulfonyl chloride was reacted with *N*-alkylanilines in the presence of Et_3N and DMAP at room temperature,[54] thus obtaining the sulfonamide derivatives shown in Figure 2.5.

[53] For a review on new drug groups (*e.g.* sulfonyl ureas or thiazide diuretics) bearing sulfonamide group core, see: a) A. Scozzafava, T. Owa, A. Mastrolorenzo, C. T. Supuran *Curr. Med. Chem*. **2003**, *10*, 925; b) Y. Tang, D. Lee, J. Wang, G. Li, J. Yu, W. Lin, J. Yoon *Chem. Soc. Rev*. **2015**, *44*, 5003.

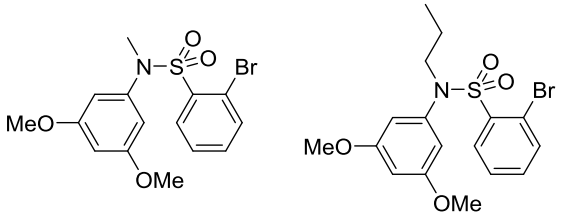


15i, 96% **15j**, 76% **15k,** 48%

15n, 70% **15o,** 88%

Figure 2.5. *o*-Bromobenzenesulfonamides prepared by reaction with *N*-alkylanilines.

This protocol did not work for the synthesis of *N*-(3,5-dimethoxyphenyl)sulfonamides, so an initial sulfonamidation with 3,5-dimethoxyaniline followed by *N*-methylation or *N*-propylation was employed to prepare derivatives **15l** and **15m**.

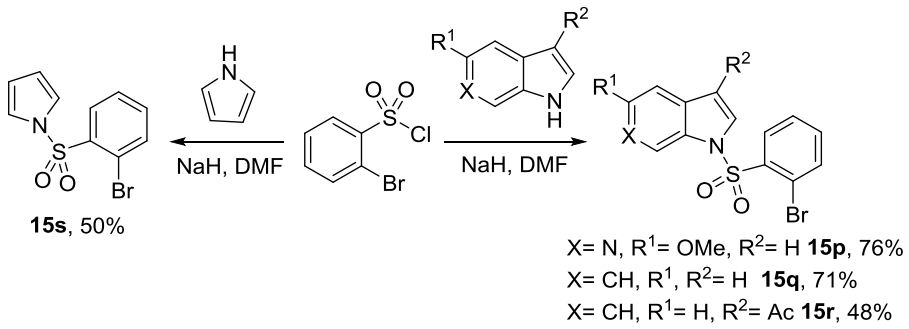


15l, 87% **15m,** 82%

Figure 2.6. Structure of sulfonamides **15l** and **15m** (overall yields displayed).

[54] a) W. R. Bowman, H. Heany, B. M. Jordan *Tetrahedron* **1991,** *47*, 10119; b) G. Goverdhan, A. R. Reddy, V.i Himabindu, G. M. Reddy *J. Saudi Chem. Soc.* **2014**, *18*, 129.

For the formation of indole and pyrrole containing sulfonamides, a stronger base system was required for the amidation reaction with *o*-bromobenzenesulfonyl chloride. Very good yields were achieved for sulfonamides **15p-s** (Scheme 2.16) when using NaH in DMF.[55]



Scheme 2.16. Synthesis of indole and pyrrole containing sulfonamides **15p-s**.

3.2. Catalytic activity of palladium pincer PCN in intramolecular direct arylation

Phenanthridinones are important structural scaffolds found in many natural products that exhibit remarkable biological and pharmaceutical properties. As a result, considerable efforts have been directed toward the development of efficient methods for their synthesis.[37] In that context, one of the most relevant works is the one reported by Bisai *et al.* in which the

[55] V. S. N. Ramakrishna, V. S. Shirsath, R. S. Kambhampati, V. S. V. V. Rao, V. Jasti WO2004048330.

phenantridinone core is obtained straightforward *via* biaryl-coupling reaction promoted by ^{t}BuOK.[56]

N-Methyl-*N*-phenyl-2-bromobenzamide **15a** was chosen as model substrate to attempt the intramolecular direct arylation in the presence of a palladium pincer complex. In a set of preliminary experiments, complexes **1** and **8** already described in the previous chapter, and **D**,[57] **G**,[58] and **I**[59] (see chapter 1, Figure 1.10, page 28) were assayed. Only non-symmetrical PCN complex **I** provided a moderate 24% yield when it was used in 0.1 mol% with KOAc as base and DMA as solvent, so in view of the negligible results obtained by the other palladacycles, **I** was elected for a more comprehensive survey of assays in order to optimize reaction conditions. *N*-Phenyl-2-bromobenzamide was also assayed in this preliminary set. Unfortunately, no coupled product was detected from such NH amide, so we decided to continue our investigation with *N*-substituted amides and sulfonamides. As shown in Table 2.1, entries 1-9, different solvents and bases were assayed to generate *N*-methylphenantridinone **16a** in the presence of complex **I**.

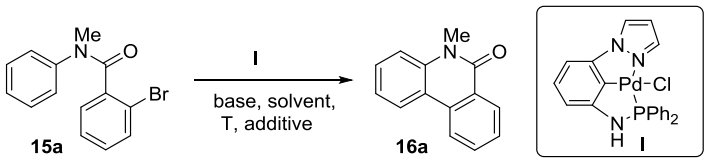
[56] S. De, S. Mishra, B. N. Kakde, D. Dey, A. Bisai *J. Org. Chem*. **2013**, *78*, 7823.

[57] F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez *Synlett* **2005**, 3116.

[58] F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez *Tetrahedron Lett*. **2006**, *47*, 3233.

[59] B. Inés, R. SanMartin, F. Churruca, E. Domínguez, M. K. Urtiaga, M. I. Arriortua *Organometallics*, **2008**, *27*, 2833.

Table 2.1. Intramolecular direct arylation in the presence of complex **I**.



	I mol%	Base	Solvent	(%)[b]
1	0.1	Et_3N	DMPU	-[c]
2	0.1	DBU	DMA	-[c]
3	0.1	KO^{t}Bu	DMF	-[c]
4	0.1	K_2CO_3	DMA	-
5[d]	0.1	K_2CO_3	DMA	<5
6	0.1	KOAc	DMA	24
7	0.1	KOAc	DMF	-[c]
8	0.1	KOAc	DMPU	8
9	0.1	KOAc	DMI	-[c]
10[d]	0.1	K_2CO_3	DMA	17
11[d]	0.1	KOAc	DMA	<5
12[e]	0.1	KOAc	DMA	7-18
13[e]	0.1	KOAc	DMA	19
14	0.1	KOAc	DMA/*o*-xylene (1:1)	23
15	0.1	KOAc	DMA/DMSO (1:1)	-[c]
16	0.1	KOAc	DMA/THF (1:1)	51
17	0.1	KOAc	DMA/H_2O (9.5:0.5)	57
18	0.1	KOAc	DMA/H_2O (9:1)	68
19	0.1	KOAc	DMA/H_2O (7.5:2.5)	<5
20[f]	0.1	KOAc	DMA/H_2O (9:1)	68
21[g]	0.1	KOAc	DMA/H_2O (9:1)	75
22[f,g]	0.1	KOAc	DMA/H_2O (9:1)	83
23	0.05	KOAc	DMA/H_2O (9:1)	<5
24[g]	0.05	KOAc	DMA/H_2O (9:1)	70
25[f,g]	0.05	KOAc	DMA/H_2O (9:1)	89
26[f,g,h]	0.03	KOAc	DMA/H_2O (9:1)	78
27[f,g,i]	0.01	KOAc	DMA/H_2O (9:1)	57

Reaction conditions: **15a** (0.3 mmol), **I** (0.1 mol%), base (1.5 equiv.), solvent (0.06 M), 130 °C, 20 h. DMPU: *N*,*N*'-Dimethylpropyleneurea; DMI: 1,3-Dimethyl-2-imidazolidinone. [b] Determined by ^{1}H NMR spectroscopy. Diethylene glycol dimethyl ether was used as internal standard. [c] Recovery of starting material. [d] 20 mol% of Brønsted acids (pivalic acid, benzoic acid and *p*-toluenesulfonic acid). [e] 25 mol% of surfactant (CTAB: Hexadecyltrimethylammonium bromide; DDA: Dimethyldioctadecylammonium bromide; TBAB: Tetrabutylammonium bromide). [f] 3.0 equiv. of KOAc were used. [g] Solvent (0.3 M). [h] Reaction time: 48 h. [i] Reaction time: 96 h.

The employment of alternative solvents with the same base resulted ineffective (entries 7-9), as happened by the addition of Brønsted acids such as pivalic acid (PivOH), benzoic or p-toluenesulfonic acid (entries 10-11).

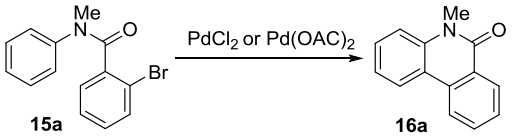
In the same way, no benefits were seen with the use of tetrabutylammonium bromide or cationic surfactants (CTAB and DDA) as additives (entries 12-13). In contrast, the mixture of solvents such as THF or water with DMA did improve the conversion rate (entries 16-18), obtaining the best results when 10% of water in DMA was employed (68%, entry 18). We also tried to change other variables such as the amount of base, solvent concentration and especially the catalyst loadings (entries 20-27). Thus, after careful experimentation, we succeeded to obtain phenanthridinone **16a** in a very good yield (89%, entry 25) with only 0.05 mol% of palladium pincer complex **I** using 3 equivalents of KOAc in a relatively concentrated solution of DMA:H_2O (9:1, 0.3M).

Motivated by the obtained results, we decided to decrease even more the catalyst loading. This way, although the desired phenanthridinone **16a** was obtained using 0.03 mol% and 0.01 mol% of complex **I** respectively (78% and 57%, entries 26-27), lower yields were achieved even at longer reaction times. Therefore, we considered that the best conditions were those shown in entry 25.

Some control experiments were carried out with commercially available palladium sources ($PdCl_2$ and $Pd(OAc)_2$, Table 2.2). In those experiments the optimized conditions were tested with 0.1 mol% and 0.05 mol% of both,

$PdCl_2$ and $Pd(OAc)_2$. It is worth mentioning that the conversion obtained by using PCN **I** was never reached, even when anhydrous DMA was employed as solvent (entries 5-6).

Table 2.2. Control experiments with commercially available palladium sources.



15a **16a**

	[Pd]	Base	Solvent	(%)[b]
1	$PdCl_2$ (0.1 mol%)	KOAc	DMA/H_2O (9:1)	29
2	$Pd(OAc)_2$ (0.1 mol%)	KOAc	DMA/H_2O (9:1)	33
3	$PdCl_2$ (0.05 mol%)	KOAc	DMA/H_2O (9:1)	10
4	$Pd(OAc)_2$ (0.05 mol%)	KOAc	DMA/H_2O (9:1)	11
5	$PdCl_2$ (0.05 mol%)	KOAc	DMA	<5
6	$Pd(OAc)_2$ (0.05 mol%)	KOAc	DMA	<5

[a] Reaction conditions: **15a** (0.3 mmol), KOAc (3 equiv.), solvent (0.3 M), 130 °C, 20 h. [b] Determined by ^{1}H NMR spectroscopy. Diethylene glycol dimethyl ether was used as internal standard.

To the best of our knowledge, these values represent the lowest catalyst loadings achieved so far not only for the direct arylation of *N*-substituted *o*-halobenzanilides, but for any biaryl coupling of an aryl halide with a non-functionalized arene.[60]

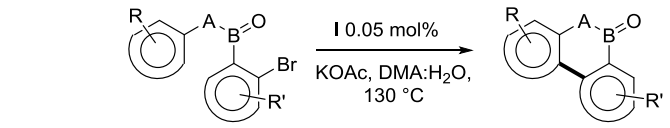
[60] For the only example of biaryl coupling of an aryl halide with a non-functionalized arene using <1 mol% catalyst see: L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186.

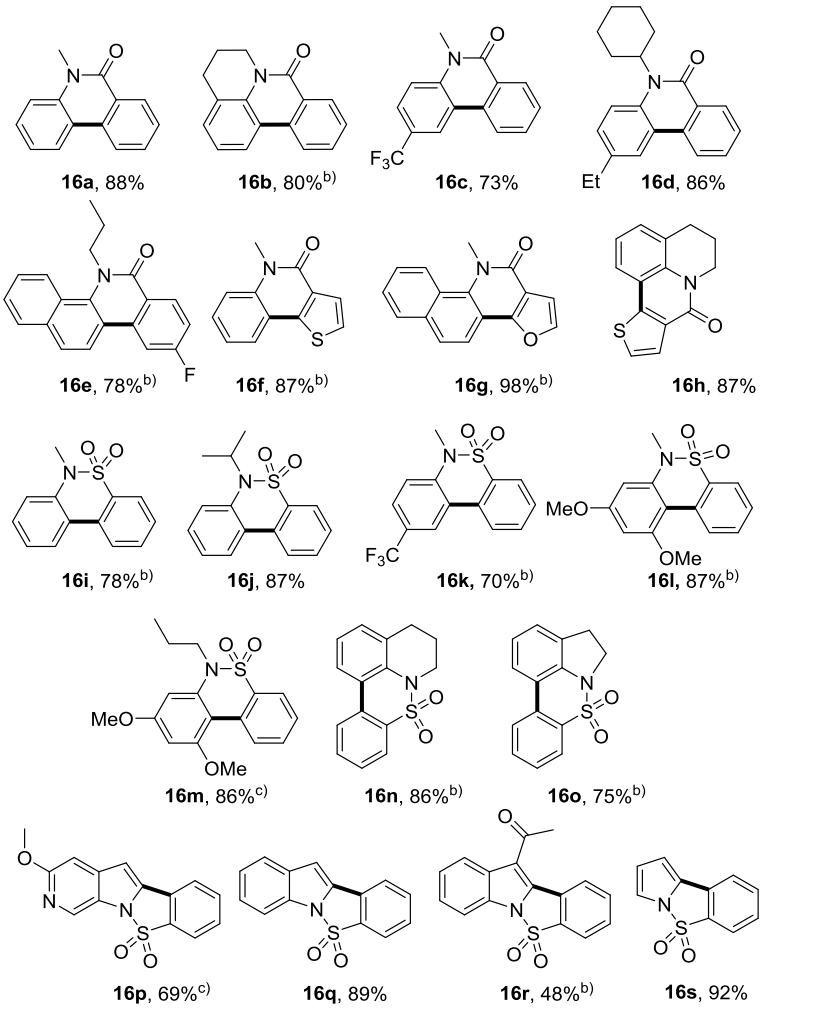
To relate this to the previous state of art, the elegant procedure reported by Fagnou and co-workers[24] afforded a turnover number (TON) of 41.5 for **16a**, significantly lower than our TON values of 1760 (entry 17) and 5700 (entry 19). It should be also pointed out that these reactions were carried out in the air atmosphere with no effect on the reaction yield, thus providing an additional advantage from a practical point of view.

Once the optimized conditions were established, we attempted to extend the scope of the reaction for a variety of *o*-bromo-*N*-alkyl- carboxamides **15b-g**. As it can be seen in Table 2.3, this procedure showed high tolerance to a variety of functional groups, since it gave us the chance to synthesize various phenanthridinones and related heterocyclic quinolinones with good to excellent yields. It could be said that the electronic nature of the substituents seemed to have a little effect on the product yields. Besides, the reaction was carried out with different aromatic and heterocycles such as naphthalene, furan, thiophene or tetrahydroquinoline, affording the expected **16e-h** products in very good yields (78-98%). Even when sterically hindered *N*-cyclohexyl amide **15d** was used the desired phenantridinone **16d** was obtained in a 86% yield.

Considering the excellent activity shown by the palladium complex **I** to access biaryl lactams, we attempted the applicability of this protocol to structurally related *o*-halo-*N*-arylsulfonamides **15i-s** with the intention to further extend the potential of our approach. Sulfonamide group is considered as an important pharmacophore, and sulfonamide containing

Table 2.3. Scope of direct arylation catalyzed by complex **I**.





a) Reaction conditions: **15** (0.3 mmol), **I** (0.05 mol%), KOAc (3 equiv.), DMA:H_2O (9:1, 0.3M), 130 °C, 20 h, under air. Isolated yields. b) 1.5 equiv. of KOAc were used. c) 0.09 mol% of 1 was used.

compounds, including sultams, display a vast array of biological activity.[61] Although there have been some recent report on the use of palladium-catalyzed direct arylation reactions applied to the field of cyclic sultams, considerably high loadings of palladium catalyst (1-10 mol%) have been required.[62]

Following our aims, a series of *o*-bromo-*N*-(hetero)arylbenzene sulfonamides **15i-s** were easily prepared as it has been explained above. Then, they were reacted with only 0.05 mol% pincer catalyst **I** (Table 2.3) under the optimized conditions. As displayed in Table 2.3, the direct functionalization of *N*-(hetero)arylsulfonamides with such low catalyst loadings afforded regioselectively the corresponding biaryl sultams **16i-s**, and the presence of alkoxy or trifluoromethyl groups did not affect the reaction custome.

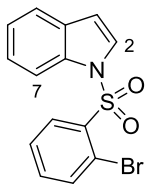
It is worth mentioning that we also obtained good results in the construction of benzopyrroloisothiazole-, benzoisothiazolindole- and benzo[4,5]isothiazolopyrrolopyridine-*S*,*S*-dioxides **3p-s,** even though they bear a more constrained 5-membered sultam ring. It should be pointed that, up to date, the preparation of these tetracyclic systems has been only

[61] For selected recent applications see: a) K.-C. Tsai, L.-W. Teng, Y.-M. Shao, Y.-C Chen, Y.-C. Lee, M. Li, N.-W. Hsiao *Bioorg. Med. Chem. Lett*. **2009**, *19*, 5665; b) G. Compain, A. Martin-Mingot, A. Maresca, S. Thibaudeau, C. T. Supuran *Bioorg. Med. Chem.* **2012**, *21*, 1555; c) A.-B. Nørholm, P. Francotte, L. Olsen, C. Krintel, K. Frydenvang, E. Goffin, S. Challal, L. Danober, I. Botez-Pop, P. Lestage, B. Pirotte, J. S. Kastrup *J. Med. Chem.* **2013**, *56*, 8736.

[62] a) L. Zhang, M. Geng, P. Teng, D. Zhao, X. Lu, J.-X. Li *Ultrason. Sonochem.* **2012**, *19*, 250; b) C. B. Bheeter, J. K. Bera, H. Doucet *Adv. Synth. Catal*. **2012**, *354*, 3533.

possible in moderate yields using remarkably high catalyst amounts (>5 mol%).[63] This fact shows that is not trivial to perform this intramolecular cyclization. It is also true that the yields we have obtained for **16h-o** are not as high as the ones achieved for the corresponding 6-membered ring sultams. In any case, there are in accordance with literature precedents and it is remarkable that despite the fact of having employed significantly lower amounts (0.05-0.09 mol%) of catalyst, the protocol turned into one of the most effective methodology to generate benzoisothiazoloindoles and related heterocycles so far.

Indole derivatives with constrained sulfonamide ring have gained interest as novel 5-HT_6 receptor ligands in the last years, and as such, have shown relevant activity in central nervous system (CNS) disorders such as schizophrenia, dementia, Alzheimer's disease and Parkinson's disease. Particularly, benzoisothiazoloindoles **IV** and benzothiazinoindoles **V** have been recognized for being potent 5-HT_6 receptor ligands with good affinity towards 5-HT_6R and selectivity over known GPCRs. [64]



15q

Taking that into account, we decided to obtain at least one example of each structure employing our methodology. For that purpose, we chose 1-((2-

[63] V. S. N. Ramakrishna, K. Ramasastri, K. Prabhakar, K. Jagadishbadu, R. B. Thrinath, G. Parandhama, A. Sobhanadri, P. G. Narasimhareddy, K. S. Anil, D. D. Amol, D. Adireddy, K. C. Anil, K. D. Pramod, *J. Enz. Inhib. Med. Chem*. **2012**, *27*, 443.

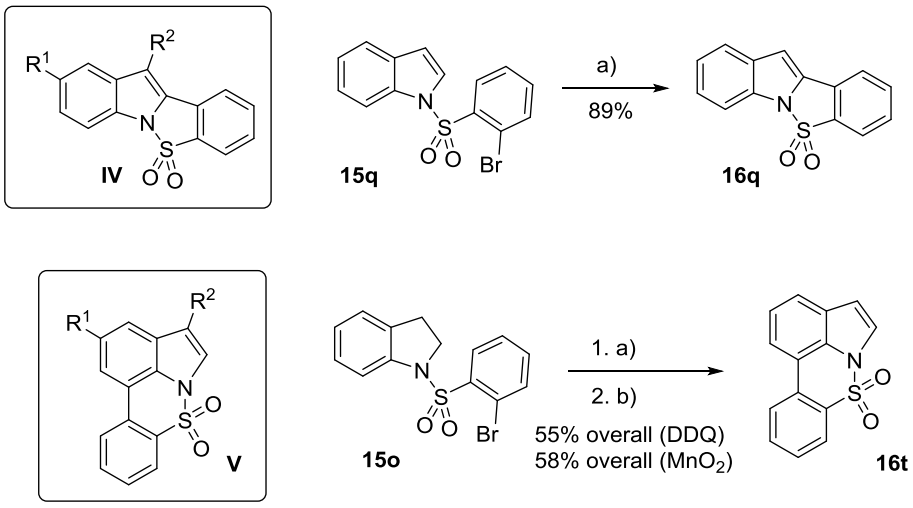
[64] a) V. Jasti, V. S. N. Ramakrishna, R. S. Kambhampati, S. R. Battula, A. Veeraraeddy, V. S. V. V. Rao WO 2004/000849 A1; b) V. S. N. Ramakrishna, R. S. Kambhampati, V. S. Shirsath, V. Jasti WO 2005/005439 A1; c) A. Ishtiyaque, V. S. N. Ramakrishna *Neuroscience & Medicine* **2011**, *2*, 87.

bromophenyl)sulfonyl)-1*H*-indole **15q** as substrate. This molecule could undergo the intramolecular direct arylation at two possible positions, C2 and C7, since, according to the higher nucleophilicity of the indole C2 position,[65] a higher reactivity could be expected for this position as well. Moreover, it has been described that 7-bromoindole derivatives are essential for the regioselective preparation of unsubstituted benzothiazinoindoles **V**.[66] In our hands, when sulfonamide **15q** was submitted to the optimized conditions benzo[4,5]isothiazolo[2,3-*a*]indole-5,5-dioxide **16q** was regioselectively obtained (Scheme 2.15).

Accordingly, we envisaged a complementary protocol, still based on our direct arylation procedure, to the benzo[5,6]thiazino[4,3,2-*hi*]indole 7,7-dioxide **16t** as an interesting framework in medicinal chemistry. Alternatively, we carried out the oxidation of benzothiazinoindoline **16o**, previously prepared by arylation of *N*-(*o*-bromobenzene sulfonyl)indoline **15o**, thus affording the target indole derivative **16t** in a good yield over two steps (Scheme 2.17). The oxidation step was performed by two different procedures (DDQ and MnO_2). Although almost equal yields were achieved, we preferred the latter (MnO_2) on account of the milder conditions (room temperature) and the easier separation-purification protocol.

[65] a) T. Terentiev *Chem. Abstr*. **1948**, *42*, 558; b) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin in *Handbook of Heterocyclic Chemistry, 3rd ed.*, Elsevier, Amsterdam, **2010**.

[66] a) V. S. N. Ramakrishna, V. S. Shirsath, R. S. Kambhampati, A. D. Deshpande, P. Kothmirkar, V. Jasti WO 2006095360; b) K. Ramasastri, K. Prabhakar, D. D. Amol, A. Sobhanadri, R. K. Kameswara, R. G. P. Narasimha, K. S. Anil, V. S. N. Ramakrishna *Synth. Commun*. **2008**, *38*, 2419.



Scheme 2.17. Access to benzoisothiazoloindoles and benzothiazinoindoles.

As mentioned above, one of the major drawbacks of transition metal catalyzed reactions in drug discovery is the presence of trace metals contaminants in the products, as only residual palladium levels below 10 ppm are allowed in drug products. [67] We predicted that the use of a highly active palladium source like **I** in such a low amount (0.05 mol%) would avoid such contamination issues while still accomplishing the desired transformations. Accordingly, we decided to measure the palladium content in benzothiazinodihydroquinoline **16n** using ICP-MS. The measurement determined that palladium amount was as low as 0.29 ppm. Therefore, we

[67] a) *Recoverable and Recyclable Catalysts*, (Ed.: M. Benaglia), John Wiley & Sons, Chippenham, UK, **2009**; b) S. Phillips, P. Kauppinen *Platinum Metals Rev.* **2010**, *54*, 69.

can conclude that our method not only provides a cost-effective and more sustainable access to biaryl amide and sultam containing heterocycles, but also offers an additional benefit regarding the avoidance of scavenger resins or further purification steps[67] in order to suppress metal contamination in the products.

The recycling of the reaction media was also assayed. Thus, after submitting sulfonamide **15n** to the optimized reaction conditions, water was added, the mixture was extracted with ethyl acetate and the aqueous layer was concentrated to dryness. To this crude oil **15n**, KOAc and DMA were added and the reaction repeated. However, a significant drop in the conversion rate was observed (24%), and further runs provided negligible results.

In addition, we evaluated the possible participation of palladium nanoparticles by examination of transmission electron microscopy (TEM) images from the reaction crude (Figure 2.7 and 2.8). The interference caused by the presence of stoichiometric amounts of potassium bromide was avoided by using a cationic exchange resin in order to remove selectively potassium ions. No such Pd nanoparticles were detected in the organic or aqueous layers after initial work-up, even when TEM was combined with Energy-dispersive X-ray spectroscopy (EDS).

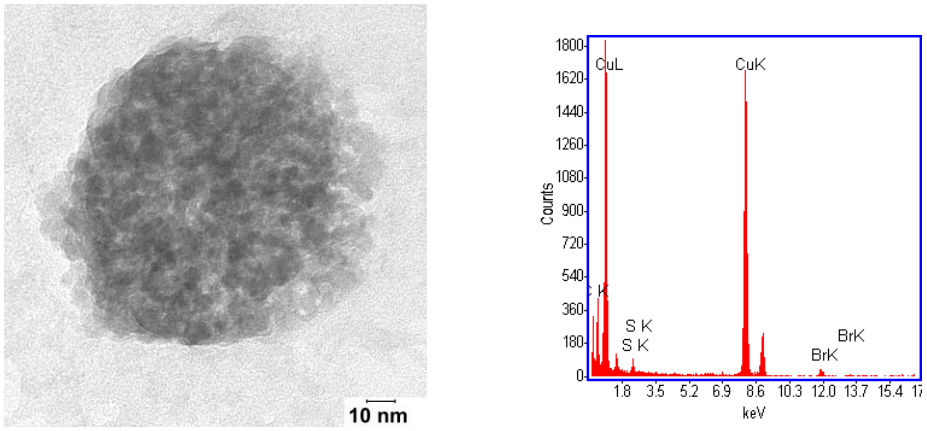


Figure 2.7. TEM and EDS of aqueous layer.

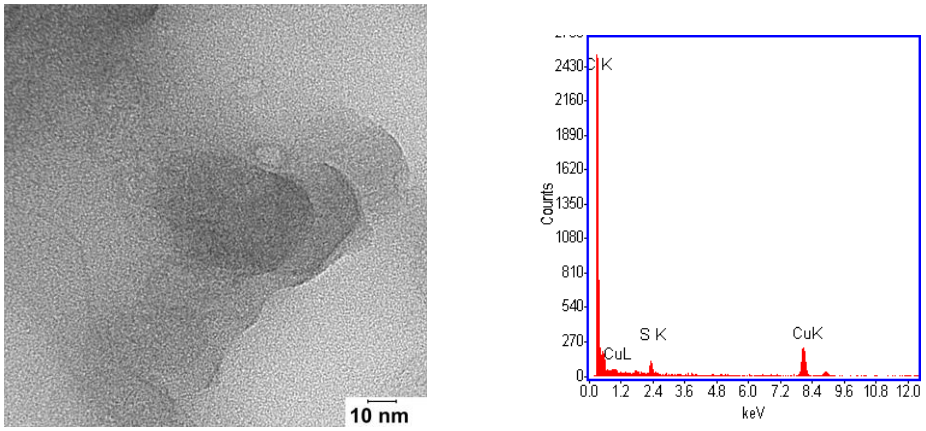


Figure 2.8. TEM and EDS of organic layer.

Conversion rate *vs* time curve (Figure 2.9) showed neither sigmoidal shape nor induction time, thus suggesting the intermediacy of homogeneous catalysts.[68]

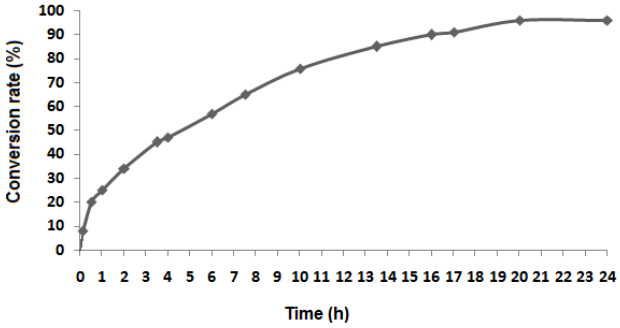


Figure 2.9. Conversion rate (%) of 1-((2-bromophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline **15n** *vs* time .

In 2003, Finke and Widegren reported some useful procedures to help in the distinction between homogeneous and heterogenous catalysis. Among them, the results from the addition of particular additives or poisons to the reaction in substoichiometric and overstoichiometric amounts, can clarify this problem.[69] Indeed, heterogeneous catalysts only expose a fraction of the

[68] Kinetic plots with clear sigmoidal shapes and induction periods are often associated to the catalytic participation of heterogeneous species. For a discussion on the different parameters to be analyzed in the determination of the nature of the catalytic species see: a) E. Bayram, J. C. Linehan, J. L. Fulton, J. A. S. Roberts, N. K. Szymczak, T. D. Smurthwaite, S. Özkar, M. Balasubramanian, R. G. Finke *J. Am. Chem. Soc.* **2011**, *133*, 18889. See also: b) J. A. Widegren, R. G. Finke *J. Mol. Catal. A: Chemical* **2003**, *198*, 317; c) N. T. S. Phan, M. Van Der Sluys, C. W. Jones *Adv. Synth. Catal.* **2006**, *348*, 609; d) K. Sommer, W. Yu, J. M. Richardson, M. Weck, C.W. Jones *Adv. Synth. Catal.* **2005**, *347*, 161.

[69] a) J. A. Windegren, R. G. Finke *J. Mol. Catal A* **2003**, *198*, 317; b) M.. A.Asraf, H. A. Younus, M. Yusubovc, F. Verpoort *Catal. Sci. Technol*. **2015**, *5*, 4901.

active metal atoms in their surface, so the addition of certain additives in substoichiometric amounts is enough to poison (partially or totally) the catalyst. In contrast, homogeneous catalysts are unaffected by such amounts.[70] In that context, it is known that mercury metal has an ability to poison metal(0) particles, both by amalgamating the metal or adsorbing on the metal surface.[71] Thus, the inhibition of the reaction by mercury is an evidence of heterogeneous catalysts. In the same context, addition of pyridine and PVPy in overstoichiometric amounts to the reaction mixture is used to detect formation of metal nanoparticles. If a substantial decrease in the catalyst activity is seen with the addition of PVPy in comparison with that of pyridine, that would be indicative of metal(0) species.

As it can be observed in Table 2.4 (entry 1), when a drop of mercury was added to the reaction mixture, no conversion was observed. Regarding to the addition of other poisoning additives in sub- and overstoichiometric amounts, the yields in the presence of CS_2 decreased drastically and in the case of PPh_3 they were lower regardless the amount of additive added, as displayed in Table 2.4 (entries 2-6). Finally, overstoichiometric addition of pyridine led to the drop of the yield to 8%, while by addition of PVPy the

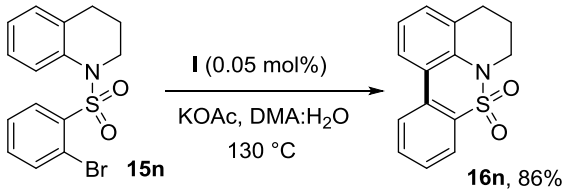
[70] Finke et al. have reported that poisoning of a catalyst by using substoichiometric amount (less than 1.0 equiv. per atom) of certain chemicals constitutes a suggestive evidence of the participation of heterogeneous catalysts. For a review, see: N. T. S. Phan, M. Van Der Sluys, C. W. Jones *Adv. Synth. Catal.* **2006**, *348*, 609.

[71] a) C. Paal, W. Hartmann *Chem. Ber.* **1918**, *51*, 711; b) G. Süss-Fink, M. Faure, T. R. Ward *Angew. Chem. Int. Ed* **2002**, *41*, 99; c) S. Jatta, B. Dutta, R. Bera, S. Koner, *Inorg. Chem.* **2008**, *47*, 5512; d) J. Demel, J. Lamac, J. Cejka, P. Stepnicka *ChemSusChem* **2009**, *2*, 442.

conversion was unchanged (entries 7 and 8). This series of poisoning assays account for the possible participation of heterogeneous species.

The somewhat puzzling outcome from the previous recycling, TEM, kinetic and poisoning measurements might be related to a mechanistic pathway based on a cocktail of *in situ* generated and preformed catalysts[72] after steady decomposition of **I**.

Table 2.4. Summary of poisoning experiments.



	Poisoning additive	Conv. (%)[a]
1	Hg (one drop)	0
2	CS_2 (0.5 equiv. per metal atom)	2
3	CS_2 (2.0 equiv.per metal atom)	0
4	PPh_3 (0.03 equiv.. per metal atom)	76
5	PPh_3 (0. 3 equiv. per metal atom)	71
6	PPh_3 (4.0 equiv. per metal atom)	70
7	Py (150 equiv.. per metal atom)[b]	8
8	PVPy (300 equiv. per metal atom)[c]	88

[a)] Measured by ^{1}H-NMR. Diethyleneglycol dimethyl ether was used as internal standard. [b)] Py: Pyridine [c)] PVPy: Polyvinylpyridine.

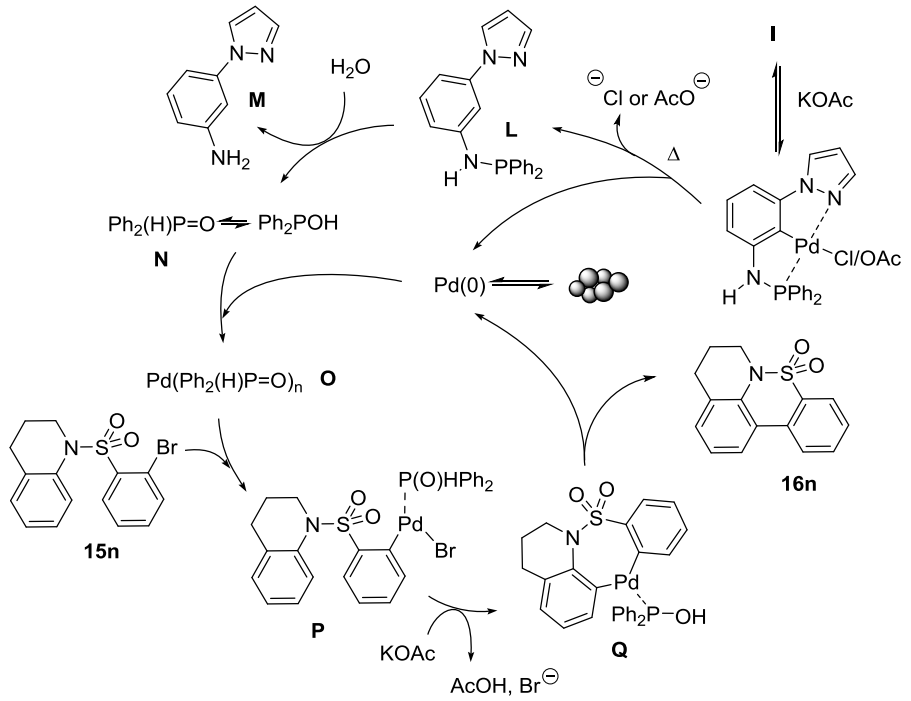
[72] For a discussion on the interconversion of catalytic species in Heck-type reactions, see: A. S. Kashin; V. P. Anannikov *J. Org. Chem.* **2013**, *78*, 11117.

A tentative proposal for the formation of benzothiazino dihydroquinoline **16n** is shown in Scheme 2.16. Hydrolysis[73] of phosphinoamine **L** generates 3-(1*H*-pyrazol-1-yl)aniline **M** and diphenylphosphine oxide or its tautomer diphenylphosphinous acid **N**, which upon complexation with Pd(0) species provides phosphinito complex(es) **O**.[74,75] After oxidative addition of arylhalide **15n** and formation of palladacyclic intermediate **Q**, reductive elimination renders target **16n** and releases Pd(0) species that re-enter the catalytic cycle. The above intermediates **L**-**Q** were detected by Electrospray Ionization Mass Spectrometry (ESI-MS). In addition, the use of diphenylphosphine oxide as ligand along with $Pd(OAc)_2$ (0.05 mol%) under optimized conditions (KOAc, DMA:H_2O, 130 ºC) provided a 54% yield of **16n** from *o*-bromosulfonamide **15n**.

[73] For the hydrolysis of phosphinoamine derivatives, see: S. Priya, M. S. Balakrishna, J. T. Mague, S. M. Mobin *Inorg. Chem.* **2003**, *42*, 1272.

[74] For a review on metal complexes of substituted phosphinites, see: D. M. Roundhill, R. P. Sperline, W. B. Beaulieu *Coord. Chem. Rev.* **1978**, *26*, 263.

[75] For the participation of palladium-diphenylphosphine oxide complexes in cross-coupling reactions, see: a) J. Jiménez-Bülle, R. Gaviño *Catal. Commun.* **2008**, *9*, 826; b) I. Pryjomska, H. Bartosz-Bechowski, Z. Ciunik, A. M. Trzeciak, J. J. Ziółkowski *Dalton Trans.* **2006**, 213.



Scheme 2.18. Proposed mechanism for the direct intramolecular coupling of *o*-bromosulfonamide **15n** in the presence of palladium complex **I**.

To sum up, we have developed a method for the intramolecular direct arylation of arenes *via* C-H bond functionalization with only 0.05 mol% palladium pincer complex **I**. The previous catalyst promotes efficiently the direct functionalization of a series of *N*-arylbenzanilides and *N*-arylsulfonamides providing a novel versatile and sustainable access to phenanthridinones, biaryl sultams and related heterocyclic derivatives. A number of experiments indicate a relatively complex mechanism that might

involve different catalytically active species and cooperative catalysis between them.

4. EXPERIMENTAL PROCEDURES

4.1. General methods and materials

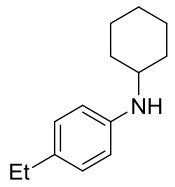
All reagents were purchased and used as received except when indicated. All solvents used in reactions were dried and purified according to standard procedures.[76] All air- or moisture-sensitive reactions were performed under argon atmosphere. The glassware was oven dried (140 ºC) overnight and purged with argon prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) at 20 ºC. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (δ= 7.26 for ^{1}H and δ= 77.00 for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz). Melting points were determined in a capillary tube on a Gallenkamp instrument and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230-400 mesh ASTM). IR spectra were recorded using an ATR on a JASCO FT/IR4100 in the interval between 400 and 400 cm^{-1} with 4 cm^{-1} resolution, and only noteworthy absorptions are reported in cm^{-1}. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. ICP-MS measurements were carried out on a Thermo Elemental

[76] a) W. L. F. Armarego, C. Chai in *Purification of Laboratory Chemicals, 5th ed.*, Elsevier Science, **2009**; b) B. G. Williams, M. S. Lawton *Org. Chem.* **2010**, *75*, 8351.

X7 Series ICP-MS equipped with an ASX-520 autosampler. MS spectra were recorded on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions. HRMS were recorded using a Micromass GCT spectrometer by electronic impact (EI) or electrospray ionization (ESI), or using a ultra performance liquid chromatography (UPLC) (Acquity model, Waters), in tandem with a QTOF mass spectrometer (Synapt G2 HDMS model), with an ESI source. Transmission electron microscopy (TEM) work was done on a Philips SuperTwin CM200 operated at 200 kV and equipped with LaB6 filament and EDAX EDS microanalysis system. The samples were prepared by dispersion into ethanol and keeping the suspension in an ultrasonic bath for 15 min, after a drop of suspension was spread onto a TEM copper grid (300 Mesh) covered by a holey carbon film followed by drying under vacuum.

4.2. Typical procedure for syntesis of amines

_N_-Cyclohexyl-4-ethylbenzeneamine.



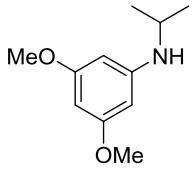
A mixture of 4-ethylaniline (1.25 mL, 10 mmol), cyclohexanone (1 mL, 10 mmol) and activated zinc dust (2.6 g, 40 mmol) in AcOH:H_2O (9:1, 9 mL) was stirred for 30 min at room temperature and then heated to 60 °C for 2 h. After cooling, the mixture was diluted with MeOH (4 mL) and filtered through a fritted funnel. The solids were washed with MeOH (2 x 5 mL) and the combined filtrates evaporated under reduced pressure. Ice (~ 10 g) and CH_2Cl_2 (5 mL) were added to the residue, and then 25% aqueous NH_4OH until pH 10 was reached. The organic layer was separated and the aqueous phase was washed with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to afford *N*-cyclohexyl-4-ethylbenzenamine[77] as an orange oil (1.4 g, 71%).

^{1}H NMR ($CDCl_3$) δ 7.02 (d, J = 8.4 Hz, 2H, H_{arom}), 6.57 (d, J = 8.4 Hz, 2H, H_{arom}), 3.41-3.05 (m, 2H, CH_2), 2.56 (q, J = 7.6 Hz, 2H,CH_3CH_2), 2.08 (dd,

[77] Z. Wu, L. Zhou, Z. Jiang, D. Wu, Z. Li, X. Zhou *Eur. J. Org. Chem*. **2010**, 4971.

J = 12.7, 3.2 Hz, 2H, CH_2), 1.86-1.73 (m, 2H, CH_2), 1.70-1.65 (m, 1H, CH), 1.43-1.26 (m, 4H, CH_2), 1.22 (t, *J* = 7.6 Hz, 3H, CH_3CH_2).

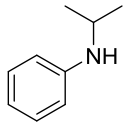
***N*-Isopropyl-3,5-dimethoxyaniline.**



The same procedure was applied to 3,5-dimethoxyaniline (1.53 g, 10 mmol) and acetone (1 mL, 10 mmol) to provide *N*-isopropyl-3,5-dimethoxyaniline as a colorless oil (1.9 g, 99 %).

^{1}H NMR ($CDCl_3$) δ 5.92 (s, 1H, H_{arom}), 5.85 (s, 2H, H_{arom}), 3.77 (s, 6H, OCH_3), 3.68-3.56 (m, 1H, CH), 1.23 (d, *J* = 6.3 Hz, 6H, CH_3).

***N*-Isopropylaniline.**[78]



The same procedure was applied to aniline (0.91 mL, 10 mmol) and acetone (1 mL, 10 mmol) to provide *N*-isopropylaniline as a colorless oil (810 mg, 60 %).

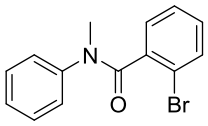
[78] P. Linciano, M. Pizzetti, A. Porcheddu, M. Taddei *Synlett* **2013**, *24*, 2249.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (t, J = 7.9 Hz, 2H, H_{arom}), 7.05 (t, J = 7.3 Hz, 1H, H_{arom}), 6.90 (d, J = 7.9 Hz, 2H, H_{arom}), 3.97-3.83 (m, 1H, CH), 3.70 (bs, 1H, NH), 1.50 (d, J = 6.4 Hz, 3H, CH_3).

4.3. Synthesis of amides 15a-h

General procedure A. To a solution of the carboxylic acid (1.0 mmol) in dry toluene (1 mL per mmol) under argon, $SOCl_2$ (6 mmol) was added and the mixture was heated to 70 °C until completion of the reaction (1-2 h) was observed by IR spectroscopy. After cooling down, the solvent was evaporated under reduced pressure, and the crude mixture was redissolved in dry CH_2Cl_2 (5 mL per mmol) under argon and cooled to 0 °C. Then, Et_3N (1.35 mmol) and the N-alkylaniline (1.25 mmol) were added dropwise and the reaction mixture was stirred under argon at room temperature for 10 h. The resultant mixture was poured onto a separatory funnel and washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* and the so-obtained residue was purified by flash column chromatography (hexanes:EtOAc).

2-Bromo-*N*-methyl-*N*-phenylbenzamide 2a.[79]

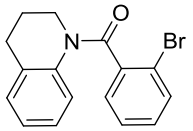


The general procedure was followed, and compound **15a** was obtained as a colorless oil (245.6 mg, 85%).

^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 7.7 Hz, 1H, H_{arom}), 7.33 (d, J = 7.2 Hz, 2H, H_{arom}), 7.16-7.02 (m, 6H, H_{arom}), 3.37 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 170.9 (NCO), 143.7 (C_{arom}), 135.6 (qC_{arom}), 133.7 (qC_{arom}), 130.7 (C_{arom}), 129.8 (C_{arom}), 129.1 (C_{arom}), 128.5 (C_{arom}), 128.1 (C_{arom}), 127.7 (C_{arom}), 122.7 (CBr), 37.1 (NCH_3).

***N*-(2-Bromobenzoyl)-1,2,3,4-tetrahydroquinoline 15b.**[80]



The general procedure was followed, and compound **15b** was obtained as a yellowish powder (163.8 mg, 52%).

m.p. 103-105 °C ($CHCl_3$) (Lit.[80] 106-107 ºC).

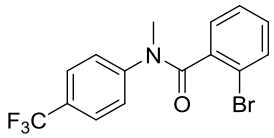
[79] A. Ryokawa, H. Togo *Tetrahedron* **2001**, *57*, 5915.

[80] S. De, S. Ghosh, S. Bhunia, J. A. Sheikh, A. Bisai *Org. Lett*. **2012**, *14*, 4466.

^{1}H NMR ($CDCl_3$) (rotameric mixture) δ8.12-7.58 (m, 5H for major + minor rotamers, H_{arom}), 7.39 -6.94 (m, 2H for major + minor rotamers, H_{arom}), 6.74-6.47 (m, 1H for major + minor rotamers, H_{arom}), 4.11-3.48 (m, 2H for major + minor rotamers, CH_2), 2.84 (br s, 2H for major + minor rotamers, CH_2), 2.14-2.02 (br, 2H for major + minor rotamers, CH_2).

^{13}C NMR ($CDCl_3$) (rotameric mixture) δ 168.2 (NCO), 138.8 (qC_{arom}), 138.6 (qC_{arom}), 138.2 (qC_{arom}), 138.1 (qC_{arom}), 133.0 (qC_{arom}), 132.9 (qC_{arom}), 130.3, 130.2, 129.7, 129.5, 128.5, 128.3, 127.9, 127.6, 127.4, 127.2 (C_{arom}), 125.9 (qC_{arom}), 125.8 (qC_{arom}), 125.0, 124.9, 124.5, 124.4 (C_{arom}), 120.1 (CBr), 120.0 (CBr), 47.1 (CH_2), 46.9 (CH_2), 43.4 (CH_2), 43.3 (CH_2), 27.2 (CH_2), 26.9 (CH_2).

2-Bromo-*N*-methyl-*N*-(4-trifluoromethylphenyl)benzamide 15c.[81]



The general procedure followed, and compound **15c** was obtained as a yellowish powder (292.7 mg, 82%).

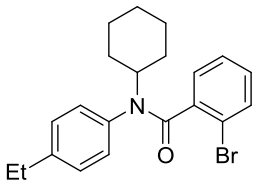
m.p. 103-105 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) (rotameric mixture) δ7.52-6.91 (m, 8H for major + minor rotamers, H_{arom}), 3.50 (br s, 3H for major + minor rotamers, NCH_3).

[81] G. Zhang, X. Zhao, Y. Yan, C. Ding *Eur. J. Org. Chem*. **2012**, 669.

^{13}C NMR ($CDCl_3$) (rotameric mixture) δ 163.3 (NCO), 141.1 (qC_{arom}), 132.7 (qC_{arom}), 127.5, 125.1 (C_{arom}), 123.6 (q, $J_{C\text{-}F}$= 271 Hz, CF_3), 121.7, 120.87, 120.27, 120.07, 116.5 (C_{arom}), 114.2 (CBr), 31.4 (NCH_3).

2-Bromo-*N*-cyclohexyl-*N*-(4-ethylphenyl)benzamide 15d.



The general procedure was followed, and compound **15d** was obtained as a colorless oil (292.7 mg, 86%).

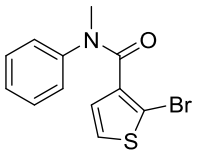
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 2H, H_{arom}), 7.11-6.84 (m, 6H, H_{arom}), 4.76 (tt, J = 12.0, 3.6 Hz, 1H, CH), 2.50 (q, J = 7.6 Hz, 2H, CH_2CH_3), 2.00 (d, J = 11.1 Hz, 2H, CH_2), 1.77 (d, J = 13.0 Hz, 2H, CH_2), 1.59 (d, J = 12.9 Hz, 1H, CH_2), 1.45 (qt, J = 17.6, 5.5 Hz, 2H, CH_2), 1.21 (ddd, J = 15.2, 13.4, 5.0 Hz, 2H, CH_2), 1.11 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.04-0.85 (m, 1H, CH_2).

^{13}C NMR ($CDCl_3$) δ 168.5 (NCO), 143.9 (qC_{arom}), 139.4 (qC_{arom}), 135.8 (qC_{arom}), 132.3, 129.9, 129.1, 128.4, 127.7, 126.4 (C_{arom}), 119.4 (CBr), 54.6 (CH), 31.4 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 15.0 (CH_3).

IR (ATR) υ_{max} 3051, 2934, 2855, 1648, 1511, 1397, 1364, 1328, 1260, 728 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{21}H_{24}BrNO$: 385.1041; found: 385.1028.

2-Bromo-*N*-methyl-*N*-phenylthiophene-3-carboxamide 15f.



The general procedure was followed, and compound **15f** was obtained as a green prisms (280.2 mg, 95%).

m.p. 72-75 °C (EtOAc).

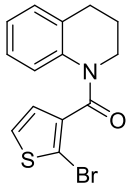
^{1}H NMR ($CDCl_3$) δ 7.16 (d, J = 6.8 Hz, 2H, H_{arom}), 7.12-7.07 (m, 1H, H_{arom}), 7.04 (t, J = 6.6 Hz, 2H, H_{arom}), 6.91 (d, J = 5.1 Hz, 1H, H_{arom}), 6.54 (d, J = 3.8 Hz, 1H, H_{arom}), 3.39 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 165.2 (NCO), 143.3 (qC_{arom}), 137.6 (C_{arom}), 129.0, 127.5, 127.1, 126.6, 126.2 (C_{arom}), 112.3 (CBr), 37.3 (NCH_3).

IR (ATR) υ_{max} 3091, 1641, 1590, 1497, 1372, 1113, 745 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{12}H_{10}BrNOS$: 294.9666; found: 294.9661.

(2-Bromothiophen-3-yl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone 15h.



The general procedure was followed, and compound **15h** was obtained as a colorless oil (160.5 mg, 50%).

^{1}H NMR ($CDCl_3$) δ 7.18 (d, J = 5.6 Hz, 1H, H_{arom}), 7.13 (d, J = 7.3 Hz, 1H, H_{arom}), 7.11-7.01 (m, 1H, H_{arom}), 6.98-6.75 (m, 3H, H_{arom}), 3.90 (t, J = 6.4 Hz, 2H, CH_2), 2.83 (t, J = 6.6 Hz, 2H, CH_2), 2.12-2.01 (m, 2H, CH_2).

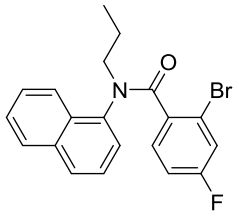
^{13}C NMR ($CDCl_3$) δ 169.3 (NCO), 145.9 (qC_{arom}), 135.1 (qC_{arom}), 130.8 (qC_{arom}), 130.4, 129.0, 128.0, 126.2 (C_{arom}), 125.4 (CBr), 121.6, 111.9 (C_{arom}), 45.0 (NCH_2), 27.0, 22.3 (CH_2).

IR (ATR) υ_{max} 3105, 3070, 2937, 2894, 1637, 1486, 1411, 1382, 1328, 1264, 751 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_{12}BrNOS$: 320.9823, found: 320.9818.

General procedure B. To a solution of the carboxylic acid (1 mmol) in dry toluene (1 mL per mmol) under argon, $SOCl_2$ (3 mmol) was added and the mixture was heated to 70 °C until completion of the reaction (1-2 h) was observed by IR spectroscopy. After cooling down, the solvent was evaporated under reduced pressure. The crude mixture was re-dissolved in dry CH_2Cl_2 (5 mL per mmol) under argon and cooled to 0 °C. Then, Et_3N (1.35 mmol) and the aniline (1.25 mmol) were added dropwise and the reaction mixture was stirred under argon at room temperature for 10 h. The resultant mixture was poured onto a separatory funnel and washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* and the so-obtained residue was redissolved in EtOAc:hexanes (1:1) and passed through a short plug of silicagel. After evaporation of the solvent under reduced pressure, the amide was dissolved in dry DMF (2 mL per mmol) under argon and added dropwise to a suspension of NaH (1.2 mmol) in dry DMF (1 mL per mmol) at 0 °C under argon. After 30 min stirring at the same temperature, the alkyl iodide (1.05 mmol) was added dropwise and the resulting mixture stirred at room temperature overnight. The reaction was diluted with EtOAc (5 mL) and saturated aqueous NH_4Cl (10 mL) was added. The organic phase was separated, and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, evaporated under reduced pressure and the so-obtained residue was purified by flash column chromatography (hexanes:EtOAc).

2-Bromo-3-fluoro-*N*-(1-naphthyl)-*N*-propylbenzamide 15e.



The general procedure was followed, and compound **15e** was obtained as violet prisms (157.9 mg, 41%).

m.p. 107-110 °C (EtOAc).

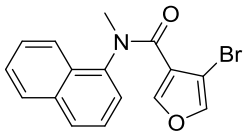
^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 1H, H_{arom}), 7.82 (d, J = 8.2 Hz, 1H, H_{arom}), 7.71 (d, J = 8.3 Hz, 1H, H_{arom}), 7.64 (tt, J = 7.0, 3.5 Hz, 1H, H_{arom}), 7.58-7.46 (m, 2H, H_{arom}), 7.32-7.21 (m, 2H, H_{arom}), 6.63-6.52 (m, 2H, H_{arom}), 4.55 (ddd, J = 13.1, 10.0, 6.2 Hz, 1H, CH_2), 3.31 (ddd, J = 13.1, 10.0, 5.0 Hz, 1H, CH_2), 1.97-1.76 (m, 1H, CH_2), 1.75-1.56 (m, 1H, CH_2), 0.98 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 167.9 (NCO), 160.7 (d, $J_{C\text{-}F}$ = 223 Hz, CF), 140.2 (qC_{arom}, J = 7 Hz), 137.4, 134.4 (qC_{arom}), 134.0 (C_{arom}, J = 8 Hz), 130.1 (qC_{arom}), 129.0 (C_{arom}, J = 20 Hz), 128.7 (qC_{arom}), 127.5, 126.6, 126.4, 125.2, 122.4, 117.1, 116.8 (C_{arom}), 114.2 (CBr, J = 9 Hz), 113.9 (C_{arom}, J = 24 Hz), 50.6 (CH_2), 21.1 (CH_2), 11.3 (CH_3).

IR (ATR) υ_{max} 3063, 2965, 2934, 2872, 1655, 1572, 1407, 1257, 776 cm^{-1}.

HRMS (*m/z*): [M+2] calc. for $C_{20}H_{17}BrFNO$: 387.0453; found: 385.0457.

2-Bromo-*N*-methyl-*N*-(1-naphthyl)furan-3-carboxamide 15g.



The general procedure was followed, and compound **15g** was obtained as a violet powder (177.7 mg, 54%).

m.p. 104-106 °C (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 9.3 Hz, 2H, H_{arom}), 7.84 (d, J = 8.2 Hz, 1H, H_{arom}), 7.58 (qd, J = 6.9, 1.2 Hz, 2H, H_{arom}), 7.42 (t, J = 8.1 Hz, 1H, H_{arom}), 7.29 (d, J = 7.8 Hz, 1H, H_{arom}), 6.87 (d, J = 2.2 Hz, 1H, H_{arom}), 5.35 (d, J = 2.2 Hz, 1H, H_{arom}), 3.52 (s, 3H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (NCO), 142.9, 139.9 (qC_{arom}), 134.4 (qC_{arom}), 130.0 (qC_{arom}), 128.7, 128.7, 127.5, 127.4, 126.7 (C_{arom}), 126.3 (qC_{arom}), 126.0, 125.6, 122.5 (C_{arom}), 120.4 (CBr), 37.9 (NCH_3).

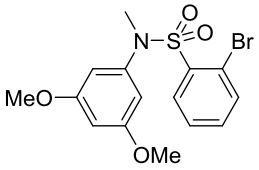
IR (ATR) υ_{max} 3120, 3051, 1637, 1576, 1436, 1159, 772 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{16}H_{12}BrNO_2$: 329.0051; found: 329.0052.

4.4. Synthesis of sulfonamides 2i-s

General procedure C. To a solution of 3,5-dimethoxyaniline (1 mmol), Et_3N (1.1 mmol) and DMAP (0.2 mmol) in dry THF (0.05 M), 2-bromo benzenesulfonyl chloride (1 mmol) was added and the resulting solution was stirred overnight under argon at room temperature. The reaction was diluted with EtOAc (10 mL), and HCl 2M (5 mL) was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* and the residue was redissolved in EtOAc:hexanes (1:1) and passed through a short plug of silicagel. After evaporation of the solvent under reduced pressure, the amide was dissolved in dry DMF (2 mL per mmol) under argon and added dropwise to a suspension of NaH (1.2 mmol) in dry DMF (1 mL per mmol) at 0 °C under argon. After 30 min stirring at the same temperature, the alkyl iodide (1.05 mmol) was added dropwise and the resulting mixture stirred at room temperature overnight. The reaction was diluted with EtOAc (5 mL) and saturated aqueous NH_4Cl (10 mL) was added. The organic phase was separated, and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, evaporated under reduced pressure and the so-obtained residue was purified by flash column chromatography (hexanes:EtOAc).

2-Bromo-*N*-(3,5-dimethoxyphenyl)-*N*-methylbenzenesulfonamide 15l.



The general procedure was followed, and compound **15l** was obtained as yellowish needles (269.5 mg, 70%).

m.p. 91-95 °C (EtOAc).

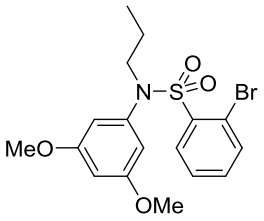
^{1}H NMR ($CDCl_3$) δ 7.95-7.92 (m, 1H, H_{arom}), 7.73-7.65 (m, 1H, H_{arom}), 7.37-7.28 (m, 2H, H_{arom}), 6.36 (d, J = 2.0 Hz, 2H, H_{arom}), 6.28 (t, J = 2.0 Hz, 1H, H_{arom}), 3.67 (s, 6H, OCH_3), 3.40 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 160.8 (qC_{arom}), 142.5 (qC_{arom}), 138.1 (qC_{arom}), 135.6, 133.8, 132.9, 127.4 (C_{arom}), 120.5 (CBr), 104.9, 99.4 (C_{arom}), 55.4 (OCH_3), 39.3 (NCH_3).

IR (ATR) υ_{max} 3009, 2944, 2836, 1594, 1457, 1422, 1336, 1207, 1163, 1045, 951, 754 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{16}BrNO_4S$: 321.0364; found: 321.0366.

2-Bromo-*N*-(3,5-dimethoxyphenyl)-*N*-propylbenzenesulfonamide 15m.



The general procedure was followed, and compound **15m** was obtained as green prisms (243.7 mg, 75%).

m.p. 71-73 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 7.91-7.87 (m, 1H, H_{arom}), 7.77-7.61 (m, 1H, H_{arom}), 7.35-7.22 (m, 2H, H_{arom}), 6.39 (d, J = 2.2 Hz, 2H, H_{arom}), 6.30 (t, J = 2.2 Hz, 1H, H_{arom}), 3.85-3.77 (t, J = 7.8 Hz, 2H, CH_2), 3.67 (s, 6H, OCH_3), 1.53 (tq, J = 7.8, 7.3 Hz, 2H, CH_2), 0.92 (t, J = 7.4 Hz, 3H, CH_3).

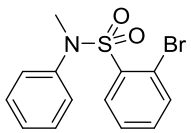
^{13}C NMR ($CDCl_3$) δ 160.6 (qC_{arom}), 140.0 (qC_{arom}), 138.3 (qC_{arom}), 135.3, 133.5, 133. 1, 127.3 (C_{arom}), 120.3 (CBr), 107.1, 99.9 (C_{arom}), 55.4 (OCH_3), 54.1 (CH_2), 22.1 (CH_2), 11.0 (CH_3).

IR (ATR) υ_{max} 3001, 2959, 2934, 2880, 2840, 1594, 1461, 1422, 1336, 1203, 1153, 1051, 754 cm^{-1}.

HRMS (ESI) (*m/z*): $[M+H]^+$ calc. for $C_{17}H_{21}BrNO_4S$: 414.03451; found: 414.03656.

General procedure D.To a solution of *N*-alkylaniline (1 mmol), Et_3N (1.1 mmol) and DMAP (0.2 mmol) in dry THF (0.05 M), 2-bromo benzenesulfonyl chloride (1 mmol) was added and the resulting solution was stirred overnight under argon at room temperature. The reaction was diluted with EtOAc (10 mL), and HCl 2M (5 mL) was added. The organic phase was separated, the aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the so-obtained residue was purified by flash column chromatography (hexanes:EtOAc).

2-Bromo-*N*-methyl-*N*-phenylbenzenesulfonamide 15i.[54]

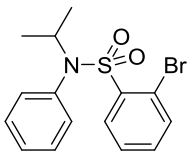


The general procedure was followed, and compound **15i** was obtained as a colorless oil (312.0 mg, 96%).

^{1}H NMR ($CDCl_3$) δ 7.94-7.83 (m, 1H, H_{arom}), 7.76-7.63 (m, 1H, H_{arom}), 7.35-7.31 (m, 2H, H_{arom}), 7.28-7.20 (m, 5H, H_{arom}), 3.44 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 140.9 (qC_{arom}), 138.1 (qC_{arom}), 135.6, 133.7, 132.9, 129.2, 127.4, 127.3, 127.0 (C_{arom}), 120.5 (CBr), 39.3 (NCH_3).

2-Bromo-*N*-isopropyl-*N*-phenylbenzenesulfonamide 15j.



The general procedure was followed, and compound **15j** was obtained as a white powder (268.3 mg, 76%).

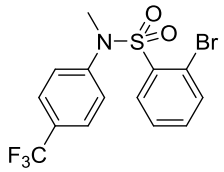
m.p. 68-70 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J = 7.8, 1.8 Hz, 1H, H_{arom}), 7.73 (dd, J = 7.8, 1.2 Hz, 1H, H_{arom}), 7.35-7.19 (m, 5H, H_{arom}), 7.13-7.05 (m, 2H, H_{arom}), 4.81 (hept, J = 6.7 Hz, 1H, CH), 1.16 (d, J = 6.7 Hz, 6H, CH_3).

^{13}C NMR ($CDCl_3$) δ 138.9 (qC_{arom}), 135.3 (C_{arom}), 134.1 (qC_{arom}), 133.4, 132.9, 132.8, 128.7, 127.3 (C_{arom}), 120.3 (CBr), 51.4 (CH), 22.1 (CH_3).

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{16}BrNO_2S$: 353.0085; found: 353.0086.

2-Bromo-*N*-methyl-*N*-(4-trifluoromethylphenyl)benzenesulfonamide 15k.



The general procedure was followed, and compound **15k** was obtained as a yellowish oil (188.6 mg, 48%).

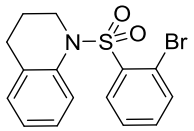
^{1}H NMR ($CDCl_3$) δ 8.03-7.90 (m, 1H, H_{arom}), 7.76-7.63 (m, 1H, H_{arom}), 7.54 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.43-7.31 (m, 4H, H_{arom}), 3.44 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 144.2 (qC_{arom}), 137.6 (qC_{arom}), 135.8, 134.1, 132.9, 127.6, 126.2, 126.2, 126.1, 125.9 (C_{arom}), 122.0 (qC_{arom}), 123.9 (q, *J* = 295 Hz, CF_3), 120.4 (CBr), 38.8 (NCH_3).

IR (ATR) υ_{max} 3059, 2998, 2930, 1612, 1336, 1324, 1267, 1159, 1116, 1070, 880, 840, 757 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_{11}BrF_3NO_4S$: 392.9646; found: 392.9644.

1-((2-Bromophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline 15n.



The general procedure was followed, and compound **15n** was obtained as an orange powder (245.7 mg, 70%).

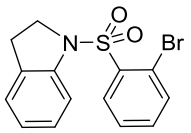
m.p. 96-98 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.12 (dd, *J* = 7.7, 1.8 Hz, 1H, H_{arom}), 7.70 (dd, *J* = 7.7, 1.4 Hz, 1H, H_{arom}), 7.49-7.30 (m, 3H, H_{arom}), 7.11-6.94 (m, 3H, H_{arom}), 3.97-3.84 (t, *J* = 6.7 Hz, 2H, CH_2), 2.76 (t, *J* = 6.7 Hz, 2H, CH_2), 2.00-1.87 (m, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 140.1 (qC_{arom}), 137.3 (qC_{arom}), 135.8, 133.8, 132.1 (C_{arom}), 129.8 (qC_{arom}), 129.4, 127.7, 126.3, 124.4, 122.7 (qC_{arom}), 120.3 (CBr), 46.7 (CH_2), 26.9 (CH_2), 22.7 (CH_2).

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{14}BrNO_2S$: 350.9929; found: 350.9927.

1-((2-Bromophenyl)sulfonyl)indoline 15o.[82]



The general procedure was followed, and compound **15o** was obtained as a brownish powder (296.5 mg, 88%).

m.p. 93-95 °C ($CHCl_3$).

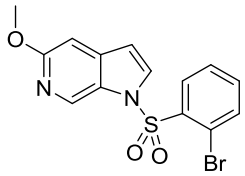
^{1}H NMR ($CDCl_3$) δ 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H, H_{arom}), 7.71 (dd, *J* = 7.7, 1.3 Hz, 1H, H_{arom}), 7.41 (m, 2H, H_{arom}), 7.21 (d, *J* = 8.0 Hz, 1H, H_{arom}), 7.15 (d, *J* = 7.4 Hz, 1H, H_{arom}), 7.08 (t, *J* = 7.6 Hz, 1H, H_{arom}), 6.94 (td, *J* = 7.4, 0.8 Hz, 1H, H_{arom}), 4.26 (t, *J* = 8.5 Hz, 2H, CH_2), 3.12 (t, *J* = 8.5 Hz, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 141.6 (qC_{arom}), 138.6 (qC_{arom}), 135.8, 133.9, 132.1 (C_{arom}), 131.2 (qC_{arom}), 127.6, 127.5, 125.2, 123.3 (C_{arom}), 120.5 (CBr), 113.8 (C_{arom}), 50.6 (CH_2), 27.9 (CH_2).

[82] C. B. Bheeter, J. K. Bera, H. Doucet *Adv. Synth. Catal*. **2012**, *354*, 3533.

General procedure E. A solution of 2-bromobenzenesulfonyl chloride (1.25 mmol) in dry DMF (5 mL per mmol) was added dropwise to a suspension of NaH (1.25 mmol) in dry DMF (8 ml per mmol) at 0 °C under argon. The resulting mixture was stirred for 1h at room temperature and cooled down to 0 °C. A solution of the pyrrol/indol derivative (1 mmol) in DMF (5 mL per mmol) was then dropwise added and the resulting mixture was stirred at room temperature for 6 h. Ice (~ 10 g) was added, the organic phase was separated, the aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the so-obtained residue was purified by flash column chromatography (hexanes:EtOAc).

1-((2-Bromophenyl)sulfonyl)-5-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine 15p.



The general procedure was followed, and compound **15p** was obtained as a white powder (278.1 mg, 76%).

m.p. 89-93 °C (EtOAc).

^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H, H_{arom}), 8.27-8.12 (m, 1H, H_{arom}), 7.81 (d, J = 3.6 Hz, 1H, H_{arom}), 7.60 (d, J = 7.7 Hz, 1H, H_{arom}), 7.46 (t, J = 7.3 Hz, 1H,

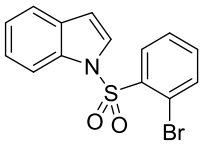
H_{arom}), 7.37 (dt, *J* = 7.6, 3.8 Hz, 1H, H_{arom}), 6.81 (s, 1H, H_{arom}), 6.51 (d, *J* = 3.6 Hz, 1H, H_{arom}), 3.85 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$) δ 160.2 (qC_{arom}), 140.5 (qC_{arom}), 137.4(qC_{arom}), 136.1, 135.1, 133.1, 131.9, 131.2, 128.1, 128.0 (C_{arom}), 120.7 (CBr), 106.1, 100.2 (C_{arom}), 53.9 (OCH_3).

IR (ATR) υ_{max} 3149, 3120, 1569, 1440, 1372, 1253, 1174, 1134, 1026, 995, 739, 657 cm^{-1}

HRMS (ESI) (*m/z*): $[M+H]^+$ calc. for $C_{14}H_{12}BrN_2O_3S$: 366.97465; found: 366.97431.

1-((2-Bromophenyl)sulfonyl)-1*H*-indole 15q.



The general procedure was followed, and compound **15q** was obtained as a brownish powder (261.3 mg, 78%).

m.p. 87-92 °C (EtOAc).

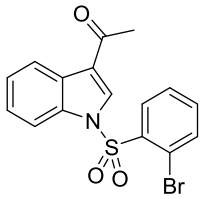
^{1}H NMR ($CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.6 Hz, 1H, H_{arom}), 7.60 (d, *J* = 3.7 Hz, 1H, H_{arom}), 7.54-7.47 (m, 1H, H_{arom}), 7.40 (ddd, *J* = 7.9, 7.1, 2.6 Hz, 2H, H_{arom}), 7.30-7.22 (m, 1H, H_{arom}), 7.16 (td, *J* = 7.6, 1.6 Hz, 1H, H_{arom}), 7.04 (dt, *J* = 8.9, 2.8 Hz, 2H, H_{arom}), 6.50 (d, *J* = 3.7 Hz, 1H, H_{arom}).

^{13}C NMR ($CDCl_3$) δ 138.0 (qC_{arom}), 136.0, 134.8, 134.5 (qC_{arom}), 131.4, 130.6 (qC_{arom}), 128.2, 127.8, 124.4, 123.4, 121.6 (C_{arom}), 120.7 (CBr), 113.0, 107.5 (C_{arom}).

IR (ATR) υ_{max} 1440, 1364, 1173, 1130 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_{10}BrNO_2S$: 334.9616; found: 334.9616.

1-(1-((2-Bromophenyl)sulfonyl)-1*H*-indol-3-yl)ethan-1-one 15r.



The general procedure was followed, and compound **15r** was obtained as a white powder (188.5 mg, 50%).

m.p. 119-123 °C (EtOAc).

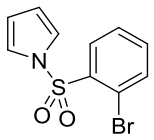
^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H, H_{arom}), 8.40-8.28 (m, 2H, H_{arom}), 7.62 (dt, *J* = 8.3, 4.1 Hz, 1H, H_{arom}), 7.60-7.47 (m, 2H, H_{arom}), 7.41 (td, *J* = 7.7, 1.6 Hz, 1H, H_{arom}), 7.35-7.21 (m, 2H, H_{arom}), 2.59 (s, 3H, $COCH_3$).

^{13}C NMR ($CDCl_3$) δ 193.5 (CO), 136.6 (qC_{arom}), 136.3, 135.6, 134.6 (C_{arom}), 134.5 (qC_{arom}), 132.2, 128.2 (C_{arom}), 127.5 (qC_{arom}), 125.6, 124.9, 123.3, 120.8 (CBr), 120.3 (qC_{arom}), 112.5, 27.8 (C_{arom}).

IR (ATR) υ_{max} 3141, 3059, 1670, 1533, 1447, 1378, 1188, 1174, 1051, 1024, 973, 747 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{16}H_{12}BrNO_3S$: 376.9721; found: 376.9722.

1-((2-Bromophenyl)sulfonyl)-1*H*-pyrrole 15s.[83]



The general procedure was followed, and compound **15s** was obtained as brownish prisms (142.5 mg, 50%).

m.p. 83-85 °C ($CHCl_3$) (Lit.[83] 85-87 ºC).

^{1}H NMR ($CDCl_3$) δ 7.78-7.67 (m, 2H, H_{arom}), 7.48-7.37 (m, 2H, H_{arom}), 7.24 (dd, J = 5.2, 2.8 Hz, 2H, H_{arom}), 6.35-6.32 (m, 2H, H_{arom}).

^{13}C NMR ($CDCl_3$) δ 138.9 (qC_{arom}), 136.0, 134.7, 130.4, 128.0, 121.8 (C_{arom}), 120.3 (CBr), 113.1 (C_{arom}).

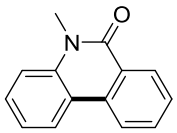
.

[83] N. Murugesan, Z. Gu, P. D. Stein, S. Bisaha, S. Spergel, R. Girotra, V. G. Lee, J. Lloyd, R. N. Misra, J. Schmidt, A. Mathur, L. Stratton, Y. F. Kelly, E. Bird, T. Waldron, E. C.-K. Liu, R. Zhang, H. Lee, R. Serafino, B. Abboa-Offei, P. Mathers, M. Giancarli, A. A. Seymour, M. L. Webb, S. Moreland, J. C. Barrish, J. T. Hunt *J. Med. Chem.***1998**, *41*, 5198.

4.5. Intramolecular direct arylation of amides and sulfonamides.

General procedure for direct arylation. DMA (0.8 mL) and water (0.1 mL) were added to a screw-capped tube charged with substrate **15** (0.35 mmol) and KOAc (1.05 mmol) at room temperature. Then, a solution of pincer complex **I** in DMA (1.75 mM, 0.1 mL, 0.175 μmol of **1**) was added, the tube was closed and it was heated to 130 °C for 20 h. After cooling, the crude was diluted with H_2O (2 mL) and washed with EtOAc (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexanes:EtOAc) to give the desired product **16.**

5-Methylphenanthridin-6(*5H*)-one 16a.[79]



The general procedure for direct arylation was followed, and compound **16a** was obtained as a white powder (184.0 mg, 88%).

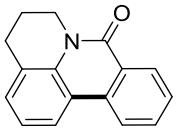
m.p. 78-81 °C ($CHCl_3$) (Lit.[79] 106-107 ºC (hexane)).

^{1}H NMR ($CDCl_3$) δ 8.56 (dd, J = 8.0, 1.3 Hz, 1H, H_{arom}), 8.28 (dt, J = 3.3, 4.7 Hz, 2H, H_{arom}), 7.81-7.70 (m, 1H, H_{arom}), 7.64-7.50 (m, 2H, H_{arom}), 7.42

(d, *J* = 7.8 Hz, 1H, H_{arom}), 7.32 (td, *J* = 8.2, 4.1 Hz, 1H, H_{arom}), 3.82 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 161.7 (NCO), 138.1 (qC_{arom}), 133.5 (qC_{arom}), 132.4, 129.6, 128.9, 127.9 (C_{arom}), 125.6 (qC_{arom}), 123.2, 122.5, 121.6 (C_{arom}), 119.3 (qC_{arom}), 115.1 (C_{arom}), 29.9 (NCH_3).

5,6-Dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridin-8-one 16b.[80]



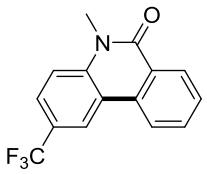
The general procedure for direct arylation was followed, and compound **16b** was obtained as white powder (188.1 mg, 80%).

m.p. 80-82 °C ($CHCl_3$) (Lit.[80] 87-89 ºC).

^{1}H NMR ($CDCl_3$) δ8.55 (dd, *J* = 8.0, 1.1 Hz, 1H, H_{arom}), 8.26 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.12 (dd, *J* = 7.9, 0.8 Hz, 1H, H_{arom}), 7.74 (ddd, *J*= 8.3, 7.2, 1.5 Hz, 1H, H_{arom}), 7.57 (t, *J* = 7.6 Hz, 1H, H_{arom}), 7.29 (dd, *J* = 7.3, 1.3 Hz, 1H, H_{arom}), 7.20 (dd, *J* = 9.6, 5.7 Hz, 1H, H_{arom}), 4.43-4.21 (m, 2H, CH_2), 3.01 (t, *J* = 6.2 Hz, 2H, CH_2), 2.24-2.07 (m, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 161.2 (NCO), 134.5 (qC_{arom}), 133.6 (qC_{arom}), 132.2, 129.5, 128.5, 127.8 (C_{arom}), 125.6 (qC_{arom}), 125.4 (qC_{arom}), 121.9, 121.8, 121.3 (C_{arom}), 119.2 (qC_{arom}), 42.8 (CH_2), 28.2 (CH_2), 20.8 (CH_2).

5-Methyl-2-(trifluoromethyl)phenanthridin-6(5*H*)-one 16c.[81]



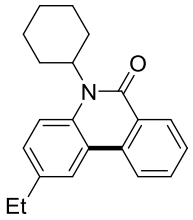
The general procedure for direct arylation was followed, and compound **16c** was obtained as a white powder (202.3 mg, 73%).

m.p. 175-177 °C ($CHCl_3$) (Lit.[81] 133-134 ºC).

^{1}H NMR ($CDCl_3$) δ 8.56 (dd, J = 8.0, 1.3 Hz, 1H, H_{arom}), 8.51 (bs, 1H, H_{arom}), 8.29 (d, J = 8.1 Hz, 1H, H_{arom}), 7.80 (m, 2H, H_{arom}), 7.65 (td, J = 7.6, 1.0 Hz, 1H, H_{arom}), 7.50 (d, J = 8.7 Hz, 1H, H_{arom}), 3.84 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 161.6 (NCO), 140.3 (qC_{arom}), 132.9 (C_{arom}), 132.6 (qC_{arom}), 129.1, 128.9, 126.0 (C_{arom}), 126.0 (q, $J_{C\text{-}F}$ = 294 Hz, CF_3), 125.8 (qC_{arom}), 121.7, 120.7 (C_{arom}), 119.3 (qC_{arom}), 115.4 (C_{arom}), 30.2 (NCH_3).

5-Cyclohexyl-2-ethylphenanthridin-6(*5H*)-one 16d.



The general procedure for direct arylation was followed, and compound **16d** was obtained a as colorless oil (262.4 mg, 86%).

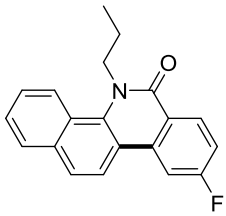
^{1}H NMR ($CDCl_3$) δ 8.51 (d, J = 7.9 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H, H_{arom}), 8.08 (d, J = 1.2 Hz, 1H, H_{arom}), 7.71 (t, J = 7.5 Hz, 1H, H_{arom}), 7.55 (m, 2H, H_{arom}), 7.33 (dd, J = 8.7, 1.6 Hz, 1H, H_{arom}), 4.84 (bs, 1H, CH), 2.78 (t, J = 7.6 Hz, 2H, CH_2CH_3), 2.70 (m, 2H, CH_2), 1.84 (m, 5H, CH_2), 1.60-1.38 (m, 3H, CH_2), 1.32 (t, J = 7.6 Hz, 3H, CH_2CH_3).

^{13}C NMR ($CDCl_3$) δ 162.0 (NCO), 137.9 (qC_{arom}), 135.9 (qC_{arom}), 133.6 (qC_{arom}), 132.1, 128.8, 128.6, 127.7 (C_{arom}), 126.7 (qC_{arom}), 122.5, 121.3 (C_{arom}), 120.0 (qC_{arom}), 115.8 (qC), 58.1 (CH), 29.1, 28.3, 26.8, 25.6 (CH_2), 15.8 (CH_3).

IR (ATR) υ_{max} 2966, 2930, 2851, 1651, 1601 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{21}H_{23}NO$: 305.1780; found: 305.1783.

9-Fluoro-5-propylbenzo[*c*]phenanthridin-6(5*H*)-one 16e.



The general procedure for direct arylation was followed, and compound **16e** was obtained as a white powder (238.0 mg, 78%).

m.p. 125-128 °C (EtOAc).

^{1}H NMR ($CDCl_3$) δ 8.31-8.19 (m, 3H, H_{arom}), 8.19-8.12 (m, 1H, H_{arom}), 7.94-7.86 (m, 1H, H_{arom}), 7.73 (d, J = 8.7 Hz, 1H, H_{arom}), 7.59-7.44 (m, 3H,

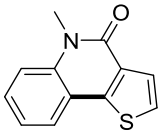
H_{arom}), 4.62-4.45 (m, 2H, CH_2), 2.03-1.83 (m, 2H, CH_2), 0.80 (t, J = 7.4 Hz, 3H, CH_2CH_3).

^{13}C NMR ($CDCl_3$) δ 167.9 (NCO), 162.2 (d, $J_{C\text{-}F}$ = 249 Hz, CF), 135.7, 134.2, 130.3 (qC_{arom}), 128.6 (C_{arom}), 127.8 (qC_{arom}, $J_{C\text{-}F}$ = 7 Hz), 126.4, 125.3, (C_{arom}), 124.7 (Carom, $J_{C\text{-}F}$ = 8 Hz), 124.6 (qC_{arom}), 124.3, 121.0 (C_{arom}, $J_{C\text{-}F}$ = 23 Hz), 119.9 (C_{arom}), 117.2 (qC_{arom}), 113.9 (C_{arom}, $J_{C\text{-}F}$ = 23 Hz), 53.9 (NCH_2), 22.1 (CH_2), 11.1 (CH_3).

IR (ATR) υ_{max} 3059, 2962, 2926, 2872, 1644, 1612 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{20}H_{16}FNO$: 305.1216; found: 305.1214.

5-Methylthieno[3,2-*c*]quinolin-4(5*H*)-one 16f.[84]



The general procedure for direct arylation was followed, and compound **16f** was obtained as a yellow powder (187.1 mg, 87%).

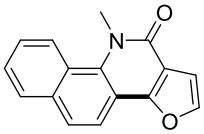
m.p. 129-131 °C (EtOAc) (Lit.[84] 141-143 °C (diisopropyl ether)).

^{1}H NMR ($CDCl_3$) δ 7.77 (dd, J = 7.8, 1.2 Hz, 1H, H_{arom}), 7.70 (d, J = 5.3 Hz, 1H, H_{arom}), 7.53-7.45 (t, J = 7.5 Hz, 1H, H_{arom}), 7.39 (s, 1H, H_{arom}), 7.33 (d, J = 5.3 Hz, 1H, H_{arom}), 7.27-7.19 (t, J = 7.2 Hz, 1H, H_{arom}), 3.76 (s, 3H, NCH_3).

[84] E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, C. Zoni *Eur. J. Org. Chem*. **2005**, 2091.

^{13}C NMR ($CDCl_3$) δ 158.7 (NCO), 145.3, 137.4, 130.8 (qC_{arom}), 129.3, 126.5, 124.8, 124.2, 122.4 (C_{arom}), 118.0 (qC_{arom}), 115.1 (C_{arom}), 29.4 (NCH_3).

10-Methylbenzo[*h*]furo[3,2-*c*]quinolin-11(10*H*)-one 16g.



The general procedure for direct arylation was followed, and compound **16g** was obtained as yellow oil (244.1 mg, 98%).

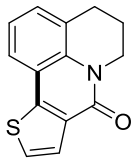
^{1}H NMR ($CDCl_3$) δ 8.52-8.45 (m, 1H, H_{arom}), 8.02 (d, J = 8.5 Hz, 1H, H_{arom}), 7.96-7.91 (m, 1H, H_{arom}), 7.74 (d, J = 8.5 Hz, 1H, H_{arom}), 7.68 (d, J = 2.0 Hz, 1H, H_{arom}), 7.60-7.55 (m, 2H, H_{arom}), 7.12 (d, J = 2.0 Hz, 1H, H_{arom}), 4.13 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 161.8 (NCO), 156.2 (qC_{arom}), 144.3 (qC_{arom}), 136.9 (qC_{arom}), 135.1 (qC_{arom}), 129.1, 126.7, 125.5, 125.4, 124.6, 124.5, 118.1 (C_{arom}), 115.0 (qC_{arom}), 110.8 (qC_{arom}), 108.1 (C_{arom}), 40.5 (NCH_3).

IR (ATR) υ_{max} 1648, 1609, 1278, 1260, 751 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{16}H_{11}NO_2$: 249.0790, found: 249.0791.

5,6-Dihydro-4*H*,8*H*-pyrido[3,2,1-*ij*]thieno[3,2-*c*]quinolin-8-one 16h.



The general procedure for direct arylation was followed, and compound **16h** was obtained as a yellow powder (209.7 mg, 87%).

m.p. 78-81 °C (EtOAc).

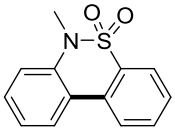
^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 5.3 Hz, 1H, H_{arom}), 7.66 (d, J = 7.7 Hz, 1H, H_{arom}), 7.35 (d, J = 5.2 Hz, 1H, H_{arom}), 7.27 (d, J = 6.6 Hz, 1H, H_{arom}), 7.15 (t, J = 7.6 Hz, 1H, H_{arom}), 4.30 (t, J = 6.1 Hz, 2H, CH_2), 3.01 (t, J = 6.1 Hz, 2H, CH_2), 2.21-2.06 (m, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 158.4 (NCO), 145.4 (qC_{arom}), 134.1 (qC_{arom}), 130.6 (qC_{arom}), 128.9, 126.3 (C_{arom}), 126.0 (qC_{arom}), 124.7, 122.2, 122.0 (C_{arom}), 117.9 (qC_{arom}), 42.3 (CH_2), 28.1 (CH_2), 20.9 (CH_2).

IR (ATR) υ_{max} 3080, 2934, 2876, 1630, , 1321, 1293, 736, 707 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_{213}NOS$: 241.0561, found: 241.0562.

6-Methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 16i.[54]



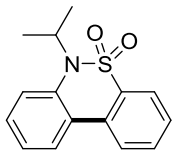
The general procedure for direct arylation was followed, and compound **16i** was obtained as yellowish powder (191.1 mg, 78%).

m.p. 85-87 °C ($CHCl_3$)[54].

^{1}H NMR ($CDCl_3$) δ 7.99 (dd, J = 13.1, 8.2 Hz, 1H, H_{arom}), 7.75-7.66 (m, 1H, H_{arom}), 7.53 (ddd, J = 15.6, 11.6, 4.5 Hz, 1H, H_{arom}), 7.38-7.28 (m, 1H, H_{arom}), 3.45 (s, 3H, NCH_3).

^{13}C-NMR ($CDCl_3$) δ 139.5, 134.2 (qC_{arom}), 132.4, 130.4 (C_{arom}), 129.1 (qC_{arom}), 128.2, 125.5, 125.4, 124.7 (C_{arom}), 124.0 (qC_{arom}), 122.5, 119.4 (C_{arom}), 32.7 (NCH_3).

6-Isopropyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide 16j.



The general procedure for direct arylation was followed, and compound **16j** was obtained as a white powder (237.6 mg, 87%).

m.p. 89-91 °C (EtOAc).

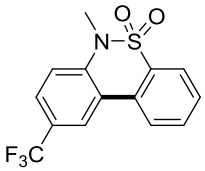
^{1}H NMR ($CDCl_3$) δ 8.03-7.81 (m, 3H, H_{arom}), 7.68 (td, J = 7.8, 1.4 Hz, 1H, H_{arom}), 7.55 (td, J = 7.6, 1.1 Hz, 1H, H_{arom}), 7.48-7.40 (m, 3H, H_{arom}), 4.44 (hept, J = 6.8 Hz, 1H, CH), 1.09 (d, J = 6.8 Hz, 6H, CH_3).

^{13}C NMR ($CDCl_3$) δ 137.2, 136.6, 133.2 (qC_{arom}), 132.4, 129.6 (C_{arom}), 128.8 (qC_{arom}), 128.5, 127.4, 127.2, 125.7, 125.6 (C_{arom}), 123.1 (qC_{arom}), 54.9 (CH), 21.69 (CH_3).

IR (ATR) υ_{max} 3059, 2976, 1336, 1260, 1181, 732 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{15}NO_2S$: 273.0824, found: 273.0824.

6-Methyl-9-(trifluoromethyl)-6*H*-dibenzo[*c*,*e*][1,2]thiazine-5,5-dioxide 16k.



The general procedure for direct arylation was followed and compound **16k** was obtained as a yellowish oil purified by C18 reverse phase column chromatography, CH_3CN: H_2O (7:3) (219.1 mg, 70%).

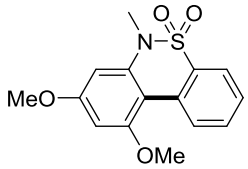
^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1H, H_{arom}), 8.13-7.92 (m, 2H, H_{arom}), 7.82-7.75 (m, 2H, H_{arom}), 7.69-7.61 (m, 1H, H_{arom}), 7.39 (d, J = 8.5 Hz, 1H, H_{arom}), 3.53 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 141.9, 134.4 (qC_{arom}), 132.8 (C_{arom}), 131.2 (qC_{arom}), 129.1, (C_{arom}), 127.7 (qC_{arom}), 127.0, 126.3, 125.6 (C_{arom}), 125.8 (q, $J_{C\text{-}F}$ = 294 Hz, CF_3), 123.8 (qC_{arom}), 122.7, 118.8 (C_{arom}), 31.9 (NCH_3).

IR (ATR) υ_{max} 1336, 1267, 1167, 1124, 736 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_{10}F_3NO_2S$: 313.0384, found: 313.0382.

8,10-Dimethoxy-6-methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine-5,5-dioxide 16l.



The general procedure for direct arylation was followed, and compound **16l** was obtained as white prisms (265.4 mg, 87%).

m.p. 96-98 °C (EtOAc).

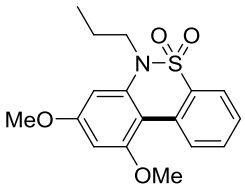
^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 8.2 Hz, 1H, H_{arom}), 7.94 (d, J = 7.8 Hz, 1H, H_{arom}), 7.59 (t, J = 7.8 Hz, 1H, H_{arom}), 7.43 (t, J = 7.6 Hz, 1H, H_{arom}), 6.46 (bs, 2H, H_{arom}), 3.92 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.35 (s, 3H, NCH_3).

^{13}C NMR ($CDCl_3$) δ 161.3, 159.2, 141.9 , 133.2 (qC_{arom}), 131.5 (C_{arom}), 131.0 (qC_{arom}), 129.0, 126.5, 121.9 (C_{arom}), 107.7 (qC_{arom}), 97.1, 95.8 (C_{arom}), 55.9 (OCH_3), 55.5 (OCH_3), 33.3 (NCH_3).

IR (ATR) υ_{max} 1609, 1576, 1328, 1149, 1041 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{15}H_{15}NO_4S$: 305.0722, found: 305.0723.

8,10-Dimethoxy-6-propyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 16m.



The general procedure for direct arylation was followed, and compound **16m** was obtained as colorless oil (286.5 mg, 86%).

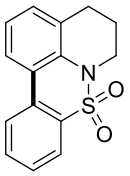
^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 8.2 Hz, 1H, H_{arom}), 7.93 (dd, J = 7.8, 1.2 Hz, 1H, H_{arom}), 7.65-7.51 (m, 1H, H_{arom}), 7.46 (dd, J = 10.9, 4.2 Hz, 1H, H_{arom}), 6.54 (d, J = 2.3 Hz, 1H, H_{arom}), 6.49 (d, J = 2.3 Hz, 1H, H_{arom}), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.78 (t, J = 7.8 Hz, 2H, NCH_2), 1.53 (tq, J = 7.8, 7.3 Hz, 2H, CH_2), 0.74 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 160.8, 159.1, 140.6, 134.3 (qC_{arom}), 131.3 (C_{arom}), 131.0 (qC_{arom}), 128.9, 126.3, 122.0 (C_{arom}), 109.0 (qC_{arom}), 99.0, 96.1 (C_{arom}), 55.8 (OCH_3), 55.6 (OCH_3), 50.4 (CH_2), 21.5 (CH_2), 11.0 (CH_3).

IR (ATR) υ_{max} 2965, 2940, 2876, 2840, 1609, 1580, 1461, 1328, 1178, 1145, 1051, 826, 754 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{17}H_{19}NO_4S$: 333.1035, found: 333.1037.

5,6-Dihydro-4*H*-benzo[5,6][1,2]thiazino[4,3,2-*ij*]quinoline-8,8-dioxide 16n.



The general procedure for direct arylation was followed, and compound **16n** was obtained as a yellow powder (233.1 mg, 86%).

m.p. 103-105 °C (EtOAc).

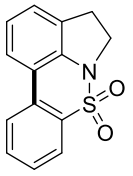
^{1}H NMR ($CDCl_3$) δ 8.01 (dd, J = 7.8, 1.0 Hz, 1H, H_{arom}), 7.95 (d, J = 8.0 Hz, 1H, H_{arom}), 7.85 (dd, J = 7.7, 1.0 Hz, 1H, H_{arom}), 7.69 (ddd, J = 8.9, 7.8, 1.4 Hz, 1H, H_{arom}), 7.54 (td, J = 7.7, 1.0 Hz, 1H, H_{arom}), 7.25-7.22 (m, 1H, H_{arom}), 7.18 (dd, J = 9.6, 5.7 Hz, 1H, H_{arom}), 4.10-3.91 (m, 2H, CH_2), 2.95 (t, J = 6.3 Hz, 2H, CH_2), 2.24-1.96 (m, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 134.7, 133.9, 132.4 (qC_{arom}), 132.3, 130.6, 127.9 (C_{arom}), 127.8 (qC_{arom}), 125.4, 123.5, 123.0, 122.5, 121.8 (C_{arom}), 41.7 (CH_2), 27.4 (CH_2), 21.8 (CH_2).

IR (ATR) υ_{max} 2951, 2919, 2843, 1321, 1271, 1147, 757 cm^{-1}.

HRMS (*m/z*)$[M]^+$ calc. for $C_{15}H_{13}NO_2S$: 271.0667, found: 271.0669.

4,5-Dihydrobenzo[5,6][1,2]thiazino[4,3,2-*hi*]índole-7,7-dioxide 16o.[82]



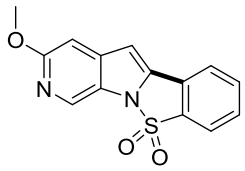
The general procedure for direct arylation was followed, and compound **16o** was obtained as a white powder (192.8 mg, 75%).

m.p. 115-117 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.11 (dd, J = 7.9, 1.0 Hz, 1H, H_{arom}), 7.97 (d, J = 7.9 Hz, 1H, H_{arom}), 7.82-7.61 (m, 2H, H_{arom}), 7.53 (m, 1H, H_{arom}), 7.35-7.19 (m, 1H, H_{arom}), 7.15 (t, J = 7.6 Hz, 1H, H_{arom}), 4.28 (t, J = 8.5 Hz, 2H, CH_2), 3.33 (t, J = 8.5 Hz, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 142.1, 133.0 (qC_{arom}), 132.8 (C_{arom}), 132.4, 131.1 (qC_{arom}), 128.3, 125.9, 124.0, 123.5, 121.8 (C_{arom}), 118.2 (qC_{arom}), 44.7 (CH_2), 28.3 (CH_2).

3-Methoxybenzo[4',5']isothiazolo[2',3':1,5]pyrrolo[2,3-*c*]pyridine 10,10-dioxide 16p.



The general procedure for direct arylation was followed, and compound **16p** was obtained as a white powder (197.4 mg, 69%).

m.p. >200°C (EtOAc).

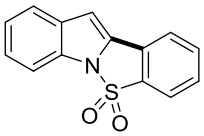
^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H, H_{arom}), 7.88 (d, J = 7.8 Hz, 1H, H_{arom}), 7.79 (d, J = 7.6 Hz, 1H, H_{arom}), 7.72 (td, J = 7.6, 1.1 Hz, 1H, H_{arom}), 7.61 (td, J = 7.6, 1.2 Hz, 1H, H_{arom}), 6.91 (d, J = 0.9 Hz, 1H, H_{arom}), 6.74 (s, 1H, H_{arom}), 3.99 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$) δ 160.4, 142.7, 138.8 , 137.9 (qC_{arom}), 134.2, 130.6, 130.2 (C_{arom}), 126.9, 126.3 (qC_{arom}), 123.3, 122.7, 101.2, 99.3 (C_{arom}), 54.1 (OCH_3).

IR (ATR) υ_{max} 2951, 2926, 2857, 1472, 1457, 1407, 1324, 1253, 1235, 1185 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_{10}N_2O_3S$: 297.0460, found: 297.0463.

Benzo[4,5]isothiazolo[2,3-*a*]indole 5,5-dioxide 16q.



The general procedure for direct arylation was followed, and compound **16q** was obtained as yellow powder (227.3 mg, 89%).

m.p. >200 °C (EtOAc).

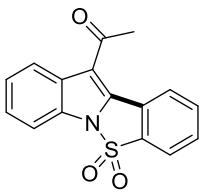
^{1}H-NMR ($CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 1H, H_{arom}), 7.72 (m, 2H, H_{arom}), 7.68-7.58 (m, 2H, H_{arom}), 7.50 (t, J = 7.2 Hz, 1H, H_{arom}), 7.38 (t, J = 7.3 Hz, 1H, H_{arom}), 7.25 (t, J = 8.9 Hz, 1H, H_{arom}), 6.83 (s, 1H, H_{arom}).

^{13}C-NMR ($CDCl_3$) δ 138.3 (qC_{arom}), 134.0 (C_{arom}), 133.1, 133.0, 132.8 (qC_{arom}), 129.3 (C_{arom}), 127.7(qC_{arom}), 125.9, 123.5, 122.6, 122.5, 122.4, 111.8, 101.0 (C_{arom}).

IR (ATR) υ_{max} 2922, 2851, 1601, 1465, 1454, 1436, 1321, 1287, 1156, 732 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{14}H_9NO_2S$: 255.0423, found: 255.0427.

1-(5,5-Dioxidobenzo[4,5]isothiazolo[2,3-*a*]indol-11-yl)ethan-1-one 16r.



The general procedure for direct arylation was followed, and compound **16r** was obtained as a white powder (142.6 mg, 48%).

m.p. 169-171 °C (EtOAc).

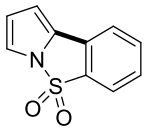
^{1}H NMR ($CDCl_3$) δ 9.04 (d, J = 8.0 Hz, 1H, H_{arom}), 7.97 (d, J = 7.5 Hz, 1H, H_{arom}), 7.89 (d, J = 7.7 Hz, 1H, H_{arom}), 7.80 (m, 2H, H_{arom}), 7.65 (td, J = 7.6, 1.0 Hz, 1H, H_{arom}), 7.52-7.41 (m, 2H, H_{arom}), 2.84 (s, 3H, $COCH_3$).

^{13}C NMR ($CDCl_3$) δ 194.4 (CO), 138.2, 136.2 (qC_{arom}), 134.9 (C_{arom}), 131.9 (qC_{arom}), 131.2 (C_{arom}), 129.9 (qC_{arom}), 128.0, 126.4 (qC_{arom}), 126.3, 124.6, 122.3, 122.3 (C_{arom}), 117.0 (qC_{arom}), 112.2 (C_{arom}), 32.0 ($COCH_3$).

IR (ATR) υ_{max} 3102, 2994, 2951, 2855, 1673, 1547, 1457, 1436, 1347, 1267, 1181, 1041, 966, 754 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{16}H_{11}NO_3S$: 285.0334, found: 255.0341.

Benzo[*d*]pyrrolo[1,2-*b*]isothiazole 5,5-dioxide 16s.



The general procedure for direct arylation was followed, and compound **16s** was obtained as na orange powder (188.6 mg, 92%).

m.p. 98-100 °C (EtOAc).

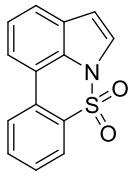
^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 7.8 Hz, 1H, H_{arom}), 7.64-7.49 (m, 2H, H_{arom}), 7.42-7.33 (m, 1H, H_{arom}), 7.15 (dd, J = 3.0, 0.9 Hz, 1H, H_{arom}), 6.48 (dd, J = 3.4, 0.9 Hz, 1H, H_{arom}), 6.42 (t, J = 3.2 Hz, 1H, H_{arom}).

^{13}C NMR ($CDCl_3$) δ 136.9 (qC_{arom}), 134.3 (C_{arom}), 129.3 (qC_{arom}), 128.1 (qC_{arom}), 127.7, 122.5, 120.9, 117.3, 116.3, 105.4 (C_{arom}).

IR (ATR) υ_{max} 3134, 2626, 2847, 1605, 1461, 1324, 1170, 1059, 1024, 747, 711 cm^{-1}.

HRMS (*m/z*): $[M]^+$ calc. for $C_{10}H_7NO_2S$: 205.0198, found: 205.0203.

4.6. Oxidation of dihydrobenzothiazinoindole 7,7-dioxide 16t.[85]



Method A. Dichloromethane (5 mL) was added to a mixture of 4,5-dihydrobenzo[5,6][1,2]thiazino[4,3,2-*hi*]indole 7,7-dioxide **16o** (12 mg, 0.05 mmol) and activated manganese dioxide (100 mg, 1.15 mmol) at room temperature in a medium-pressure glass reactor equipped with a magnetic stirrer. The reaction mixture was stirred at room temperature for 7 days, , under 7-bar overpressure of O_2. The resulting mixture was filtered through a short path of celite and the solvent evaporated *in vacuo* to provide a residue that was purified by flash chromatography using hexane/ethyl acetate (7:3) as eluent. Target benzothiazinoindole dioxide **3t** (9.8 mg, 77%) was obtained as a pink powder.

m.p. 141-143 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H, H_{arom}), 8.20 (d, J = 8.0 Hz, 1H, H_{arom}), 7.98 (d, J = 7.7 Hz, 1H, H_{arom}), 7.83-7.72 (m, 3H, H_{arom}), 7.63 (t, J = 7.7 Hz, 1H, H_{arom}), 7.48 (t, J = 7.8 Hz, 1H, H_{arom}), 6.96 (d, J = 3.5 Hz, 1H, H_{arom}).

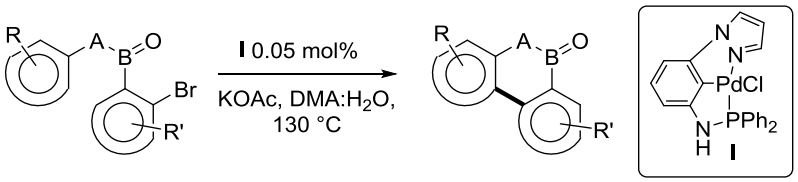
[85] R. V. S. Nirogi, S. V. Shreekrishna, K. R. Sastri, D. A. Dinkar, K. Prabhakar, J. Venkateswarlu WO 2006095360.

^{13}C NMR ($CDCl_3$) δ 134.1 (qC_{arom}), 133.5 (qC_{arom}), 133.1, 131.9 (qC_{arom}), 129.8 (qC_{arom}), 128.6, 124.4, 124.2, 124.1, 123.2, 122.6, 118.9 (C_{arom}), 116.7 (qC_{arom}), 111.1 (C_{arom}).

Method B. Toluene (10 mL) was added to a mixture of 4,5-dihydrobenzo[5,6][1,2]thiazino[4,3,2-*hi*]indole 7,7-dioxide **16o** (50 mg, 0.2 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 309 mg, 1.4 mmol) at room temperature in a round bottom reaction flask equipped with a magnetic stirrer under argon. This mixture was heated to 110 ºC for 24 h, allowed to cool, diluted with ethyl acetate (10 mL) and washed with Na_2SO_3 (3 x 5 mL of a saturated solution in water), $NaHCO_3$ (3 x 5 mL of a saturated solution in water), and NaCl (3 x 5 mL of a saturated solution in water). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oily residue which was was purified by flash chromatography using hexane:ethyl acetate (7:3) as eluent. Target benzothiazinoindole dioxide **16t** (36.2 mg, 73%) was obtained as a pink powder.

5. CONCLUSIONS

- Phenanthridinones, biaryl sultams and related heterocyclic derivatives can be successfully obtained by reaction of *N*-arylbenzanilides or *N*-arylsulfonamides in the presence of low amounts (0.05 mol%) of palladium pincer complex **I**.



- TEM and conversion *vs* time curve suggest the intermediacy of homogeneous catalysts. However, the participation of heterogeneous species cannot be ruled out, as it can be concluded from poisoning assays carried out.
- The developed method offers also a benefit regarding the avoidance of scavenger resins or further purification steps in order to suppress metal contamination in the products.

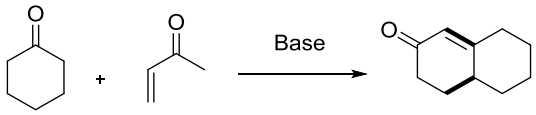
III

Palladium-catalyzed cycloisomerization reactions

INTRODUCTION

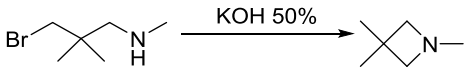
1.1. Cycloisomerization

The synthesis of ring-systems is essential in the art of organic synthesis. Cyclic compounds abound in chemistry, from strained three membered rings to macrocyclic molecules. A common synthetic challenge is the creation of a ring within a certain target compound. In the simplest analysis, a chemist has two possible approaches, an annulation or a cyclization strategy. When an annulation, two separate reactive entities are combined to create a ring by the formation of two new bonds (Scheme 3.1).



Scheme 3.1. Example of an annulation.

In contrast, a cyclization involves the formation of a ring by the reaction of two ends of a linear sequence (Scheme 3.2). [1]



Scheme 3.2. Example of a cyclization reaction.

Cycloisomerisation reactions comprise a particularly efficient subset of the latter class, as these reactions occur with quantitative atom economy. It is

[1]a) A. D. McNaught A. Wilkinson in *IUPAC, Compendium of Chemical Terminology*, *2nd ed*. Blackwell Science, **1997**; b) *Handbook of Cyclization Reactions*, (Ed.: S, Ma), WILEY-VCH, Weinheim, **2010**.

defined as rearrangement of polyunsaturated substrates by which C–C bonds are formed and at least one degree of unsaturation is consumed to make a cyclic product. Moreover, nothing is wasted in a cycloisomerization reaction; all the atoms in the starting materials are present in the products. Such rearrangement has been demonstrated to provide atom-economy, efficient approaches to cyclic or bicyclic compounds from readily available starting materials. [2]

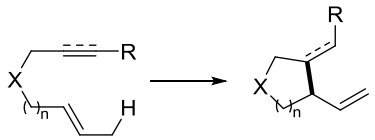
Within the compilation of chemical reactions there exist a number of well-known, historical cyclization reactions that are not usually classified as cycloisomerizations. Reactions such as the intramolecular Michael, Stetter and Diels-Alder reactions belong in this category.

For many, the archetypal cycloisomerization reaction is the intramolecular Alder-ene reaction of enynes, a process where a 1,6- or 1,7-enyne or diene displaying an allylic hydrogen rearranges into a vinyl-substituted cyclic moiety under transition metal catalysis (Scheme 3.3). This reaction has been known for over 60 years in its uncatalyzed, thermal form.[3] The development of appropriate catalytic system was reported initially by Trost,[4] who first noticed the process during investigations on palladium catalyzed alkylation reactions.

[2] Atom economy refers to the conversion efficiency of a chemical process in terms of the atoms involved. See: a) B. M. Trost *Acc. Chem. Res*. **2002**, *35*, 695; b) B. M. Trost *Angew. Chem. Int. Ed.* **1995**, *34*, 259; c) B. M. Trost *Science* **1991**, *254*, 1471; d) M. Bartlett *Chem.New Zealand* **2012**, 11.

[3] K. Alder, F. Pascher, A. Schmitz *Ber. Dtsch. Chem. Ges. B.* **1943**, *76*, 27.

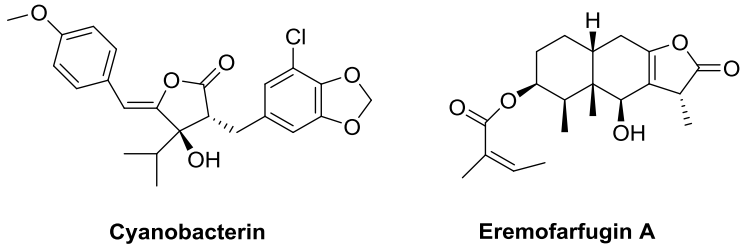
[4] a) B. M. Trost, M. Lautens *J. Am. Chem. Soc*. **1985**, *107*,1781; b) B. M. Trost *Acc. Chem. Res*. **1990**, *23*, 34.



Scheme 3.3. Alder-ene cyclization.

1.2. Cycloisomerization of alkynoic acids

Among the many types of cycloisomerization, it is worth noting the transition-metal catalyzed intramolecular addition of a carboxylic acid to a terminal alkyne. This is an important transformation in organic synthesis, as it provides access to the γ- alkylidene lactone motif, which is present in a vast number of biologically active natural products, such as cyanobacterin[5] and eremofarfugin A[6] shown in Figure 3.1.



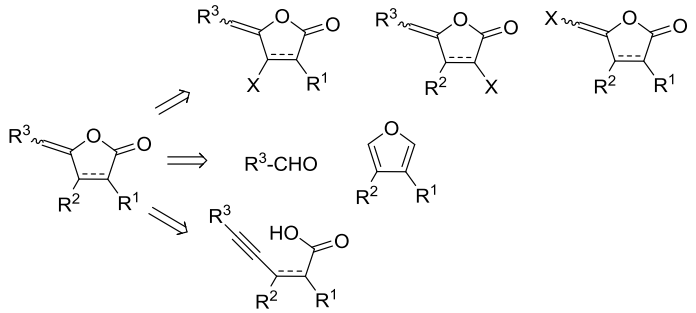
Cyanobacterin **Eremofarfugin A**

Figure 3.1. Biologically active natural products showing γ- alkylidene lactone motif.

[5] a) C. P. Mason, K. R. Edwards, R. E. Carlson, J. Pignatello, F. K. Gleason, J. M. Wood *Science* **1982**, *215*, 400; b) Y. Haga, M. Okazaki, Y. Shuto *Biosci. Biotechnol. Biochem.* **2003**, *67*, 2183; c) R. Raju, R. Garcia, R. Müller *J. Antibiot.* **2014**, *67*, 725.

[6] a) M. Tori, Y. Shiotani, M. Tanaka, K. Nakashima, M. Sono *Tetrahedron Lett.* **2000**, *41*, 1797; b) M. Tori , K. Otose, H. Fukuyama, J. Murata, Y. Shiotani, S. Takaoka, K. Nakashima, M. Sono, M. Tanaka *Tetrahedron* **2010**, *66*, 5235.

The preparation of enol lactones has long been an important target and continues to be actively pursued. Due to these structural and biological interesting properties, several routes towards γ- or δ-alkylidene lactones have been developed over the years.[7] These routes could be classified into three main strategies (Scheme 3.4), i) coupling reactions with already formed lactones,[8] ii) condensation reactions[9] and iii) electrophilic lactonization, such as halolactonization and cycloisomerization.[10]



Scheme 3.4. Main routes for the access to γ-alkylidene lactones.

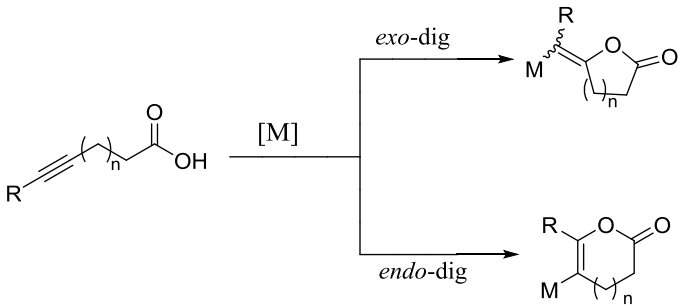
[7] a) D. M. Knight *Contemp. Org. Synth.* **1994**, *1*, 287; b) I. J. Collins *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 1377; c) R. Brückner *Curr. Org. Chem.* **2001**, *5*, 679; d) M. V. N. De Souza *Mini-Rev. Org. Chem.* **2005**, *2*, 546; e) .-M. Weibel, A. Blanc, P. Pale *Chem. Rev.* **2008**, *108*, 3149; f) M. Alvarez- Corral, M. Muñoz-Dorado, I. Rodriguez-Garcia *Chem. Rev.* **2008**, *108*, 3174; g) *Natural Lactones and Lactams*, (Ed.: T. Janecki), Wiley-VCH, Weinheim, **2014**.

[8] a) J. Castulik, C. Mazal *Tetrahedron Lett.* **2000**, *41*, 2741; b) F. Bellina, C. Anselmi, R. Rossi *Tetrahedron Lett.* **2002**, *43*, 2023; c) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner *J. Org. Chem.* **2004**, *69*, 3943; d) E. J. Tollefson, D. D. Dawson, C. A. Osborne, E. R. Jarvo *J. Am. Chem. Soc.* **2014**, *136*, 14951.

[9] a) K. Y. Lee, J. M. Kim, J. N. Kim *Synlett* **2003**, 357; b) C. Haase, P. Langer *Synlett* **2005**, 453; c) *Biotransformations in Organic Chemistry, 6th ed.*,(Ed.: K.Faber), Springer-Velarg, Heidelberg, **2011**.

[10] a) Y. I. Gevaza, V. I. Staninets *Chem. Heterocycl. Compd.* **1988**, *24*, 1073 b) J.-C. Harmange, B. Figadère *Tetrahedron: Asymmetry* **1993**, *4*, 1711; c) A. Nagendiran, O. Verho, C. Haller, E. V. Johston, J.-E. Bäckvall *J. Org.Chem.* **2014**, *79*, 1399.

In this regard, recent progress has been made in the cycloisomerization of alkynoic acids. To obtain the desired cyclic lactones arising from *exo*-dig ring closure instead of the isomeric *endo*-dig products (Scheme 3.5), control of regioselectivity in the cyclization step is required. [11]



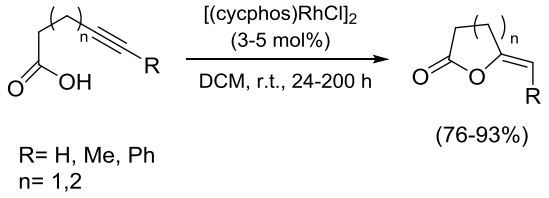
Scheme 3.5. *Exo*-dig or *endo*-dig cycloisomerization.

Generally, this selectivity can be controlled by the choice of a metal catalyst, as well as by a careful design of the reaction conditions. A number of transition metal complexes (Rh, Hg, Ru, Ag, Au, Cu, Pd) have been shown to catalyze these transformations with variable degrees of regio- and stereoselectivity.[12]

[11] a) F. Alonso, I. P. Beletskaya, M. Yus *Chem. Rev.* **2004**, *104*, 3079; b) I. Nakamura, Y. Yamamoto *Chem. Rev.* **2004**, *104*, 2127; c) M. Beller, J. Seayad, A. Tillack, H. Jiao *Angew. Chem. Int. Ed.* **2004**, *43*, 3368; d) K. Gilmore, I. V. Alabugin *Chem. Rev.* **2011**, *111*, 6513.

[12] For recent selected examples, see: a) T. L. Mindt, R. Schibli *J. Org. Chem*. **2007**, *72*, 10247; b) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genet, V. Michelet *J. Am. Chem. Soc*. **2006**, *128*, 3112; c) H. Harkat, J.-M. Weibel, P. Pale *Tetrahedron Lett.* **2006**, *47*, 6273; d) H. Imagawa, Y. Fujikawa, A. Tsuchihiro, A. Kinoshita, T. Yoshinaga, H. Takao, M. Nishizawa *Synlett* **2006**, 639; e) I. Takei, Y. Wakebe, K. Suzuki, Y. Enta, T. Suzuki, Y. Mizobe, M. Hidai *Organometallics* **2003**, *22*, 4639; f) M. Jimenez-Tenorio, M. C. Puerta, P. Valerga, F. J. Moreno-

Rhodium was one of the first metals used for this transformation. To the best of our knowledge, Marder *et al.* are the only ones who used it to catalyze the addition of carboxylic acids to alkynes and applied more specifically to the cyclization of alkynoic acids to alkylidene lactones.[13] Thus, high yield lactonizations were accomplished in the presence of the rhodium(I) complex $[(cycphos)RhCl]_2$ (cycphos = 1,2-bis(dicyclohexylphosphino)ethane) at room temperature in dichloromethane (Scheme 3.6).



Scheme 3.6. Lactonizations accomplished in the presence of $[(cycphos)RhCl]_2$.

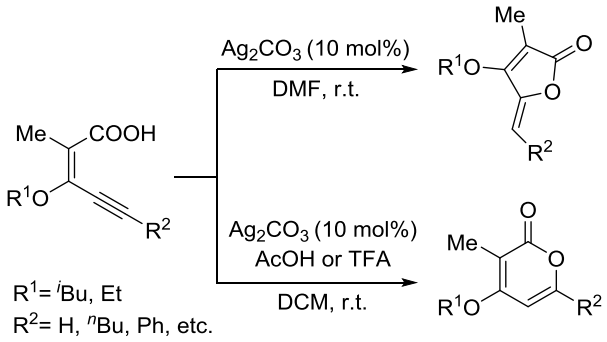
Silver and, more recently, gold have proved to catalyze effectively such cyclizations with even better regioselectivity[7f,14]. For instance, Shindo *et al.* described the remarkable switching effect of Brønsted acids in the

Dorado, F. M. Guerra, G. M. Massanet *Chem. Commun.* **2001**, 2324; g) R. Nolla-Saltiel, E. Robles-Marin, S. Porcel *Tetrahedron Lett.* **2014**, *55*, 4484.

[13] a) D. M. T. Chan, T. B. Marder, D. Milstein, N. J. Taylor *J. Am. Chem. Soc*. **1987**, *109*, 6385; b) T. B. Marder, D. M. T. Chan, W. C. Fultz, J. C. Calabrese, D. Milstein *J. Chem. Soc., Chem. Commun.* **1987**, 1885.

[14] For example on use of Ag as a catalyst, see: a) M. M. Rammah, M. Othman, K. Ciamala, C. Strohmann, M. B. Rammah *Tetrahedron* **2008**, *64*, 3505; b) G. Fang, X. Bi *Chem. Soc. Rev.* **2015**, in-press DOI:10.1039/C5CS00027K; Au catalysis: c) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genet, V. Michelet *J. Am. Chem. Soc.* **2006**, *128*, 3112; d) E. Genin, P. Y. Toullec, P. Marie, S. Antoniotti, C. Brancour, J.-P. Genet, V. Michelet *Arkivoc* **2007**, *5*, 67; e) E. Marchal, P. Uriac, B. Legoin, L. Toupet *Tetrahedron* **2007**, *63*, 9979; f) P. Y. Toullec, E. Genin, S. Antoniotti, J.-P. Genet, V. Michelet *Synlett* **2008**, 707; g) K. Belger, N. Krause *Org. Biomol. Chem.* **2015**, *13*, 8556.

intramolecular cyclization of (*E*)-2-en-4-ynoic acids catalyzed by Ag_2CO_3 (Scheme 3.7).[15]



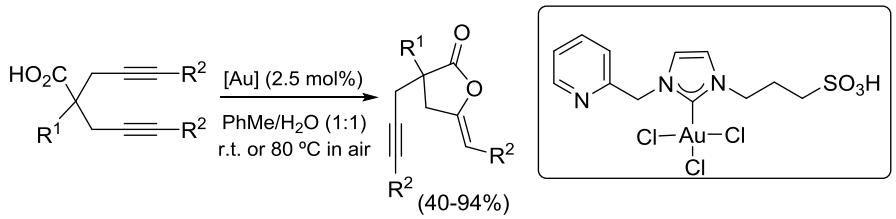
Scheme 3.7. (*E*)-2-en-4-ynoic acids catalyzed by Ag_2CO_3.

A conventional 5-*exo-dig* cyclization occurred if acid was not added, affording tetronic acids, while with 0.5 equivalents of acid, the reaction was switched to a 6-*endo-dig* cyclization, achieving 2-yrones.

In regard to gold catalysis in this area, Cadierno and co-workers synthesized a novel water-soluble Au(III)-NHC complex (Scheme 3.8) and applied it in the intramolecular cyclization of γ-alkynoic acids into enol-lactones under biphasic toluene/water conditions.[16]

[15] Y. Yamamoto, I. D. Gridnev, N. T. Patil, T. Jin *Chem. Commun*. **2009**, 5075.

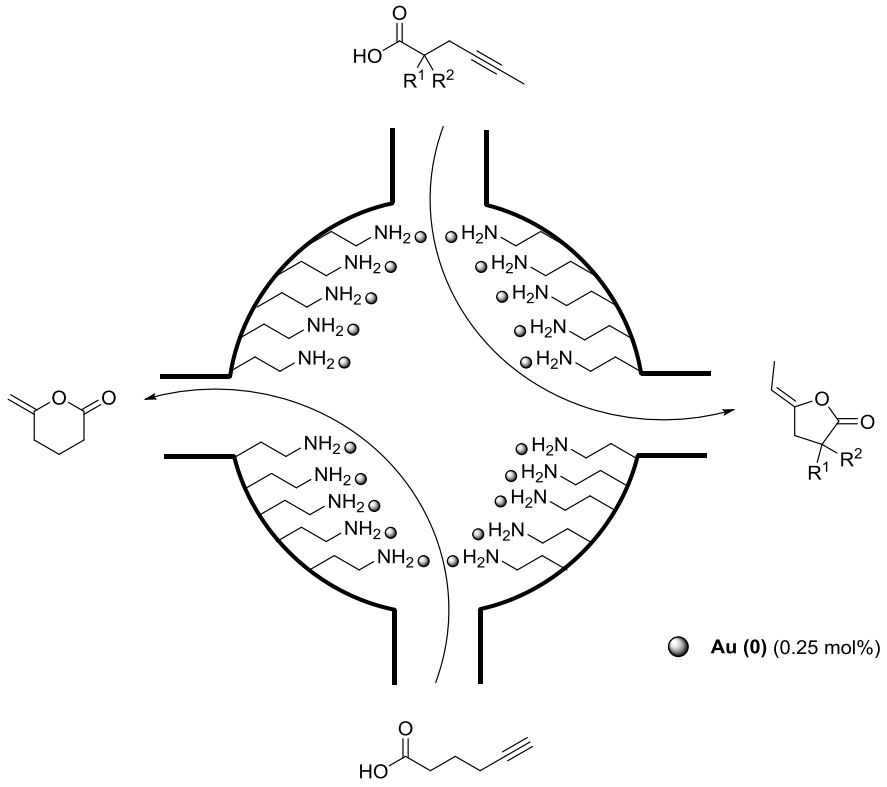
[16] E. Tomás-Mendivil, P. Y. Toullec, J. Díez, S. Conejero,V. Michelet, V. Cadierno *Org. Lett*. **2012**, *14*, 2520.



Scheme 3.8. Intramolecular cyclization of γ-alkynoic acids using an Au(III) complex.

Not only homogeneous catalysts have been used for these transformations. Heterogeneous catalysts offer the opportunity of tackle the difficulties in recycling, observed in homogeneous catalysts. An interesting example is the one reported by Bäckvall and co-workers, in which they used an heterogeneous catalyst based on Au nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Au^0-AmP-MCF). Employing this catalyst they carried out the cycloisomerization of various γ–acetylenic acids to alkylidene lactones (Scheme 3.9).[17]

[17] K. Eriksson, O. Verho, L. Nyholm, S. Oscarsson, J.-E. Bäckvall *Eur. J. Org. Chem.* **2015**, 2250.

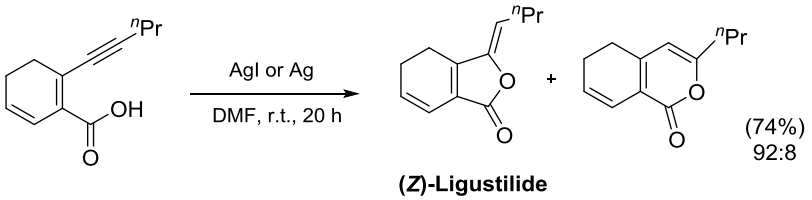


Scheme 3.9. Cycloisomerization protocol developed by Bäckvall and co-workers.

Due to the advantages of cycloisomerization, it has been applied to the synthesis of natural products. Wakamatsu and co-workers developed a high regio- and stereoselectivity process which enabled the synthesis of (*Z*)-ligustilide under very mild reaction conditions starting from the proper alkynoic acid (Scheme 3.10).[18] This natural furanone is present in an essential oil extract from *Radix Angelica sinensis*, which has broad

[18] Y. Ogawa, M. Maruno, T. Wakamatsu *Heterocycles* **1995**, *41*, 2587.

pharmaceutical applications in treating cardio-vascular diseases and ischemic brain injury.[19]



Scheme 3.10. Synthesis of (*Z*)-ligustilide *via* cycloisomerization.

1.3. Palladium in cycloisomerization of alkynoic acids

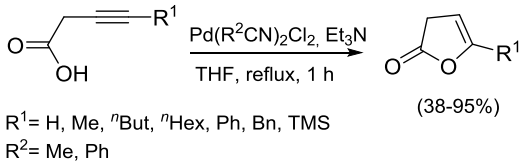
It is known that palladium catalysts are the ideal complement to ruthenium catalysts for the addition of carboxylic acids to alkynes, since the latter are exclusively used in intermolecular processes whereas the former have been mainly applied in intramolecular reactions.[20] The palladium catalyzed intermolecular addition of carboxylic acids to alkynes is restricted to very few examples. In contrast, the intramolecular versionof this reaction is a versatile tool for the direct construction of lactone rings of different size and substitution.[21] The pioneering work came from Utimoto *et al.* which

[19] W.-W. Chao**,** B.-F. Lin *Chinese Medicine* **2011**,*6*, 29.

[20] a) T. Hosokawa, S.-I. Murahashi in *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E.Negishi), Wiley, Hoboken, **2002**; b) V. Cadierno, J. Francos, J. Gimeno *Organometallics* **2011**, *30*, 852; c) *C-X bond formation, 1st ed.*, (Ed.: A. Vigalok), Springer-Verlag, Heidelber, **2010**.

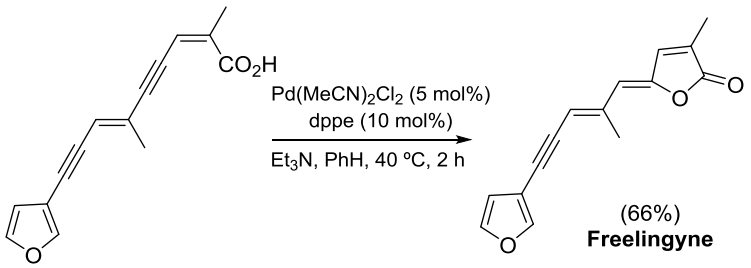
[21] For more information on the inter- and intramolecular oxypalladation of alkenes and alkynes, see: a) T. Hosokawa, S.-I. Murahashi *Heterocycles* **1992**, *33*, 1079; b) T. Hosokawa, S.-I. Murahashi *Chem. Abstr.* **1995**, *123*, 94104; c) J. Garcia-Alvarez, J. Diaz, C. Vidal *Green Chem*. **2012**, *14*, 3190.

revealed the regioselective 5-*endo-dig* cyclization of 3-alkynoic acids under the action of palladium(II) in the presence of triethylamine to afford 3-alken-4-olides in moderate to excellent yields (Scheme 3.11).[22]



Scheme 3.11. First cycloisomerization of alkynoic acidcatalyzed by palladium.

As mentioned in the previous section, several complex or natural products have been accessed by means of this protocol. For example, Katsumura *et al*. carried out successfully the lactonization of a freelingyne precursor, a sesquiterpene from *Eremophila freelingii*, which was the first isolated acetylenic terpene. Its structure represents the most unsaturated furano-sesquiterpene found in nature. The reaction had to be performed in benzene at 40 °C in the presence of dppe in order to prevent the formation of the stereoisomeric freelingyne (Scheme 3.12).[23]

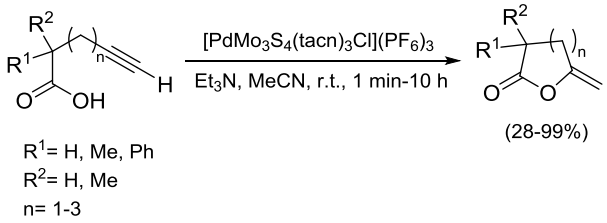


Scheme 3.12. Synthesis of freenlingyne *via* cycloisomerization.

[22] C. Lambert, K. Utimoto, H. Nozaki *Tetrahedron Lett.* **1984**, *25*, 5323.

[23] H. Mori, H. Kubo, H. Hara, S. Katsumura *Tetrahedron Lett.* **1997**, *38,* 5311.

Later, Hidai and co-workers developed a highly effective catalytic system for the cyclization of 3-, 4-, and 5-alkynoic acids to the corresponding enol lactones under very mild reaction conditions (Scheme 3.13). This system was composed of the mixed-metal sulfide cluster with a cuboidal core $[PdMo_3S_4(tacn)_3Cl](PF_6)_3$ and a small amount of triethylamine in acetonitrile. [24]



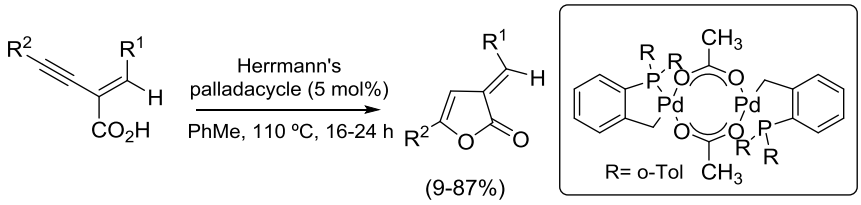
Scheme 3.13. Mixed metal-sulfide cluster used for cycloisomerization.

Most of the protocols described above require either high catalyst loadings and/or prolonged reaction times and elevated temperatures. The former is generally associated to additional purification steps to remove trace amounts of metal impurities from the final product. This can be solved by using a more sophisticated catalyst, such as palladacycles. As it has been said, these type of catalysts have high thermal stability and are easy to handle, due to their stability toward moisture and air.[25] For instance, Rossi and co-workers were one of the first groups employing palladacycles to carry out the synthesis of the alkyliden lactones depicted in Scheme 3.14. For that

[24] M. Hidai, Y. Mizobe *ACS Symp. Ser.* **1996**, *653*, 310.

[25] a) G. van Koten, M. Albrecht *Angew. Chem.Int. Ed.* **2003**, *103*, 1759; b) *Pincer and Pincer-type Complexes, 1st ed.,* (Eds.: K. J. Szabó, O. F. Wendt), Wiley-VCH, Weinheim, **2014**.

purpose, they used the palladacycle described by Herrmann *et al*. obtaining successfully the desired lactones.[26,27]



Scheme 3.14. Lactonization mediated by Herrmann's catalyst.

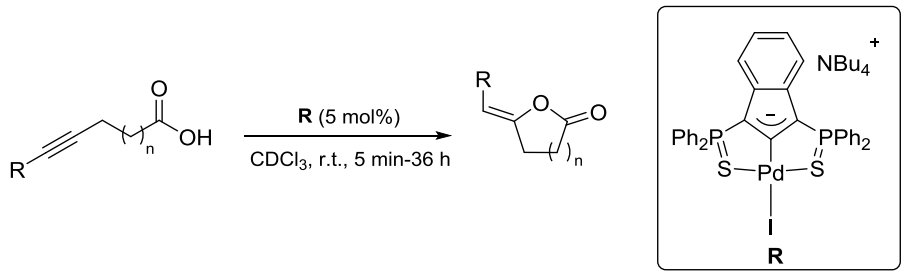
A more recent example is the one reported by Bourissou and co-workers showing the catalytic applications of an indenediide Pd complex. In this case a metal-ligand cooperation was involved. This SCS complex was able to promote the intramolecular addition of carboxylic acids to alkynes in $CDCl_3$ at room temperature (Scheme 3.15),[28] thus providing a valuable alternative to other complexes (Pd, Rh, Ru, Pt, Au) used to catalyze this transformation.[22,29]

[26] W. A. Herrmann, C. Brossner, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fisher *Angew. Chem. Int. Ed.* **1995**, *34*, 1844.

[27] R. Rossi, F. Bellina, L. Mannina *Tetrahedron Lett.* **1998**, *39*, 3017

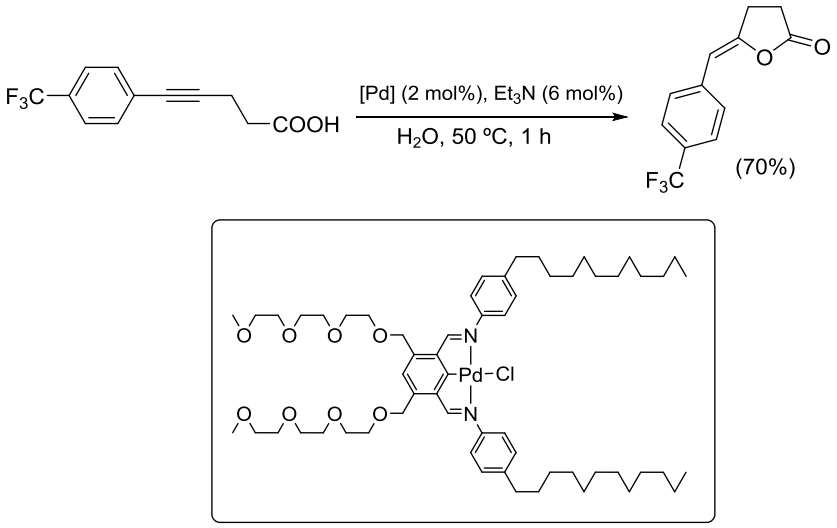
[28] N. Nebra, J. Monot, R. Shaw, B. Martin-Vaca, D. Bourissou *ACS Catal.* **2013**, *3*, 2930.

[29] a) T. Wakabayashi, Y. Ishii, K. Ishikawa, M. Hidai *Angew. Chem. Int. Ed.* **1996**, *35*, 2123; b) R. Rossi, F. Bellina, M. Biagetti, A. Catanese, L. Mannina *Tetrahedron Lett.* **2000**, *41*, 5281; c) L. B. Wolf, K. C. M. F. Tjen, H. T. ten Brink, R. H. Blaauw, H. Hiemstra, H. E. Schoemaker, E. P. J. T. Rutjes *Adv. Synth. Catal.* **2002**, *344*, 70; d) F. Neatu, L. Protesescu, M. Florea, V. I. Parvulescu, C. M. J. Teodorescu, N. Apostol, P. Y. Toullec, V. Michelet *Green Chem.* **2010**, *12*, 2145; e) J. Garcia-Alvarez, J. Diez, C. Vidal *Green Chem.* **2012**, *14*, 3190.



Scheme 3.15. Cycloisomerization promoted by SCS pincer complex **R**.

Finally, it is worth noting the work of Uozumi and co-workers, since they carried out the cycloisomerization reaction catalyzed by a pincer complex in water. In that work they examined the cyclization reaction of 5-[4-(trifluoromethyl)-phenyl]pent-4-ynoic acid catalyzed by an amorphous palladium pincer complex (Scheme 3.16).[30]



Scheme 3.16. Cyclization of 5-[4-(trifluoromethyl)-phenyl]pent-4-ynoic acid.

[30] G. Hamasaka, Y. Uozumi *Chem. Commun.* **2014**, *50*, 14516.

1.4. Background of the research group

As outlined in previous chapters (see Chapter 1, Section 1.5), our research group has a long experience in the synthesis of pincer complexes. In the last decade, we have developed various metallocycles, both symmetrical and non-symmetrical as it can be seen in Figure 3.2.[31]

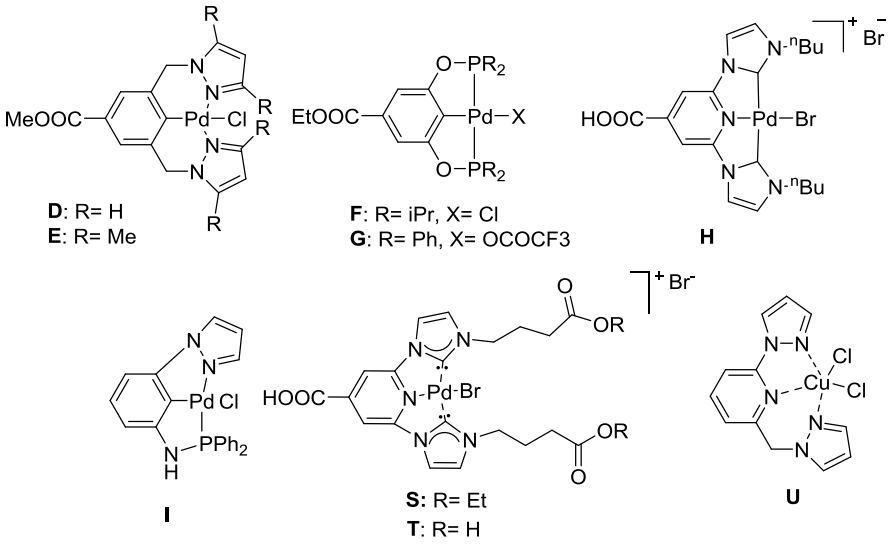
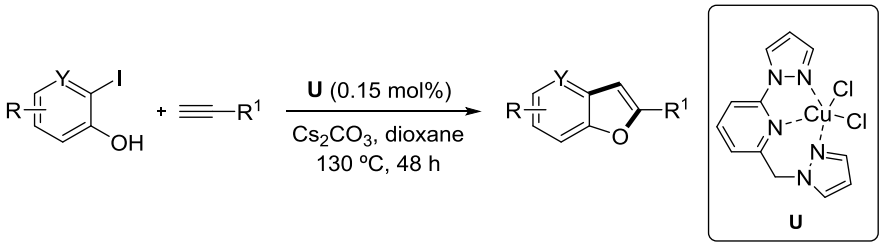


Figure 3.2. Pincer complexes synthesized by the group.

[31] a) F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez *Synlett* **2005**, 3116; b) F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez *Tethaedron Lett.* **2006**, *47*, 3233; c) F. Churruca, R. SanMartin, B. Inés, I. Tellitu, E. Domínguez *Adv. Synth. Catal.* **2006**, *348*, 1836; d) B. Inés, R. SanMartin, F. Churruca, E. Domínguez, M. K. Urtiaga, M. I. Arriortua *Organometallics* **2008**, *27*, 2833.

In addition to the synthesis of those catalysts, their activity in several organic transformations were also evaluated, showing in almost all the cases high catalytic activity. [32,33,34]

A meaningful example not mentioned in previous chapters is that of the use of Cu(II) complex **U** to synthesize benzofurans. Generally, most Cu-catalyzed coupling reactions are performed by using 5-20 mol% of the copper source.[35] However, the employment of a more efficient copper catalyst, could allow the use of lower amounts of catalyst. Thus, the heteroannulation of 2-iodophenols with arylacetylenes leading to benzofurans was performed by using only 0.15 mol% of catalyst **U**.[36]



Scheme 3.17. Heteroannulation of iodophenols and alkynes.

[32] G. R. Rosa, C. H. Rosa, F. Rominger, J. Dupont, A. L. Monteiro *Inorg. Chim. Acta* **2006**, *359*, 1947.

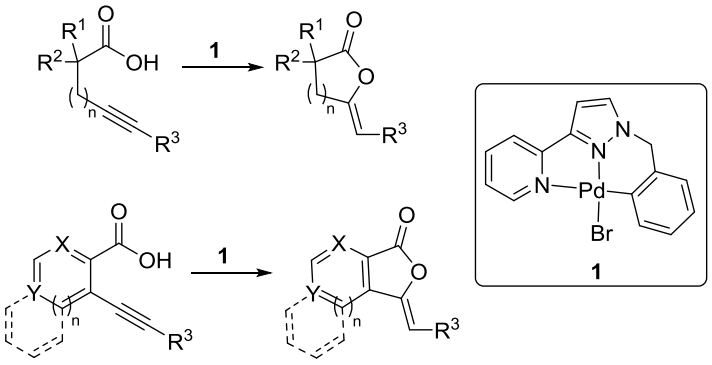
[33] R. San Martin, B. Inés, M. J. Moure, M. T. Herrero, E. Dominguez *Helv. Chim. Acta* **2012**, *95*, 955.

[34] G. Urgoitia, R. SanMartin, M. T. Herrero, E. Domínguez *Green Chem*. **2011**, *13*, 2161.

[35] For a review on several Cu-catalyzed coupling reactions, see: a) F. Monnier, M. Taillefer *Angew. Chem. Int. Ed.* **2009**, *48*, 6954; b) H. Plenio *Angew. Chem. Int. Ed.* **2008**, *47*, 6954. See also: c) J. Liu, F. Dai, Z. Yang, S. Wang, K. Xie, A. Wang, X. Chen, Z. Tan *Tetrahedron Lett.* **2012**, *53*, 5683.

[36] M. J. Moure, R. SanMartin, E. Dominguez *Adv. Synth. Catal.* **2014**, *356*, 2070.

Taking into account our background in the development of a number of pincer-type metallacycles and their application to different organic transformations, and the already existing reports on the cycloisomerization of alkynoic acids employing palladium pincer-type complexes as catalysts,[29,30] we envisioned that pincer complex **1**, whose preparation has been described in Chapter 1, could be a convenient palladium source for the synthesis of γ-alkylidene lactones (Scheme 3.18).

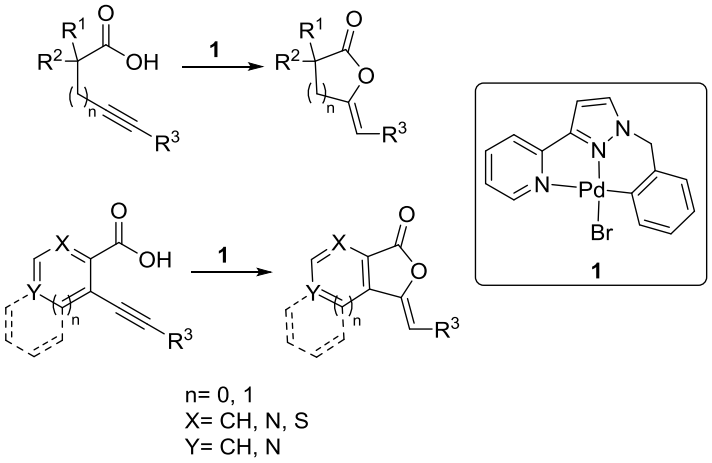


n= 0, 1
X= CH, N, S
Y= CH, N

Scheme 3.18. Synthesis of enol lactones.

2. AIMS AND OBJECTIVES

Taking into account the issues mentioned before, the aims of this work will be to perform the synthesis of γ-alkylidene lactones from alkynoic acids in the presence of the palladium NNC pincer complex **1**. In addition, a decrease of the amount of the palladium source will be also attempted.



Firstly, a survey of γ-alkynoic acids will be prepared, using different synthetic methods. After a set of assays in order to find suitable reaction conditions, the latter acids will be submitted to our optimized cycloisomerization conditions to study the catalytic activity of complex **1** in the synthesis of the corresponding γ-alkylidene lactones

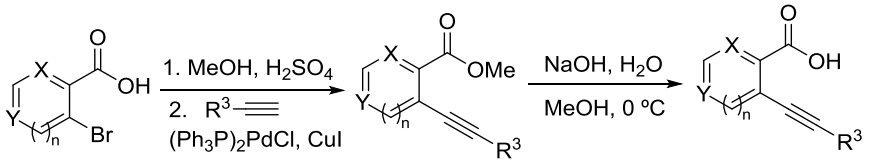
In addition, the above prepared alkynoic acids will be also assayed in a cascade process which involves reaction with several dinucleophiles.

3. RESULTS AND DISCUSSION

3.1. Synthesis of γ-acetylenic acids

Once the aims of the work were established, the next step was to prepare the required starting material to carry out the desired cycloisomerization, since, apart from **17a-b** and **17m**, most of the employed γ-acetylenic acids were not commercially available. In our case, four different synthetic paths were performed to obtain the desired acids.

The first series of acids were prepared, all bearing an aromatic or heteroaromatic core, following the methodology described by Rominger and co-workers (Scheme 3.19).[37]



Scheme 3.19. Synthetic path to aromatic γ-alkynoic acids **17h-l**.

Three steps were required, in which the first one was the esterification of the corresponding 2-halobenzoic acid. This simple step was carried out in MeOH using a catalytic amount of H_2SO_4. The obtained methyl ester was

[37] A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. De Buck Becker, M. Rudolph, C. Scholz, F. Rominger *Adv. Synth. Catal.* **2012**, *354*, 133.

then reacted with the appropriate acetylene derivative in the presence of 2 mol% of $(Ph_3P)_2PdCl_2$ and 4 mol% CuI in degassed Et_3N. After the Sonogashira cross-coupling step, a basic hydrolysis/desilylation using an aqueous solution of potassium hydroxide and MeOH as co-solvent at 0 ºC provided γ-acetylenic acids **17h-l** (Figure 3.3).

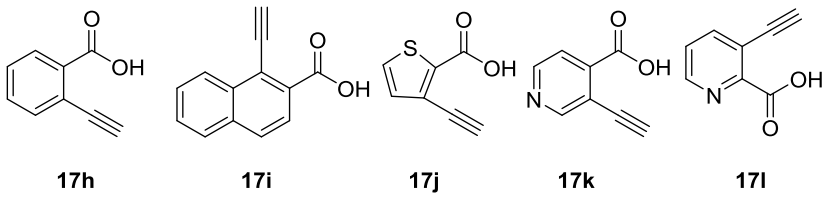


Figure 3.3. First series of alkynoic acids.

Alkynoic acids **17e** and **17f** were prepared by modifying the procedure reported by Bäckvall and co-workers.[38] Thus, the corresponding acetylenic alcohol was highly diluted in acetone and then reacted with the Jones reagent (0.5M CrO_3 in concentrated H_2SO_4/H_2O) at 0 °C, achieving the desired two acids (Figure 3.4).

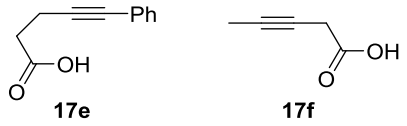
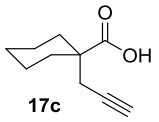
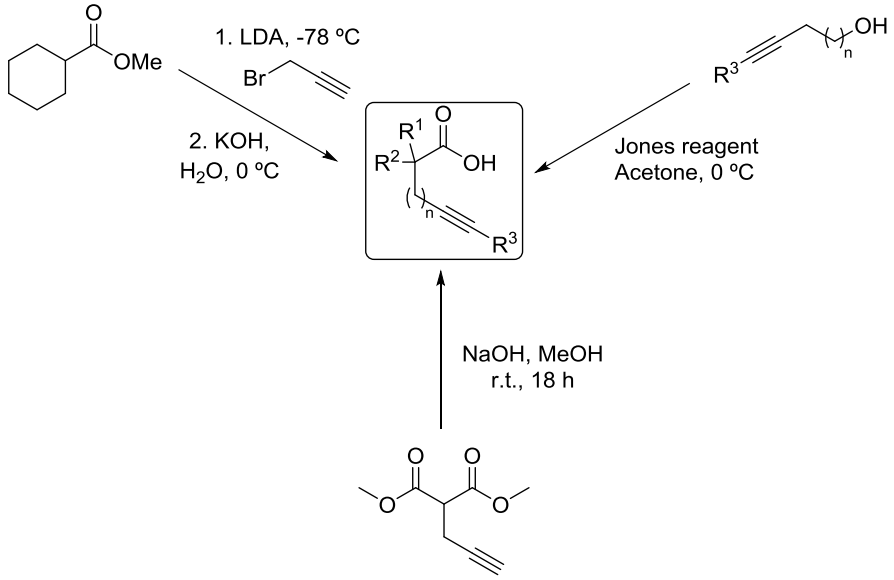


Figure 3.4. Synthesized acids by Jones oxidation.

[38] A. Nagendiran, O. Verho, C. Haller, E. V. Johnston, J.-E. Bäckvall *J. Org. Chem.* **2014**, *79*, 1399.

On the other hand, 1-(prop-2-yn-1-yl)cyclohexane-1-carboxylic acid **17c** was prepared in two steps without further purification of intermediates following the synthesis of Li and co-workers.[39] The first step of the sequence was the alkylation of methyl cyclohexanecarboxylate in LDA at -78 ºC, affording practically pure methyl 1-(prop-2-ynyl)cyclohexane carboxylate. Then, the above methyl ester was dissolved in MeOH at 0 ºC and reacted with an aqueous solution of potassium hydroxide, obtaining the desired acid **17c** (Figure 3.5).





Scheme 3.19. Different synthetic paths to access alkynoic acids.

[39] C. Sun, Y. Fang, S. Li, Y.Zhang, Q. Zhao, S. Zhu, C. Li *Org. Lett.* **2009**, *11*, 4084.

Finally, 2-(methoxycarbonyl)pent-4-ynoic acid **17d** was synthesized, this time by a simple hydrolysis. Thereby, NaOH was added to a solution of dimethyl propargylmalonate in methanol, in order to mono-hydrolyze the diester. After 18 hours the reaction was finished, obtaining the acid displayed in Figure 3.5.

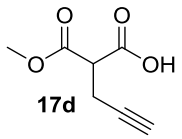


Figure 3.5. 2-(Methoxycarbonyl)pent-4-ynoic acid.

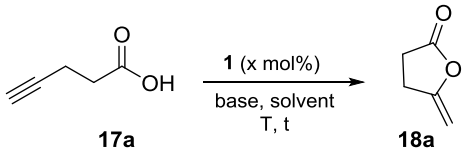
3.2. Catalytic activity of palladium pincer NNC in cycloisomerization of γ-acetylenic acids

The cycloisomerization of 4-pentynoic acid **17a** into 5-methylenedihydrofuran-2(3*H*)-one **18a** was chosen as the model reaction for the screening of reaction conditions, in which the effects of base, solvent, catalyst loading, temperature and reaction time were investigated. With the purpose of evaluating the effect of the reaction parameters, we decided that the catalyst loading of the complex **1** would be 10^{-2} mol% and the reaction concentration 0.1 M. The first assays were tried at room temperature, in the absence of base for 2 hours (Table 3.1, entries 1-3). After these trials we thought that the base, even in low amounts, might be necessary for the formation of product **18a**. Thus, we decided to perform a screening of some bases (Table 3.1, entries 4-6) at room temperature for 2 hours. The use of 5

mol% of Et_3N afforded enol lactone **18a** with 27% yield, while the use of other bases such as ^tBuOK and K_2CO_3 in the same amount turned out to be useless for the target transformation. Taking into account these results, Et_3N was chosen for further studies. Temperature and reaction time were increased (Table 3.1, entries 7 and 8), achieving the product with excellent yields in both cases. The required loading of Et_3N was then investigated, and it was found that an increase from 5 to 10 mol% resulted in a decrease of the yield from 99% to 70%, while the decrease to 2 mol% did not cause any change in the result (Table 3.1, entries 8 and 9). These results indicated that high base concentrations have an inhibitory effect on the reaction. Thereby, 2 mol% of Et_3N was taken as the best option, performing the reaction at 50 ºC to afford the product in 99% yield (Table 3.1, entry 11). Encouraged by this excellent result we decided to decrease the catalyst loading (Table 3.1, entries 12-15). As it can be seen even employing 10^{-5} mol% of complex **1** the desired lactone was obtained. An increase of the temperature to 90 ºC was required when 10^{-5} mol% of **1** was used to obtain quantitatively the alkylidene lactone **18a** in similar or shorter reaction times (Table 1, entry 15 *vs* 14 and 16).

In conclusion, the best results were obtained when the reaction was performed in $CDCl_3$ at 50°C with 2 mol% of Et_3N and a 10^{-4} mol% of palladium pincer **1** for 24 hours. We should mention that the cycloisomerization neither occurred in the absence of the pincer complex **1** (Table 3.1, entry 17) nor in the presence of such a commercially available source as $Pd(OAc)_2$.

Table 3.1. Cycloisomerization in the presence of complex **1**.

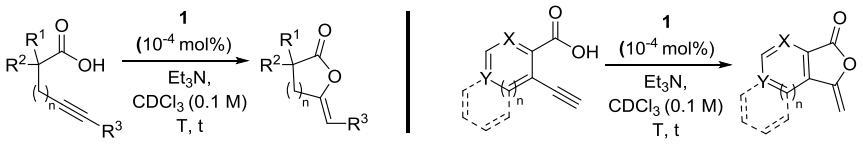


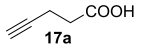
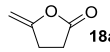
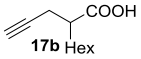
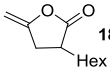
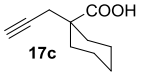
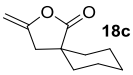
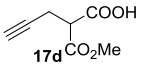
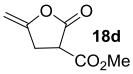
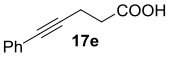
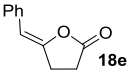
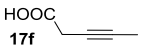
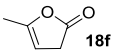
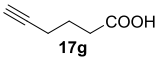
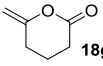
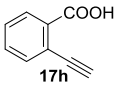
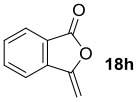
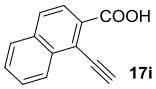
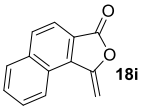
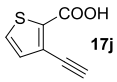
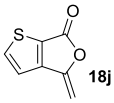
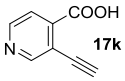
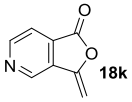
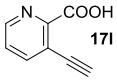
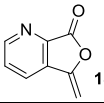
	Solvent	**1** (mol%)	Base	T (ºC)	t (h)	Conv.(%)[b]
1	$CHCl_3$	10^{-2}	---	r.t.	2	---
2	$CDCl_3$	10^{-2}	---	r.t.	2	---
3	CD_3COCD_3	10^{-2}	---	r.t.	2	---
4	$CDCl_3$	10^{-2}	K_2CO_3 (5 mol%)	r.t.	2	---
5	$CDCl_3$	10^{-2}	Et_3N (5 mol%)	r.t.	2	27
6	$CDCl_3$	10^{-2}	^tBuOK (5 mol%)	r.t.	2	---
7	$CDCl_3$	10^{-2}	Et_3N (5 mol%)	90	12	>99
8	$CDCl_3$	10^{-2}	Et_3N (5 mol%)	50	12	>99
9	$CDCl_3$	10^{-2}	Et_3N (2 mol%)	90	12	>99
10	$CDCl_3$	10^{-2}	Et_3N (10 mol%)	90	12	70
11	$CDCl_3$	10^{-2}	Et_3N (2 mol%)	50	12	>99
12	$CDCl_3$	10^{-3}	Et_3N (2 mol%)	50	24	>99
13	$CDCl_3$	10^{-4}	Et_3N (2 mol%)	50	24	>99
14	$CDCl_3$	10^{-5}	Et_3N (2 mol%)	50	24	83
15	$CDCl_3$	10^{-5}	Et_3N (2 mol%)	90	12	>99
16	$CDCl_3$	10^{-4}	Et_3N (2 mol%)	50	12	72
17	$CDCl_3$	---	Et_3N (2 mol%)	50	24	---
18[c]	$CDCl_3$	10^{-4}	Et_3N (2 mol%)	50	24	5

[a]Reaction conditions: **17a** (0.2 mmol), solvent (0.1 M); [b] Determined by ^1H NMR spectroscopy. [c] $Pd(OAc)_2$

Then the scope of the reaction was examined, showing that the catalyst worked well for the cycloisomerization of a variety of acetylenic acids **17** (Table 3.2). The reaction was proved to be highly regioselective for all of the 4-acetylenic acids that were used, affording the corresponding 5-*exo*-dig lactone. Our protocol tolerated the presence of different substituents at the α position to the carboxy group (Table 3.2, entries 2-4), although higher temperatures were required when a long *n*-hexyl chain was attached at that position (entry 2). A complete *exo*-dig regio- and diastereocontrol was achieved in all cases, even from intrinsically challenging substrates[28] such as internal alkynes, 3-alkynoic and 5-alkynoic acids (Table 3.2, entries 5-7). For the latter lactones **18e-g** an increase of the temperature was required (90 ºC) to get full conversion. A set of rigid aromatic and heteroaromatic 4-alkynoic acids **17h-l** was also submitted to the optimized reaction conditions to provide the corresponding furanes **18h-l** in good to excellent yields (entries 8-12). Deuterated chloroform ($CDCl_3$) was chosen as a very convenient solvent that allowed easy monitorization of the reaction outcome and even ^{1}H-NMR quantification.

Table 3.2. Scope of cycloisomerization catalyzed by complex **1**.



	17	18	t (h)	T (ºC)	(%)[b]
1	 17a	 18a	24	50	97[c]
2	 17b	 18b	24	70	88
3	 17c	 18c	24	50	97
4	 17d	 18d	24	50	85
5	 17e	 18e	72	50	70
6	 17f	 18f	24	90	96[c]
7	 17g	 18g	24	90	98[c]
8	 17h	 18h	4	50	94
9	 17i	 18i	24	50	76
10	 17j	 18j	24	90	98
11	 17k	 18k	24	50	95
12	 17l	 18l	24	50	96

[a]Reaction conditions: **17** (0.2 mmol), **1** (10^{-4} mol%), Et_3N (2 mol%), $CDCl_3$ (2 mL), 60-90 ºC, 24-72 h; [b] Isolated yields; [c] Determined by ^1H NMR spectroscopy. 3,4,5-Trichloropyridine was used as internal standard.

In order to know more about the catalytic profile observed for pincer complex **1**, a number of poisoning assays and kinetic studies were carried out.

The procedures reported by Finke and Widegren are helpful to make a distinction between homogeneous and heterogenous catalysis, as explained in Chapter 2 (pages 139-140).[40,41]

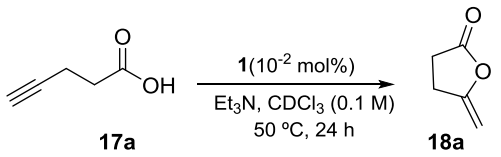
Taking that into account and as it can be observed in Table 3.3 (entry 1), when a drop of mercury was added to the reaction mixture, the desired product **18a** was still obtained in excellent yield, so no poisoning effect was observed.

With regard to the addition of other poisoning additives in sub- and overstoichiometric amounts, the yields for the cycloisomerization in the presence of CS_2 and PPh_3 were unchanged regardless of the amount of additive added, as displayed in Table 3.3 (entries 2-6).

[40] Finke et al. have reported that poisoning of a catalyst by using substoichiometric amount (less than 1.0 equiv. per atom) of certain chemicals constitutes a suggestive evidence of the participation of heterogeneous catalysts. For a review, see: a) J. A. Widegren, R. G. Finke *J. Mol. Catal. A: Chem.* **2003**, *198*, 317; b) N. T. S. Phan, M. Van Der Sluys, C. W. Jones *Adv. Synth. Catal.* **2006**, *348*, 609.

[41] a) C. Paal, W. Hartmann *Chem. Ber.* **1918**, *51*, 711; b) G. Süss-Fink, M. Faure, T. R. Ward *Angew. Chem. Int. Ed.* **2002**, *41*, 99; c) S. Jatta, B. Dutta, R. Bera, S. Koner, *Inorg. Chem.* **2008**, *47*, 5512; d) J. Demel, J. Lamac, J. Cejka, P. Stepnicka *ChemSusChem* **2009**, *2*, 442.

Table 3.3. Summary of poisoning experiments.



17a 18a

	Poisoning additive	(%)[a]
1	Hg (one drop)	99
2	CS_2 (0.5 equiv. per metal atom)	99
3	CS_2 (2.0 equiv. per metal atom)	97
4	PPh_3 (0.03 equiv. per metal atom)	99
5	PPh_3 (0. 3 equiv. per metal atom)	99
6	PPh_3 (4.0 equiv. per metal atom)	98
7	Py[b] (150 equiv. per metal atom)	99
8	PVPy[c] (300 equiv. per metal atom)	99

[a] Measured by ^{1}H-NMR. 3,4,5-Trichloropyridine was used as internal standard. [b] Py: Pyridine [c] PVPy: Polyvinylpyridine.

These results provided an evidence for the participation of homogeneous catalytic species. In the same context, addition of pyridine and PVPy in overstoichiometric amounts to the reaction mixture is used to detect formation of metal nanoparticles. If a substantial decrease in the catalyst activity is seen with the addition of PVPy in comparison with that of pyridine, that would be indicative of metal(0) species. Once again no

changes were observed in the reaction after adding these additives (entries 7 and 8).[42]

NMR monitorization of the reaction by a stacked plot was also carried out by recording ^{1}H NMR spectra at regular intervals for 24 hours (Figure 3.6). Thereby, it can be easily observed the transformation of 4-pentynoic acid **17a** into 5-methylenedihydrofuran-2(3*H*)-one **18a**. This is certainly possible thanks to the low amount (10^{-2} mol%) of catalyst employed that did not interfere in the spectra. This feature is an additional advantage of our protocol.

Figure 3.6 shows that as time evolved the signal corresponding to the acetylenic proton went decreasing while the ones belonging to the alkene moiety were appearing, and that the reaction was almost finished in 6h with no intermediates or other species involved. Integration of the ^{1}H NMR signals at different reaction times allowed a very easy conversion rate *vs* time plot.

[42] K. Sommer, W. Yu, J. M. Richardson, M. Weck, C. W. Jones *Adv. Synth. Catal*. **2005**, *347*, 161.

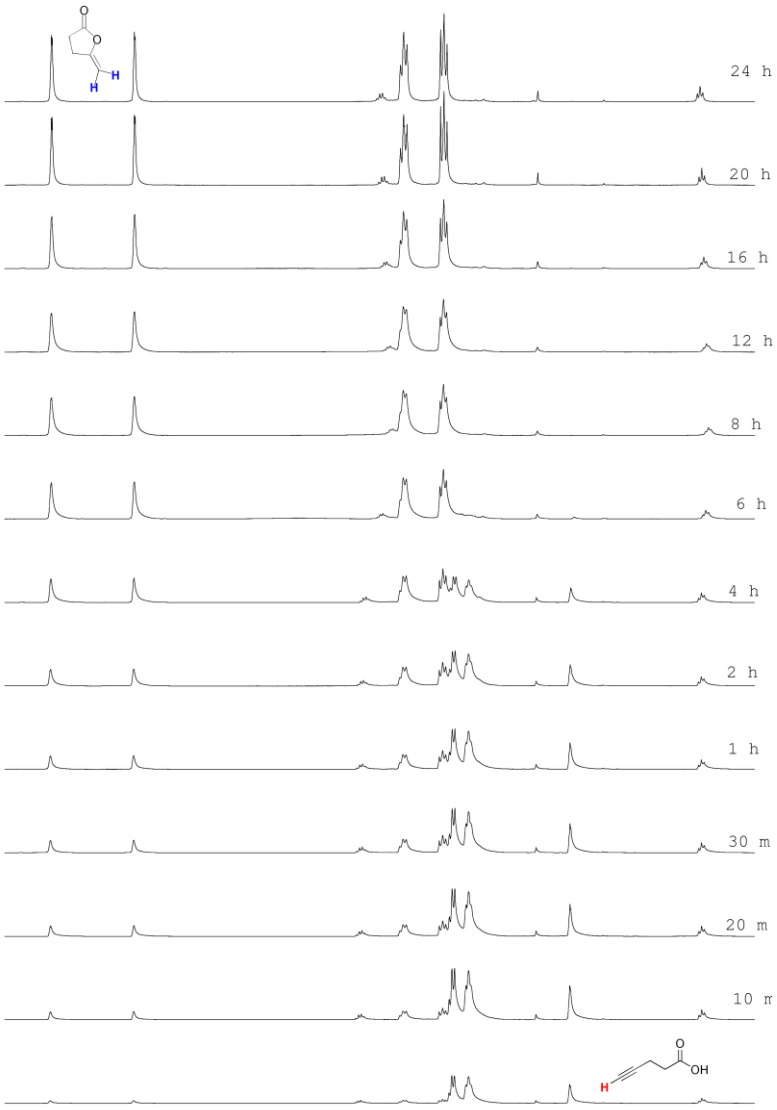


Figure 3.6. Kinetic tests in ^{1}H-NMR.

As displayed in Figure 3.7, the observed kinetic curve also accounts for the participation of homogeneous catalytic species.

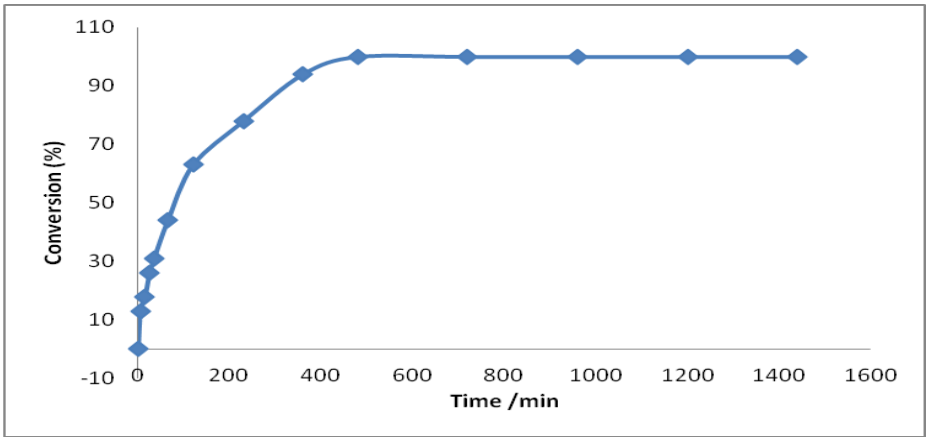


Figure 3.7. Conversion rate of 4-pentynoic acid *vs* time.

On the other hand, the reaction was carried out by a high catalyst loading (1 mol%) in order to verify that the catalyst **1** did not disintegrate during the process. After 2 hours the reaction was stopped and crude mixture was evaporated. The residue was analyzed by ^{1}H NMR, showing that the pincer complex **1** remained intact. This fact open further possibilities for a potential recycling protocol.

3.3. Cascade reaction involving double hydroamidation of γ-acetylenic acids

In view of the excellent results obtained for the cycloisomerization reaction, we envisaged that the above employed alkynoic acids could be used as suitable reactants along with dinucleophiles in metal-catalyzed cascade reactions.[43] These reactions, which employ easily available starting materials in one-pot fashion without isolating any intermediates,[44] give an easy access to relatively complex molecular scaffolds.

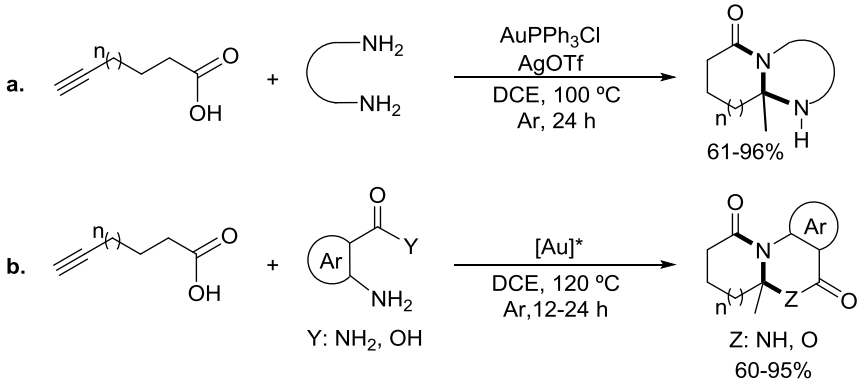
For example, cascade reaction involving diamines and alkynoic acids have attracted much attention.[45] To the best of our knowledge this transformation

[43] Selected reviews on metal-catalyzed cascade processes: a) Y. Yamamoto, I. D. Gridnev, N. T. Patil, T. Jin *Chem. Commun.* **2009**, 5075; b) N. T. Patil, Y. Yamamoto *Top. Organomet. Chem*. **2006**, *19*, 91; c) I. Nakamura, Y. Yamamoto *Chem. Rev*. **2004**, *104*, 2127; d) P.-F. Xu, H. Wei in *Calalytic cascade reactions*, (Eds.: P.-F. Xu, W. Wang), Wiley, Hoboken, **2013**.

[44] For general reviews on cascade processes, see: a) K. C. Nicolaou, J. S. Chen *Chem. Soc. Rev*. **2009**, *38*, 2993; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; c) A. D. Meijere, P. V. Zezschwitz, S. Bräse *Acc. Chem. Res.* **2005**, *38*, 413; d) J. M. Lee, Y. Na, H. Han, S. Chang *Chem. Soc. Rev.* **2004**, *33*, 302; e) A. Ajamian, J. L. Gleason *Angew. Chem. Int. Ed.* **2004**, *43*, 3754; f) L. F. Tietze *Chem. Rev*. **1996**, *96*, 115; g) L.-Q. Lu, J.-R. Chen, W.-J. Xiao *Acc. Chem. Res.* **2012**, *45*, 1278.

[45] For metal-catalyzed cascade reaction involving amines leading to formation of heterocycles, see: a) L. Zhou, D. S. Bohle, H.-F. Jiang, C.-J. Li *Synlett* **2009**, 937; b) X.-Y. Liu, C.-M. Che *Angew. Chem. Int. Ed.* **2009**, *48*, 2367; c) K. Gräbe, B. Zwafelink, S. Doye *Eur. J. Org. Chem*. **2009**, 5565; d) K. Alex, A. Tillack, N. Schwarz, M. Beller, *Org. Lett.* **2008**, *10*, 2377; e) K. Alex, A. Tillack, N. Schwarz, M. Beller *Angew. Chem. Int. Ed.* **2008**, *47*, 2304; f) X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che *Org. Lett.* **2007**, *9*, 2645; g) L. Ackermann, A. Althammer *Synlett* **2006**, 3125; h) C. Cao, Y. Li, Y. Shi, A. L. Odom *Chem. Commun.* **2004**, 2002; i) B. Ramanathan, A. J. Keith, D. Armstrong, A. L. Odom *Org. Lett.* **2004**, *6*, 2957; j) H. Siebeneicher, I. Bytschkov, S. Doye *Angew. Chem. Int. Ed.* **2003**, *42*, 3042; k) C. Cao, Y. Shi, A. L. Odom *Org. Lett.* **2002**, *4*, 2853; l) *Synthesis of*

only has been carried out using Pt and Au as catalysts. [46] For instance, in 2010 Patil *et al.* described an effective one-pot reaction catalyzed by gold that provided polycyclic compounds starting from alkynoic acids and diamines (Scheme 3.24, entry a). [47,48] Liu and co-workers, applied a specially designed gold(I) complex to the synthesis of quinazolidinones and benzoxazinones (Scheme 3.24, entry b).[49]



Scheme 3.24. Cascade reactions catalyzed by Au.

Dixon *et al*. proposed a reaction mechanism for such transformations (Scheme 3.25, pentynoic acid has been elected as a suitable starting

Heterocycles via Metal-Catalyzed Reactions that Generate One or More Carbon-Heteroatom Bonds, (Ed.: J. P. Wolfe), Springer-Verlag, Heidelberg, **2013**.

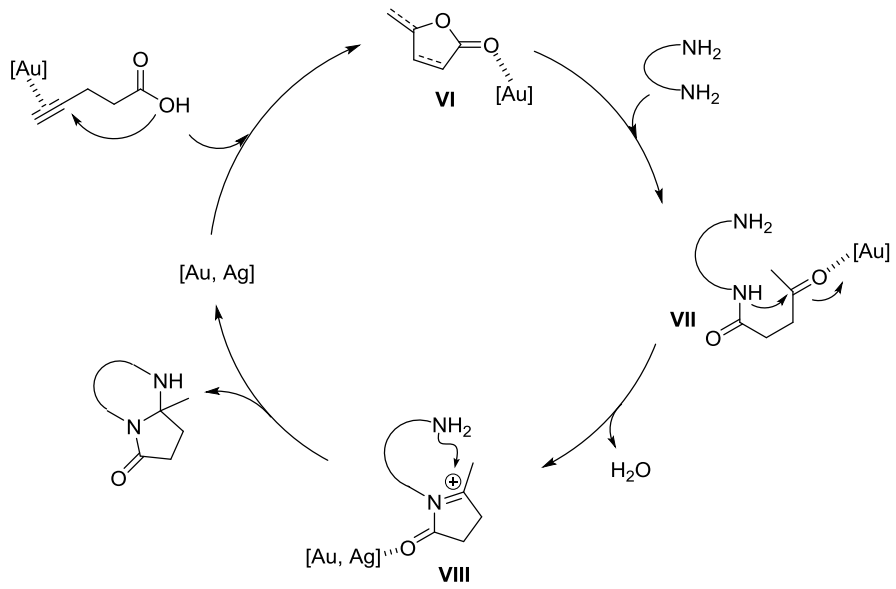
[46] a) N. T. Patil, R. D. Kavthe, V. S. Shinde, B. Sridhar *J. Org. Chem*. **2010**, *75*, 3371; b) N. T. Patil, R. D. Kavthe, V. S. Shinde, B. Sridhar *J. Org. Chem.* **2010**, *75*, 1277.

[47] N. T. Patil, A. K. Mutyala, P. Lakshmi, B. Gajula, B. Sridhar, G. R. Pottireddygari, T. Rao *J. Org. Chem*. **2010**, *75*, 5963.

[48] For related process carried out by a similar catalytic system, see: T. Yang, L. Campbell, D. J. Dixon *J. Am. Chem. Soc*. **2007**, *128*, 12070.

[49] E. Feng, Y. Zhou, D. Zhang, L. Zhang, H. Sun, H. Jiang, H. Liu *J. Org. Chem*. **2010**, *75*, 3274.

material) based on cycloisomerization as key step. This allowed to explain some addition processes to alkynoic acids catalyzed by $AuPPh_3Cl$ and AgOTf.[48] Subsequently, this proposal has been accepted and adopted by several authors.[47]



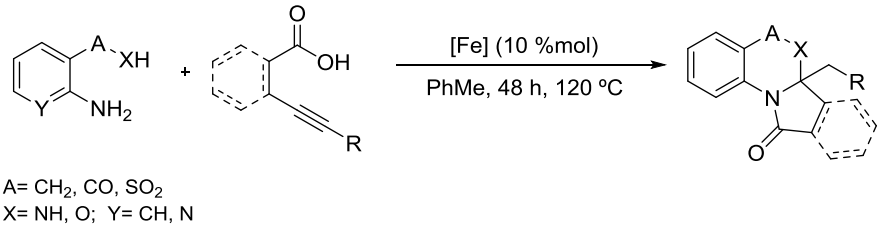
Scheme 3.25. Mechanistic proposal for the Au/Ag-catalyzed cascade reaction.

Thereby, alkynoic acid is first activated by the catalyst to afford activated enol-lactone intermediate **VI**.[50] Subsequently, one of the free amino groups of the dinucleophile attacks the latter intermediate to form aminolysis product **VII**. This ketoamide **VII** might evolve into *N*-acyliminium

[50] a) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J. P. Genet, V. Michelet *J. Am. Chem. Soc*. **2006**, *128*, 3112; b) H. Harkat, J.-M. Weibel, P. Pale *Tetrahedron Lett.* **2006**, *47*, 6273; c) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon *J. Am.Chem. Soc*. **2009**, *131*, 10796.

intermediate **VIII** *via* cyclization/dehydration.[51] Finally, nucleophilic attack by the other amino group could yield the final product.

Recently, our research group also has carried out this cascade reaction employing Fe sources as catalysts (Scheme 3.26).[52] Iron has several advantages, among them, it is one of the most abundant metals on Earth and therefore one of the cheapest. In addition, its presence in important biological processes makes it one of the least harmful metal sources to the environment.[53] Another factor to consider is the commercial availability of iron derivatives and the easy access to them.[54]



Scheme 3.26. Cascade reactions catalyzed by Fe developed by our research group.

[51] X. Y. Liu, C. M. Che *Angew. Chem. Int. Ed.* **2008**, *47*, 3805.

[52] J. Diaz de Sarralde, M. T. Herrero, R. SanMartin, E. Domínguez P201430635.

[53] a) R. Monterroso, M. Fan, F. Zhang, Y. Gao, T. Popa, M. D. Argyle, B. Towler, Q. Sun *Fuel* **2014**, *116*, 341; b) R. Hudson, G. Hamasaka, T. Osako, Y. M. A. Yamada, C. J. Li, Y. Uozumi, A. Moores *Green Chem.* **2013**, *15*, 2141.

[54] a) M. W. Zettler in *Encyclopedia of Reagents for Organic Synthesis*; (Ed.: L. Paquette), Wiley, New York **1995**; b) A. D. White in *Encyclopedia of Reagents for Organic Synthesis*; (Ed.: L. Paquette) Wiley, New York, **1995**; c) B. R. King in *Encyclopedia of Inorganic Chemistry*, Wiley, New York **1994**.

As it has been mentioned before, our research group has a long experience in the application of metal-catalyzed reactions to the synthesis of heterocycles, such as benzo[*b*]furanes, benzo[*d*]oxazoles, benzofuroindoles, benzoimidazolones, xanthones, pyrrolo phenanthridines or pyrazolodibenzodiazepines.[55] Taking all these issues into account and that nobody has used Pd as catalyst in the aforementioned cascade process between alkynoic acids and dinucleophiles, we decided to employ our new synthesized NNC palladium pincer **1** in this context.

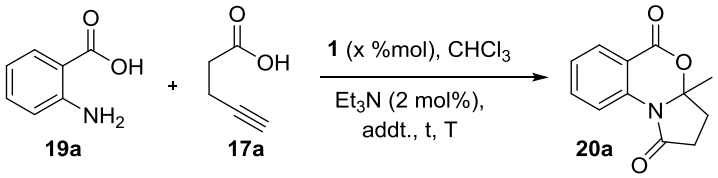
Thus, we started the screening of the reaction conditions with commercially available 2-aminobenzoic acid **19a** and 4-pentynoic acid **17a** as the model substrates. All the experiments were carried out in chloroform in a sealed tube, employing 2 mol% of Et_3N as base and pincer complex **1** (10^{-2} mol%) as the palladium source. The results of this study are summarized in Table 3.4. The first experiment, in the absence of any additive at 60 ºC for 96 hours, provided target benzopyrrolooxazine-1,5-dione **20a** in a poor 14% yield. Therefore different additives at a 10^{-2} mol% level were assayed (entries 2-9). Although the first trials (cesium carbonate, p-toluenesulfonic acid and boron trifluoride or aluminum trichloride Lewis acids) provided negligible results (entries 2-5), when $FeBr_2$ and $FeCl_3$ were used the yield

[55] a) M. J. Moure, R. SanMartin, E. Domínguez *Angew. Chem. Int. Ed.* **2012**, *51*, 3220; b) S. Hernández, I. Moreno, R. SanMartin, G. Gómez, M. T. Herrero, E. Domínguez *J. Org. Chem.* **2010**, *75*, 434; c) N. Barbero, R. SanMartin, E. Domínguez *Green Chem.* **2009**, *11*, 830; d) M. Carril, R. SanMartin, E. Domínguez, I. Tellitu *Green Chem.* **2007**, *9*, 219; e) M. Carril, R. SanMartin, I. Tellitu, E. Domínguez *Org. Lett.* **2006**, *8*, 1467; f) F. Churruca, R. SanMartin, M. Carril, M. K. Urtiaga, X. Xolans, I. Tellitu, E. Domínguez *J. Org. Chem.* **2005**, *70*, 3178.

was substantially increased (entries 6-7). On account of the higher solubility of $FeBr_2$ in organic solvents and considering that the aforementioned methodology protocol set up by our group relied on the use of the latter iron(II) salt, it was chosen for further assays. Once the additive was established, we decided to increase the temperature to 120 ºC, and to our delight a good yield (79%, entry 8) was achieved. Encouraged by this result we decreased the catalyst loading to 10^{-4} mol% (entry 9) and along with it, the additive loading was also decreased to 10^{-4} mol% (entries 10). Unfortunately, in both cases the yield dropped significantly. The use of a slight excess of the alkynoic acid (1.5 equiv.) turned out to be beneficial for the reaction outcome (entry 12 *vs* 8 and 11). When the concentration was decreased only traces of the product were observed, while an increment led to the best results, thus obtaining a 93% yield (entry 14 *vs* 12-13).

As it can be seen in entries 15 to 18, the reduction of the reaction time or the lowering of the temperature to 70 ºC led to worse results. Finally, the reaction did not proceed in the absence of catalyst **1** and the use of Et_3N resulted to be essential (entries 19 and 20). All in all, the best conditions to carry out the cascade reaction were those described in Table 3.4, entry 14.

Table 3.4. Cascade reaction in the presence of pincer complex **1**.[a]



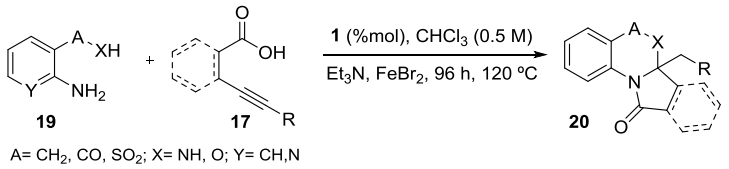
	$[CHCl_3]$/M	**1** (mol%)	Additive	T (h)	T (ºC)	(%)[b]
1	0.1	10^{-2}	----	96	60	14
2[d]	0.1	10^{-2}	Cs_2CO_3	96	60	sm
3	0.1	10^{-2}	p-TsOH	96	60	15
4	0.1	10^{-2}	$BF_3{\cdot}O(C_2H_5)_2$	96	60	20
5	0.1	10^{-2}	$AlCl_3$	96	60	27
6	0.1	10^{-2}	$FeCl_3$	96	60	45
7	0.1	10^{-2}	$FeBr_2$	96	60	48
8	0.1	10^{-2}	$FeBr_2$	96	120	79
9	0.1	10^{-4}	$FeBr_2$	96	120	39
10[c]	0.1	10^{-4}	$FeBr_2$	96	120	24
11[e]	0.1	10^{-2}	$FeBr_2$	96	120	69
12[f]	0.1	10^{-2}	$FeBr_2$	96	120	85
13[f]	0.02	10^{-2}	$FeBr_2$	96	120	traces
14[f]	0.5	10^{-2}	$FeBr_2$	96	120	93
15[f]	0.5	10^{-2}	$FeBr_2$	24	120	46
16[f]	0.5	10^{-2}	$FeBr_2$	48	120	55
17[f]	0.5	10^{-2}	$FeBr_2$	72	120	72
18[f]	0.5	10^{-2}	$FeBr_2$	96	70	57
19[d,f]	0.5	10^{-2}	$FeBr_2$	96	120	14
20[f]	0.5	---	---	96	120	sm

[a] Reaction conditions: **19a** (0.2 mmol), **17a** (1.0 equiv.), Et_3N (2 mol%), additive (10^{-2} mol%);[b] Isolated yields; [c] $FeBr_2$ (10^{-4} mol%); [d] Without Et_3N; [e] Diamine (1.5 equiv.); [f] Alkynoic acid (1.5 equiv.).

Once the procedure was defined, then the scope of this method was investigated, and the results are summarized in Table 3.5. Satisfyingly, the reaction proved to be very general under the optimized conditions, leading to the desired products **20** in good results in most of the examined cases. Firstly, a variety of alkynoic acids were studied using anthranilic acid **19a** as dinucleophile, obtaining pyrrolo- indolo- and pyridobenzooxazine diones **20a-e**. The alkynoic acids bearing sterically demanding substituents such as **17b** and **17h** gave the corresponding products **20b** and **20c** in very good yiels (87% and 90% respectively, entries 2 and 3). A slightly lower yield was achieved (61%) when hexynoic acid **17g** was used (entry 4). Even internal alkyne **17e** was found to be a useful substrate, affording the corresponding product **20e** in 75% yield (entry 5).

A similar behavior was observed when sulfonamide **18b** was employed and tested with different acids (entries 6-8). Excellent yield was obtained with 4-pentynoic acid **17a** (90%), while the use of hexynoic acid **17m** gave once again a lower yield (63%). The internal alkyne **17e** reacted well to achieve regioselectively the desired tricyclic product (75% yield, entry 8). Next, the scope of the reaction was studied employing 2-aminobenzylamine **18c** in combination with different γ-alkynoic acids (entries 9-12).

Table 3.5. Scope of cascade reaction catalyzed by complex **1**.



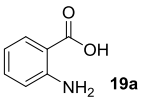
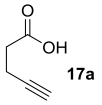
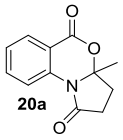
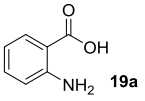
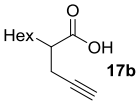
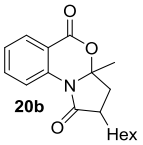
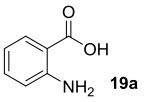
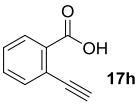
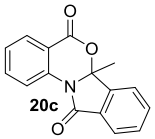
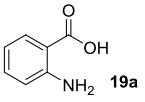
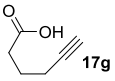
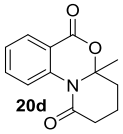
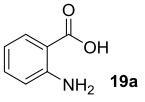
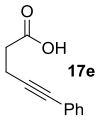
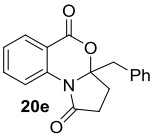
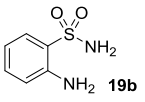
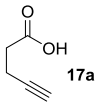
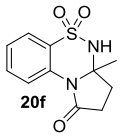
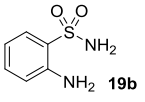
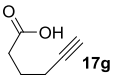
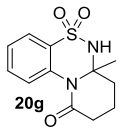
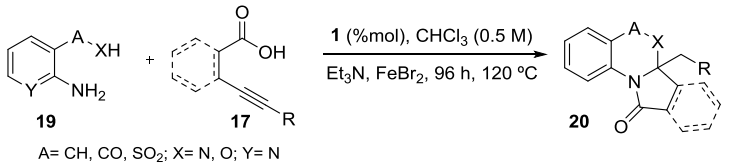
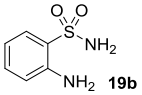
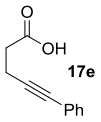
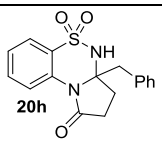
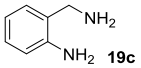
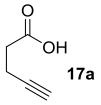
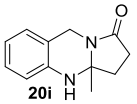
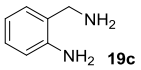
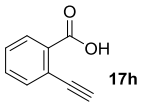
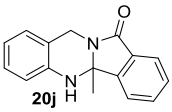
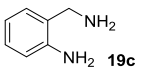
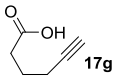
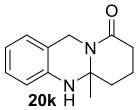
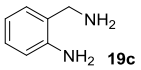
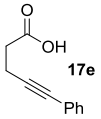
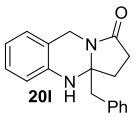
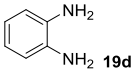
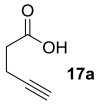
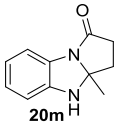
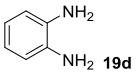
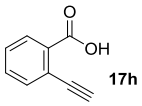
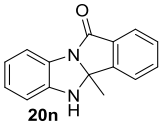
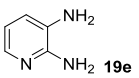
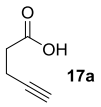
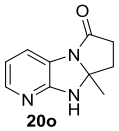
	19	**17**	**20**	(%)[b]
1	 **19a**	 **17a**	 **20a**	93
2	 **19a**	 **17b**	 **20b**	87
3	 **19a**	 **17h**	 **20c**	90
4	 **19a**	 **17g**	 **20d**	61
5	 **19a**	 **17e**	 **20e**	75
6	 **19b**	 **17a**	 **20f**	94
7	 **19b**	 **17g**	 **20g**	63

Table 3.5. Scope of cascade reaction catalyzed by complex **1** (cont.)



	19	17	20	(%)[b]
8	 **19b**	 **17e**	 **20h**	73
9	 **19c**	 **17a**	 **20i**	95
10	 **19c**	 **17h**	 **20j**	82
11	 **19c**	 **17g**	 **20k**	57
12	 **19c**	 **17e**	 **20l**	81
13	 **19d**	 **17a**	 **20m**	74
14	 **19d**	 **17h**	 **20n**	75
15	 **19e**	 **17a**	 **20o**	90

[a]Reaction conditions: **19** (0.2 mmol), **17** (0.3 equiv.), Et_3N (2 mol%), $FeBr_2$ (10^{-2} mol%), $CHCl_3$ (0.5 M), 96 h, 120 ºC;[b] Isolated yields.

The treatment of **18c** with 4-pentynoic acid **17a**, 5-phenyl-4-pentynoic acid **17e** and 2-ethynylbenzoic acid **17h** afforded the desired cyclic products with very good yields (95%, 81% and 82% respectively, entries 9, 10 and 12). However, when hexynoic acid **17g** was used only a 57% of pyridoquinazolin-9-one derivative **20k** was obtained, as happened with the other dinucleophiles.

Finally, 2-aminoaniline **19d** was reacted with the acids **17a** and **17h** (entries 13 and 14)**.** In both cases the yields were lower than expected (74% and 75% respectively), at least in comparison with the results from the same acids with other dinucleophiles. To explain this behavior it should be noted that so far, the clear differences in the nucleophilic nature of the nucleophilic moieties of the dinucleophiles **19a-c** facilitated the assumption of different roles in the proposed mechanism (one would be to promote the opening of the lactone and the other the nucleophilic addition to the acyliminium ion). Besides, there is no difference between both nucleophiles in **19d**, a feature that could hamper any of the above nucleophilic attacks to some extent. Nevertheless, when 2,3-diaminopyridine **19e** was employed the yield increased again (entry 15), probably because of the lower nucleophilicity of the amino group attached to C-2 position.

The crystallization of pyrrolobenzooxazinodiones **20a** and **20e** in dichloromethane resulted in the isolation of monocrystalline solids, as happened with the thiadiazinone **20g**. These single crystals were analyzed by X-ray diffractrometry, providing unequivocal information about their structure (see Figures 3.8, 3.9 and 3.10 displayed below) and so suggesting

that *ortho*-amino group was presumably responsible for the opening the lactone intermediate.

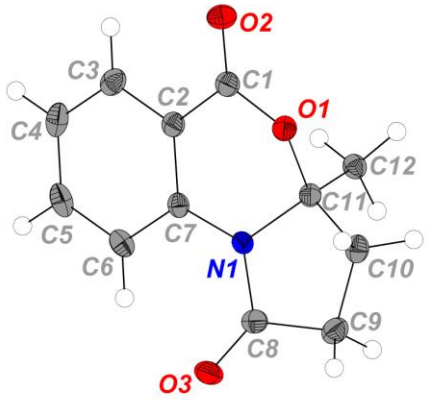


Figure 3.8. Crystal structure of 3a-methyl-3,3*a*-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione **20a**. Thermal ellipsoids are given at the 50% probability level.

In this orthorhombic crystal (space group Pbca), the presence of a quaternary center is the main responsible for the deviation of planarity at the oxazine ring and of coplanarity with the pyrrolo moiety (see for example C1-O1-C11-N1 and C7-N1-C11-C10 torsion angle values of -53.4 and 165.1 degrees respectively). The observed bond distances, angles and torsion angles for **20a** are summarized in Tables 3.6-3.8.

Table 3.6. Selected bond-distances (Å) and bond-angles (º).

Atoms	Dist.(Å)
O1-C1	1.3611 (14)
O1-C11	1.4472 (13)
O2-C1	1.2034 (14)
O3-C8	1.2151 (14)
N1-C7	1.3992 (15)
N1-C8	1.3805 (15)
N1-C11	1.4623 (14)
C9-C10	1.5318 (17)
C11-C12	1.5176 (16)
C10-H10A	0.9900

Table 3.7. Selected bond-angles (º).

Átoms	Ang.(°)
C1-O1-C11	116.20 (8)
C7-N1-O8	128.68 (9)
C7-N1-C11	117.92 (9)
C8-N1-C11	113.19 (9)
O1-C1-O2	118.87(10)
C3-C4-C5	119.62 (10)
N1-C7-C2	116.39 (10)
N1-C7-C6	123.71 (10)
C2-C7-C6	119.89 (11)
O3-C8-N1	125.54 (11)
N1-C8-C9	107.14 (9)
O1-C11-N1	109.13 (9)
N1-C11-C10	103.06 (9)
N1- C11-C12	112.67 (9)
C10-C11-C12	114.17 (9)

Tabla 3.8. Selected torsion angles (º).

Átoms	Ang.(°)
C11-O1-C1-O2	-155.38 (10)
C1-O1-C11-N1	-53.42 (11)
C8-N1-C7-C2	165.77 (10)
C11-N1-C8-O3	-176.33 (11)
C7-N1-C11-C10	165.09 (9)
C8-N11-C11-C12	103.75 (11)
C3-C2-C7-C6	-2.22 (16)
C7-C2-C3-C4	2.07 (16)
C4-C5-C6-C7	0.82 (17)
N1-C8-C9-C10	15.42 (12)
C9-C10-C11-C12	-94.76 (11)

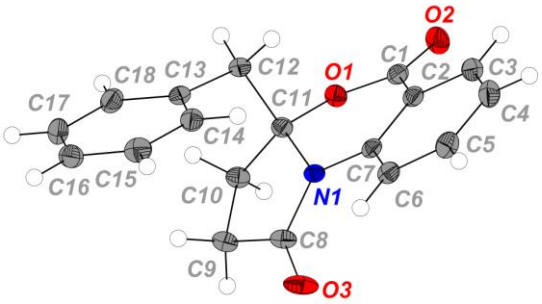


Figure 3.9. Crystal structure of 3a-benzyl-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione **20e**. Thermal ellipsoids are given at the 50% probability level.

Benzopyrrolooxazine-1,5-diona **20e** also crystallized in the orthorhombic system (Pbca). In addition to this similar molecular arrangement, bond and torsion angles in **20e** are also close to those exhibited by **20a**. Even the presence of the bulkier benzyl group did not have a detectable effect in the

aforementioned lack of coplanarity, as revealed by C7-N1-C11-C10 (164.4º). A summary of the observed bond distances, angles and torsion angles for **20e** is displayed in Tables 3.9-3.11.

Table 3.9. Selected bond-distances (Å) and bond-angles (º).

Atoms	Dist.(Å)
O1-C1	1.3604 (14)
O1-C11	1.4517 (12)
O2-C1	1.2055 (15)
O3-C8	1.2139 (15)
N1-C7	1.4016 (14)
N1-C8	1.3799 (15)
N1-C11	1.4490 (14)
C8-C9	1.5093 (16)
C11-C12	1.5386 (16)
C12-H12A	0.9900

Table 3.10. Selected bond-angles (º).

Átoms	Ang.(°)
C1-O1-C11	119.93 (9)
C7-N1-O8	127.39 (9)
C7-N1-C11	118.78 (9)
C8-N1-C11	113.83 (9)
O1-C1-O2	118.18(11)
C3-C4-C5	119.52 (11)
N1-C7-C2	116.19 (9)
N1-C7-C6	123.30 (9)
C2-C7-C6	120.50 (10)
O3-C8-N1	124.56 (10)
N1-C8-C9	107.62 (10)
O1-C11-N1	109.84 (9)
N1-C11-C10	103.67 (8)
N1- C11-C12	112.38 (9)
C11-C12-C13	111.74 (9)

Tabla 3.11. Selected torsion angles (º).

Átoms	Ang.(°)
C11-O1-C1-O2	-170.84 (10)
C1-O1-C11-N1	-39.63 (12)
C8-N1-C7-C2	152.41 (11)
C11-N1-C8-O3	-177.94 (11)
C7-N1-C11-C10	164.42 (9)
C8-N1-C11-C12	107.96 (10)
C3-C2-C7-C6	0.50 (17)
C7-C2-C3-C4	-0.53 (17)
C4-C5-C6-C7	-0.51 (17)
N1-C8-C9-C10	13.30 (12)
C12-C13-C14-C15	-175.73 (11)

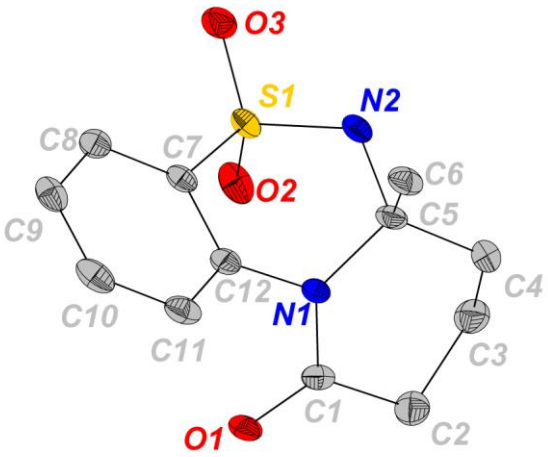


Figure 3.10. Crystal structure of 6a-methyl-6a,7,8,9-tetrahydrobenzo[*e*]pyrido[2,1-*c*][1,2,4]thiadiazin-10(6*H*)-one 5,5-dioxide **20g**.

Cyclic sultam **20g** crystallized as big colourless prisms in the monoclinic space group Cc. Only one enantiomer was present in the crystal studied, and its absolute configuration was that depicted in Figure 3.10. All the crystals of **20g** analyzed by X-Ray diffractometry (≈ 20) showed the same absolute configuration (*R* at C-5), probably due to the fact that only one enantiomer crystallized preferentially, leaving the other in an amorphous state. Anyway, more studies (e.g. chiral HPLC) should be carried out in order to verify the stereoselectivity of the presented cascade reaction protocol. For more details on structural data such as selected bond distances, bond angles and torsion angles see Tables 3.12-3.14.

Table 3.12. Selected bond-distances (Å) and bond-angles (º).

Atoms	Dist.(Å)
S1-O2	1.4365 (10)
S1-O3	1.4372 (11)
S1-N2	1.6224 (12)
S1-C7	1.7595 (14)
O1-C1	1.2280 (17)
N1-C1	1.3929 (18)
N1-C5	1.463 (5)
N1-C12	1.4318 (18)
N2-C5	1.577 (5)
C5-C6	1.526(7)

Table 3.13. Selected bond-angles (º).

Átoms	Ang.(°)
O2-S1-O3	118.45 (6)
N2-S1-C7	102.69 (6)
C5-N1-C12	113.0 (2)
O1-C1-C2	121.65 (13)
O1-C1-N1	120.14(12)
C1-C2-C3	108.97 (15)
C3-C4-C5	112.6 (3)
N2-C5-C6	107.7 (3)
N2-C5B-C4B	108.3 (6)
N1-C12-C11	122.70 (13)

Tabla 3.14. Selected torsion angles (º).

Átoms	Ang.(°)
O2-S1-N2-C5	-81.3 (3)
O3-S1-N2-C5	149.0 (3)
C12-N1-C1-O1	-2.2 (2)
C11-N1-C12-C11	67.59 (18)
N1-C1-C2-C3	-28.86 (19)
C1-C2-C3-C4	57.0 (2)
C3-C4-C5-N1	39.4 (4)
C3-C4-C5-N2	-76.4 (4)
C3-C4-C5-C6	165.2 (3)
S1-C7-C8-C9	179.66 (10)
C10-C11-C12-C7	1.4 (2))

In order to clarify if pincer complex **1** acted as a mere reservoir of palladium nanoparticles, or if heterogeneous catalytic species were involved in the reaction, an array of experiments including kinetic studies, Hg drop test, and quantitative poisoning assays were carried out.

As it can observed in Figure 3.11 neither sigmoidal shape nor induction time were noticed in the kinetic plot for the formation of pyrrolo [2,1-a]quinazolinone **20a** under the optimized conditions. In addition, when a drop of Hg was added to the reaction mixture, no inhibiting or poisoning effect was shown either. Both results are in accordance with a homogeneous catalytic system.[42,56]

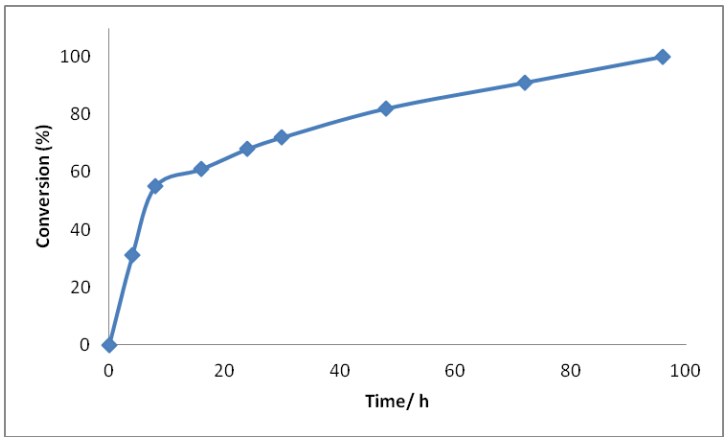


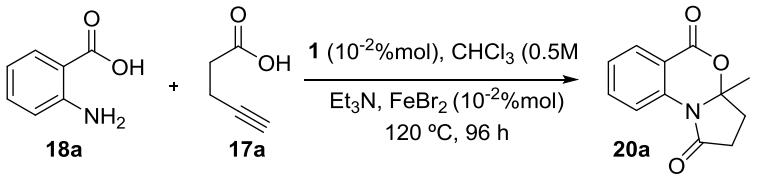
Figure 3.11. Conversion rate of anthranilic acid **19a** *vs* time.

On the other hand, as it is shown in Table 3.15, the same trend that was seen in the poisoning assays for cycloisomerization, (poor or no inhibition) was observed when adding sub- and overstoichiometric amounts of commonly known poisons/additives like CS_2 and PPh_3.[40] Besides, the catalytic activity did not show any change in the presence of overstoichiometric amounts of

[56] For the observation of kinetic curves and poisoning by amalgamation with Hg (Hg drop test) see: D. E. Bergbreiter, P. L. Osburn, J. D. Frels *Adv. Synth. Catal.* **2005**, *347*,172.

pyridine and polyvinylpyridine (PVPy). As explained in the previous section, this is another mechanistic experiment devised to distinguish between metal nanoparticles and homogeneous metal complexes.[42]

Table 3.15. Summary of poisoning experiments



	Poisoning additive	(%)[a]
1	Hg (one drop)	99
2	CS_2 (0.5 eq. per metal atom)	99
3	CS_2 (2.0 eq. per metal atom)	98
4	PPh_3 (0.03 eq. per metal atom)	99
5	PPh_3 (0.3 eq. per metal atom)	99
6	PPh_3 (4.0 eq. per metal atom)	99
7	Py [b] (150 eq. per metal atom)	98
8	PVPy [c] (300 eq. per metal atom)	99

[a] Measured by ^{1}H-NMR. Diethylene glycol dimethyl ether was used as internal standard. [b] Py: Pyridine [c] PVPy: Polyvinylpyridine.

After all the tests carried out we can propose that the pincer complex **1** could be the active catalytic species along with the added iron source, so a homogeneous catalytic system would be involved in the reaction.

To sum up, we have developed an extremely efficient route for the cycloisomerization of acetylenic acids to their corresponding enol lactones

under relatively mild reaction conditions, using palladium pincer complex **1** as catalyst. This protocol tolerates the presence of different functional groups on both α and β positions of the acetylenic acids. Furthermore, the reactions were found to be highly regioselective, resulting in selective formation of the *exo*-dig products and, for internal γ-alkynes, *Z*-alkene was steroselectively obtained. In addition, we applied this knowledge to a highly convenient, efficient cascade reaction involving alkynoic acids and dinucleophiles, thereby providing a number of relatively complex tri- and tetracyclic systems (pyrrolo-, indolo- and pyridobenzooxazinediones, pyridoquinazolinones and benzopyridothiadiazinones *inter alia*) by a one-pot procedure starting from commercially available compounds.

4. EXPERIMENTAL PROCEDURES

4.1. General methods and materials

All reagents were purchased and used as received except when indicated. All solvents used in reactions were dried and purified according to standard procedures.[57] All air- or moisture-sensitive reactions were performed under argon atmosphere. The glassware was oven dried (140ºC) overnight and purged with argon prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) at 20 ºC. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (δ=7.26 for ^{1}H and δ=77.00 for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz). Melting points were determined in a capillary tube on a Gallenkamp instrument and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230-400 mesh ASTM). IR spectra were recorded using an ATR on a JASCO FT/IR4100 in the interval between 400 and 400 cm^{-1} with 4 cm^{-1} resolution, only noteworthy absorptions are reported in cm^{-1}.Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. ICP-MS measurements were carried out on a Thermo Elemental X7 Series ICP-MS equipped with an ASX-520 autosampler. MS spectra were recorded

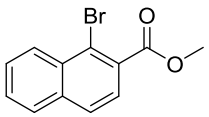
[57] a) W. L. F. Armarego, C. Chai in *Purification of Laboratory Chemicals, 5th ed.*, Elsevier Science, **2009**; b) B. G. Williams, M. S. Lawton *Org. Chem.* **2010**, *75*, 8351.

on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions. HRMS were recorded using a Micromass GCT spectrometer electrospray ionization (ESI).

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, wich was equipped with monochromated Cu kα radiation (λ= 1.54184 A) and Atlas CCD detector. Measurement was carried out at 100(2) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crysalis software package.1 The structure was solved using Olex22 and refined by full-matrix least-squares with SHELXL-97.3 Final geometrical calculations were carried out with Mercury4. and PLATON5 as integrated in WinGX.

4.2. Synthesis of alkynoic acids

General procedure for the synthesis of methyl esters. To a solution of the 2- halobenzoic acid (2 mmol) in MeOH (0.5 mL) was dropwise added a catalytic amount of concentrated H_2SO_4 (50µL, 10^{-3} mmol) in an ice bath. Then, the reaction mixture was refluxed and stirred overnight. The resulting mixture was poured into Et_2O (10 mL) and water (10 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the desired methyl ester which was used in the next steps without further purification.

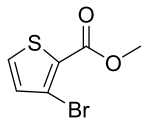


Methyl 1-bromo-2-naphthoate, 21.[58] The general procedure was followed, and compound **21** was isolated as brown prims (448.8 mg, 85%).

^{1}H NMR ($CDCl_3$) δ 8.42 (d, *J* = 8.3 Hz, 1H, H_{arom}), 7.78 (d, *J* = 8.4 Hz, 2H, H_{arom}), 7.70-7.47 (m, 3H, H_{arom}), 3.99 (s, 3H, OC*H*$_3$).

^{13}C NMR ($CDCl_3$) δ 167.8 (CO), 135.1 (qC_{arom}), 132.3 (qC_{arom}), 131.2 (qC_{arom}), 128.5, 128.2, 128.1, 127.8, 125.7 (C_{arom}), 122.6 (CBr), 52.7 (O*C*H$_3$).

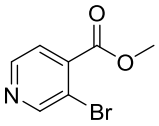
[58] A. T. Wrigth, J. D. Song, B. F. Cravatt *J. Am. Chem. Soc.* **2009**, *131*, 10692.



Methyl 3-bromothiophene-2-carboxylate, 22. The general procedure was followed, and compound **22** was isolated as a brown oil (347.5 mg, 79 %).

^{1}H NMR ($CDCl_3$) δ 7.28 (d, *J* = 5.8 Hz, 1H, H_{arom}), 7.16 (d, *J* = 5.8 Hz, 1H, H_{arom}), 3.81 (s, 3H, OCH_3);

^{13}C NMR ($CDCl_3$) δ 162.2 (CO), 130.9 (qC_{arom}), 129.3 (C_{arom}), 125.9 (C_{arom}), 119.8 (CBr), 51.8 (OCH_3).

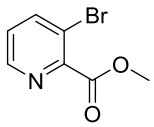


Methyl 3-bromoisonicotinate, 23.[59] The general procedure was followed, and compound **23** was isolated as a brown oil (335.3 mg, 78 %).

^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H, H_{arom}), 8.49 (d, *J* = 4.9 Hz, 1H, H_{arom}), 7.50 (d, *J* = 4.9 Hz, 1H, H_{arom}), 3.84 (s, 3H,OCH_3).

^{13}C NMR ($CDCl_3$) δ 164.7 (CO), 153.6 (C_{arom}), 148.4 (C_{arom}), 138.8 (qC_{arom}), 124.2 (C_{arom}), 118.7 (CBr), 52.9 (OCH_3).

[59] F. Pierre, P. C. Chua, S. E. O'Brien, A. Siddiqui-JainP. Bourbon, M. Haddach, J. Michaux, J. Nagasawa, M. K. Schwaebe, E. Stefan, A. Vialettes, J. P. Whitten, T. K. Chen, L. Darjania, R. Stansfield, K. Anderes, J. Bliesath, D. Drygin, C. Ho, M. Omori, C. Proffitt, N. Streiner, K. Trent, W. G. Rice, D. M. Ryckman *J. Med. Chem.* **2011**, *54*, 635

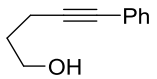


Methyl 3-bromopicolinate, 24. The general procedure was followed, and compound **24** was isolated as a brown oil (331.0 mg, 77 %).

^{1}H NMR ($CDCl_3$) δ 8.55 (dd, *J* = 4.6, 0.9 Hz, 1H, H_{arom}), 7.95 (dd, *J* = 8.2, 1.0 Hz, 1H, H_{arom}), 7.25 (dd, *J* = 8.2, 4.6 Hz, 1H, H_{arom}), 3.95 (s, 3H, OCH_3);

^{13}C NMR ($CDCl_3$) δ 165.2 (CO), 149.0 (qC_{arom}), 147.7 (C_{arom}), 141.9 (C_{arom}), 126.5 (C_{arom}), 119.1 (CBr), 53.0 (OCH_3).

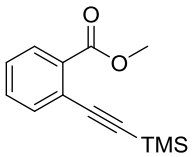
General procedure for Sonogashira cross-coupling. Under an atmosphere of argon the aryl halide (1.5 mmol) and acetylene derivative (1.8 mmol) were dissolved in 6 ml of degassed triethylamine at room temperature. Then, $(Ph_3P)_2PdCl_2$ (21.0 mg, 0.03mmol) and CuI (11.4 mg, 0.03mmol) were added sequentially and stirring at room temperature was continued overnight. The crude mixture was dissolved in DCM and the solution was filtered over a plug of silica, and then the solvent was removed under reduced pressure. This work-up procedure was repeated two times to remove triethylamine completely. The crude was purified by flash column chromatography on (Hexanes:EtOAc) to afford the desired product.



5-Phenylpent-4-yn-1-ol, 25.[60] The general procedure was followed, and compound **25** was obtained as a white powder (151.2 mg, 95%).

^{1}H NMR (CDCl3) δ 7.40 (dd, *J* = 6.6, 3.1 Hz, 2H, H_{arom}), 7.27 (dd, *J* = 5.0, 1.6 Hz, 3H, H_{arom}), 3.79 (t, *J* = 6.2 Hz, 2H, CH_2), 2.52 (t, *J* = 7.0 Hz, 2H, CH_2), 2.45 (s, 1H, O*H*), 1.85 (p, *J* = 6.6 Hz, 2H, CH_2).

^{13}C NMR ($CDCl_3$) δ 131.6 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 123.8 (qC_{arom}), 89.5 (qC), 81.1 (qC), 61.6 (*C*H_2), 31.4 (*C*H_2), 16.0 (*C*H_2).



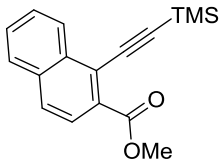
Methyl 2-[(trimethylsilyl)ethynyl]benzoate, 27.[61] The general procedure was followed, and compound **27** was obtained an orange oil (264.6 mg, 76%).

^{1}H NMR (CDCl3) δ 7.86 (dd, *J* = 7.7, 1.2 Hz, 1H, H_{arom}), 7.52 (dd, *J* = 7.6, 1.0 Hz, 1H, H_{arom}), 7.39-7.31 (m, 2H, H_{arom}), 3.88 (s, 3H, OCH_3), 0.25 (s, 9H, Si(CH_3)$_3$).

[60] A. Nagendiran, O. Verho, C. Haller, E. V. Johnston, J.E. Bäckvall *J. Org. Chem.* **2014**, *79*, 1399.

[61] A. S. K. Hashmi, C. Lothschütz, R.Döpp, M. Ackermann, J. De Buck Becker, M. Rudolph,C. Scholz, F. Rominger; *Adv. Synth. Catal.* **2012**, *354*, 133.

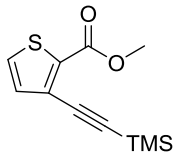
^{13}C NMR ($CDCl_3$) δ 166.9 (CO), 134.5 (C_{arom}), 132.6 (C_{arom}), 131.4 (qC_{arom}), 130.2 (C_{arom}), 128.2 (C_{arom}), 123.2 (qC_{arom}), 103.3 (qC), 99.7 (qC), 52.0 (OCH_3), -0.1 ($Si(CH_3)_3$).



Methyl 1-((trimethylsilyl)ethynyl)-2-naphthoate, 28.[58] The general procedure was followed, and compound **28** was obtained as a brown oil (406.2 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.0 Hz, 1H, H_{arom}), 7.92 (d, *J* = 8.7 Hz, 1H, H_{arom}), 7.83 (t, *J* = 6.5 Hz, 2H, H_{arom}), 7.68-7.53 (m, 2H, H_{arom}), 4.00 (s, 3H, OCH_3), 0.38 (s, 9H, $Si(CH_3)_3$).

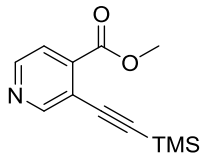
^{13}C NMR ($CDCl_3$) δ 167.5 (CO), 134.3 (qC_{arom}), 133.6 (qC_{arom}), 131.3 (qC_{arom}), 128.4, 128.1, 127.7, 127.6, 125.6 (C_{arom}), 121.8 (qC_{arom}), 106.8 (qC), 100.8 (qC), 52.1 (OCH_3), -0.1($Si(CH_3)_3$).



Methyl 3-((trimethylsilyl)ethynyl)thiophene-2-carboxylate, 29. The general procedure was followed, and compound **29** was obtained as an orange oil (353.5 mg, 99%).

^{1}H NMR ($CDCl_3$) δ 7.36 (d, *J* = 5.4 Hz, 1H, H_{arom}), 7.12 (d, *J* = 5.4 Hz, 1H, H_{arom}), 3.84 (s, 3H, OCH_3), 0.25 (s, 9H, $Si(CH_3)_3$).

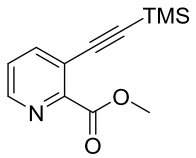
^{13}C NMR ($CDCl_3$) δ 162.6 (CO), 134.9 (qC_{arom}), 129.0 (qC_{arom}), 128.7, 125.9 (C_{arom}), 105.6 (qC), 96.0 (qC), 51.7 (OCH_3), -0.3 ($Si(CH_3)_3$).



Methyl 3-((trimethylsilyl)ethynyl)isonicotinate, 30. The general procedure was followed, and compound **30** was obtained as an orange oil (297.2 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H, H_{arom}), 8.58 (d, *J* = 5.0 Hz, 1H, H_{arom}), 7.67 (d, *J* = 4.9 Hz, 1H, H_{arom}), 3.92 (s, 3H, OCH_3), 0.25 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR ($CDCl_3$) δ 165.1 (CO), 154.9, 148.7 (C_{arom}), 138.9 (qC_{arom}), 122.7 (C_{arom}), 118.7 (qC_{arom}), 103.3 (qC), 99.9 (qC), 52.4 (OCH_3), -0.3 ($Si(CH_3)_3$).

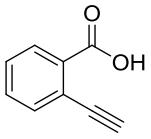


Methyl 3-((trimethylsilyl)ethynyl)picolinate, 31. The general procedure was followed, and compound **31** was obtained as an orange oil (286.7 mg, 82%).

^{1}H NMR ($CDCl_3$) δ 8.56 (dd, *J* = 4.7, 1.5 Hz, 1H, H_{arom}), 7.85 (dd, *J* = 7.9, 1.5 Hz, 1H, H_{arom}), 7.34 (dd, *J* = 7.9, 4.7 Hz, 1H, H_{arom}), 3.95 (s, 3H, OCH_3), 0.23 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR ($CDCl_3$) δ 165.1 (CO), 150.1 (qC_{arom}), 148.2, 141.8, 125.1 (C_{arom}), 120.2 (qC_{arom}), 103.4 (qC), 100.0 (qC), 52.6 (OCH_3), -0.3 ($Si(CH_3)_3$).

General procedure for the synthesis of alkynoic acids by hydrolysis/desilylation. To a solution of the corresponding methyl ester (1 mmol) in 6.5 mL of MeOH at 0 ºC, a solution of potassium hydroxide (560 mg, 10 mmol) in 3 ml of water was added. The mixture was stirred for 2 hours at room temperature. The organic layer was removed and the aqueous one acidified with aqueous diluted HCl to pH = 3. The aqueous phase was extracted with EtOAc (3 x 20 ml) and the combined organic layers were washed with brine and dried over anhydrous $NaSO_4$ and filtered, and the solvents were removed *in vacuo*. Purification by flash column chromatography achieved the afforded alkynoic acids **17**.

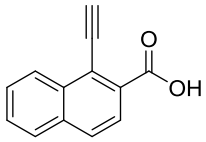


2-Ethynylbenzoic acid, 17h.[61] The general procedure was followed, and compound **17h** was obtained as a white powder (150 mg, 69%).

m.p. 125-128 °C ($CHCl_3$)(Lit.[62] 121-123 ºC).

^{1}H NMR (MeOD) δ 7.93 (dd, *J* = 7.7, 1.1 Hz, 1H, H_{arom}), 7.62 (dd, *J* = 7.6, 1.1 Hz, 1H, H_{arom}), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H, H_{arom}), 7.45 (td, *J* = 7.6, 1.4 Hz, 1H, H_{arom}), 3.74 (bs, 1H, C_{sp}-*H*), COO*H* not detectable.

^{13}C NMR ($CDCl_3$) δ 167.0 (*C*OOH), 152.0 (qC_{arom}), 138.9 (qC_{arom}), 134.4 , 130.4, 124.6, 120.9 (C_{arom}), 90.4 (qC), 89.8 (C_{sp}-H).

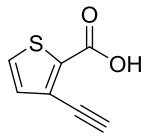


1-Ethynyl-2-naphthoic acid, 17i.[58] The general procedure was followed, and compound **17i** was obtained as a purple powder (176.4 mg, 90%).
m.p. 128-131 °C ($CHCl_3$)(Lit.[58] 121-123 ºC).

^{1}H NMR (MeOD) δ 8.53 (dd, *J* = 6.8, 2.7 Hz, 1H, H_{arom}), 7.96-7.82 (m, 3H, H_{arom}), 7.67-7.54 (m, 2H, H_{arom}), 4.27 (s, 1H, C_{sp}-*H*), COO*H* not detectable.

^{13}C NMR (MeOD) δ 168.7 (*C*OOH), 134.3 (qC_{arom}), 133.5 (qC_{arom}), 132.5 (qC_{arom}), 128.4, 127.9, 127.8, 127.4, 126.8, 125.1 (C_{arom}), 120.5 (qC_{arom}), 89.2 (C_{sp}-H), 78.8 (qC).

[62] E. Marchal, P. Uriac, B. Legouin, L. Toupet, P. van de Wegener *Tetrahedron* **2007**, *63*, 9979.



3-Ethynylthiophene-2-carboxylic acid, 17j. The general procedure was followed, and compound **17j** was obtained as an orange powder (150.5 mg, 99%).

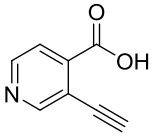
m.p. 115-119 °C ($CHCl_3$).

^{1}H NMR (MeOD) δ 7.42-7.36 (m, 2H, H_{arom}), 4.17 (s, 1H, C_{sp}-*H*), COO*H* not detectable.

^{13}C NMR (MeOD) δ 163.7 (*C*OOH), 135.9 (qC_{arom}), 128.5 (C_{arom}), 128.1 (qC_{arom}), 126.2 (C_{arom}), 87.6 (C_{sp}-H), 74.9 (qC).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_7H_5O_2S$: 153.0010; found: 153.0005.

IR (ATR) υ_{max} 3285, 2955, 2926, 2851, 1511, 1680, 1518, 1451, 1285, 711 cm^{-1}.



3-Ethynylisonicotinic acid, 17k. The general procedure was followed, and compound **17k** was obtained as a yellow powder (145.5 mg, 99%).

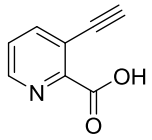
m.p. 124-127 °C ($CHCl_3$).

^{1}H NMR (DMSO) δ 8.78 (s, 1H, H_{arom}), 8.67 (d, *J* = 5.0 Hz, 1H, H_{arom}), 7.70 (d, *J* = 5.0 Hz, 1H, H_{arom}), 4.56 (s, 1H, C_{sp}-*H*), COO*H* not detectable.

^{13}C NMR (DMSO) δ 166.4 (*C*OOH), 154.8 (C_{arom}), 150.04 (C_{arom}), 141.58 (qC_{arom}), 123.0 (C_{arom}), 117.3 (qC_{arom}), 88.4 (C_{sp}-H), 79.5 (qC).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_8H_6NO_2$: 148.0399; found: 148.0389.

IR (ATR) υ_{max} 382, 2861, 1788, 1709, 1406, 1213, 808, 653. cm^{-1}.



3-Ethynylpicolinic acid, 17l. The general procedure was followed, and compound **17l** was obtained as a yellow powder (129.6 mg, 88%).

m.p. 137-140 °C ($CHCl_3$).

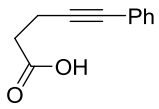
^{1}H NMR (MeOD) δ 8.90 (d, *J* = 4.8 Hz, 1H, H_{arom}), 8.77 (d, *J* = 8.1 Hz, 1H, H_{arom}), 8.21 (dd, *J* = 8.0, 5.5 Hz, 1H, H_{arom}), 4.50 (s, 1H, C_{sp}-*H*), COO*H* not detectable.

^{13}C NMR (MeOD) δ 165.9 (*C*OOH), 150.4 (qC_{arom}), 147.7, 142.8, 125.7 (C_{arom}), 119.2 (qC_{arom}), 86.1 (C_{sp}-H), 78.5 (qC).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_8H_6NO_2$: 148.0396; found: 148.0392.

IR (ATR) υ_{max} 3238, 2856, 2459, 1780, 1700, 1264, 1105, 805 cm^{-1}.

General procedure for the synthesis of alkynoic acids by Jones oxidation. Jones reagent (0.5 M CrO_3 in an aqueous 98% solution of H_2SO_4 in water) was added dropwise to a solution of the corresponding alchol (1.2 mmol) in 20 mL of acetone at 0 °C. This mixture was stirred for 4 hours at the same temperature, and then quenched with *i*-PrOH (5 mL). The resulting crude mixture was acidified with 1 M aqueous HCl to pH = 1 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL), dried over anhydrous $NaSO_4$ and filtered, and the filtrate was concentrate *in vacuo*. Purification by flash column chromatography (Hexanes:EtOAc) afforded the target alkynoic acid.



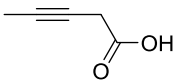
5-Phenylpent-4-ynoic acid, 17e.[60] The general procedure was followed, and compound **17e** was obtained as white prims (121.1 mg, 58%).

m.p. 96-99 °C ($CHCl_3$)(Lit.[63] 103-107 ºC).

^{1}H NMR ($CDCl_3$) δ 11.49 (s, 1H, COO*H*), 7.49-7.34 (m, 2H, H_{arom}), 7.34-7.16 (m, 3H, H_{arom}), 2.89-2.51 (m, 4H, CH_2).

^{13}C NMR ($CDCl_3$) δ 178.4 (*C*OOH), 131.6, 128.2, 127.9 (C_{arom}), 123.4 (qC_{arom}), 87.6 (qC), 81.4 (qC), 33.5 (*C*H_2), 15.1 (*C*H_2).

[63] H. Harkat, A. Y. Dembele, J.-M. Weibel, A. Blanc, P. Pale *Tetrahedron* **2009,** *65*, 1871.



Pent-3-ynoic acid, 17f.[64] The general procedure was followed, and compound **17f** was obtained as colorless prims (84.8 mg, 72%).

m.p. 78-82 °C ($CHCl_3$)(Lit.[65] 102-104 ºC).

^{1}H NMR ($CDCl_3$) δ 11.48 (s, 1H, COO*H*), 3.28 (d, *J* = 2.5 Hz, 2H, CH_2), 1.80 (t, *J* = 2.4 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 175.5 (*C*OOH), 79.9 (qC), 69.7 (qC), 25.8 (*C*H_2), 3.5 (*C*H_3).

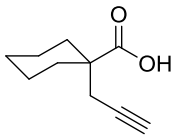
Synthesis of 1-(prop-2-yn-1-yl)cyclohexane-1-carboxylic acid, 17c.[66] In an oven dry round bottom flask LDA (1.90 mL of a 2M solution in THF/heptanes/ ethyl benzene, 3.84 mmol) was dissolved in 5 mL of dry THF and cooled to -78 ºC under argon. To this LDA solution methyl cyclohexanecarboxylate (0.5 mL, 3.5 mmol) was added in 10 min. After 1 hour, propargyl bromide (0.33 mL, 3.7 mmol) was added dropwise. The resulting mixture was kept at -78 °C for 1 hour and warmed to 25 °C over 1 hour. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (3 x 10 mL). The combined organic layers were separated, washed with 2M aqueous HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl; dried over anhydrous Na_2SO_4, filtered and

[64] B. C. Gorske, C. T. Mbofana, S. J. Miller *Org. Lett.* **2009**, *11*, 4318.

[65] A. Krueger *Science of Synthesis* **2008**, *43*, 469.

[66] C. Sun, Y. Fang, S. Li, Y.Zhang, Q. Zhao, S. Zhu, C. Li *Org. Lett.* **2009**, *11*, 4084.

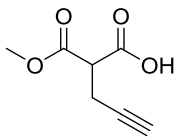
concentrated *in vacuo* to afford practically pure (^{1}H-NMR) methyl 1-(prop-2-ynyl)cyclohexane carboxylate (488 mg, 77%) as an orange liquid, which was used without further purification in the next step. To a solution of the above methyl ester (488 mg, 2.71 mmol) in 8 mL of MeOH at 0 ºC, a solution of potassium hydroxide (1.5 g, 27.1 mmol) in 5.5 mL of water was added. The mixture was stirred for 4 hours at room temperature. The organic layer was removed and the aqueous one acidified with aqueous diluted HCl to pH = 1. The aqueous phase was extracted with EtOAc (3 x 20 ml), and the combined organic layers were washed with saturated aqueous NaCl and dried over anhydrous $NaSO_4$, filtered and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography in hexanes:EtOAc (7:3) afforded pure 1-(prop-2-yn-1-yl)cyclohexane-1-carboxylic **17c**[66] acid as a colorless oil (332 mg, 74%).



^{1}H NMR ($CDCl_3$) 12.06 (bs, 1H, COO*H*), 2.42-2.44 (m, 2H, CH_2), 2.01-2.06 (m, 3H, H_{alk}), 1.18-1.55 (m, 7H, H_{alk}).

^{13}C NMR ($CDCl_3$) δ 182.3 (*C*OOH), 79.5 (C_{sp}-H). 70.7 (qC), 46.0 (*C*H_2), 32.2 (qC), 28.3, 25.0, 22.3 (*C*H_2).

Synthesis of 2-(methoxycarbonyl)pent-4-ynoic acid, 17d.[60] To a solution of dimethyl propargylmalonate (0.35 mL, 2.2 mmol) in methanol (5 mL) was added NaOH (96 mg, 2.4 mmol). The mixture was stirred at room temperature for 18 hours. Then, 10 mL of aqueous saturated sodium bicarbonate were added, and the mixture was extracted with EtOAc (3 x 10 mL). The aqueous phase was acidified to pH = 1 with concentrated HCl and extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, providing the desired 2-(methoxycarbonyl)pent-4-ynoic acid **17d** as a white powder (312.4 mg, 91%).



m.p. 68-71 °C ($CHCl_3$)(Lit.[67] 94-96 ºC).

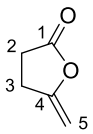
^{1}H NMR ($CDCl_3$) δ 10.99 (bs, 1H, COO*H*), 3.80 (s, 3H, COOCH_3), 3.65 (t, *J* = 7.5 Hz, 1H, C*H*), 2.81 (ddd, *J* = 7.7, 2.6, 1.4 Hz, 2H, CH_2), 2.05 (t, *J* = 2.6 Hz, 1H, C_{sp}-*H*).

^{13}C NMR (CDCl3) δ 173.4 (*C*OOH), 168.0 (*C*OOCH$_3$), 79.4 (qC), 70.8 (C_{sp}-H), 53.1 (COO*C*H$_3$), 50.1 (*C*H), 18.4 (*C*H$_2$).

[67] J. Aleman, V. del Solar, C. Martin-Santos, L. Cubo, C. Navarro *J. Org. Chem.* **2011**, *76*, 7287.

4.3. General procedure for complex 1-catalyzed cycloisomerization.

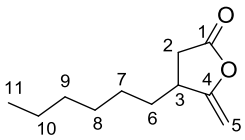
The alkynoic acid **17** (0.2 mmol), triethylamine (25 µL of a $3 \cdot 10^{-3}$M solution in $CHCl_3$, $4 \cdot 10^{-3}$ mmol), palladacycle **1** (50 µL of a $6 \cdot 10^{-7}$M solution in $CHCl_3$, $2x10^{-7}$ mmol) and $CDCl_3$ (2 mL) were placed in a screw-capped tube and heated in an oil bath at the indicated temperature for an appropriate time. The reaction mixture was subsequently filtered through a short plug of silica gel to remove triethylamine to provide pure lactone **18**, or alternatively, purified by flash column chromatography using hexanes:EtOAc (7:3) in the referred cases. The progress of the reaction was monitored by ^{1}H NMR.



5-Methylenedihydrofuran-2(3*H*)-one, 18a.[60] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50 °C for 24 h. Compound **18a** was obtained as a colorless oil (19.1 mg, 97%).

^{1}H NMR ($CDCl_3$) δ 4.75 (dd, *J* = 4.2, 2.0 Hz, 1H, H-5a/H-5b), 4.31 (dd, *J* = 4.2, 2.0 Hz, 1H, H-5a/H-5b), 2.93-2.83 (m, 2H, H-2), 2.72-2.63 (m, 2H, H-3).

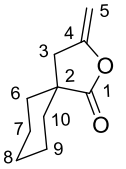
^{13}C NMR ($CDCl_3$) δ 175.0 (C-1), 155.6 (C-4), 88.7 (C-5), 28.0 (C-2), 25.1 (C-3).



4-Hexyl-5-methylenedihydrofuran-2(3*H*)-one, 18b.[60] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 70 °C for 24 h. Compound **18b** was obtained as a colorless oil (32.1 mg, 88%).

^{1}H NMR ($CDCl_3$) δ 4.71 (dd, *J* = 3.9, 2.0 Hz, 1H, H-5a/H5b), 4.30 (dd, *J* = 3.9, 2.0 Hz, 1H, H5a/H5b), 2.99 (dd, *J* = 15.9, 9.6 Hz, 1H, H-2a/H-2b), 2.74 (ddd, *J* = 14.1, 8.7, 4.9 Hz, 1H, H-2a/H-2b), 2.54 (ddt, *J* = 15.9, 7.7, 2.1 Hz, 1H, H-6a/H-6b), 1.94-1.77 (m, 1H, H-3), 1.59-1.44 (m, 1H), 1.43-1.21 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H, H-11).

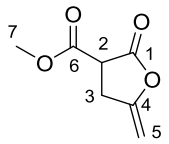
^{13}C NMR ($CDCl_3$) δ 177.2 (C-1), 154.5 (C-4), 88.6 (C-5), 39.9 (C-2), 31.6, 31.5, 30.9, 28.9, 26.9, 22.5 (C-3, C-6, C-7, C-8, C-9, C-10), 14.0 (C-11).



3-Methylene-2-oxaspiro[4.5]decan-1-one, 18c.[66] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50°C for 24 h. Compound **18c** was obtained as a colorless oil (32.4 mg, 97%).

^{1}H NMR ($CDCl_3$) δ 4.72 (dd, *J* = 4.1, 2.0 Hz, 1H, H-5a/H-5b), 4.31 (dd, *J* = 4.1, 2.0 Hz, 1H, H-5a/H-5b), 2.73 (t, *J* = 1.7 Hz, 2H, H-3), 1.83-1.68 (m, 4H, H_{alk}), 1.68-1.50 (m, 3H, H_{alk}), 1.43-1.20 (m, 3H, H_{alk}).

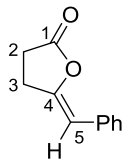
^{13}C NMR ($CDCl_3$) δ 179.7 (C-1), 153.8 (C-4), 88.9 (C-5), 44.7 (C-2), 37.2 (C-3), 32.8 (C-6, C-10), 25.1 (C-8), 22.0 (C-7, C-9).



Methyl 5-methylene-2-oxotetrahydrofuran-3-carboxylate, 18d.[60] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50°C for 24 h. Compound **18d** was obtained as a colorless oil (26.0 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (dd, *J* = 4.5, 2.3 Hz, 1H, H-5a/H-5b), 4.41 (dd, *J* = 4.4, 1.8 Hz, 1H, H-5a/H-5b), 3.83 (s, 3H, H-7), 3.76 (dd, *J* = 10.4, 7.6 Hz, 1H, H-2), 3.31 (ddt, *J* = 16.6, 7.6, 2.1 Hz, 1H, H-3a/H-3b), 3.09 (ddt, *J* = 16.6, 10.4, 1.6 Hz, 1H, H-3a/H-3b).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 167.3 (C-1, C-6), 153.1 (C-4), 89.9 (C-5), 53.4 (C-7), 46.2 (C-2), 29.3 (C-3).

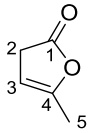


(*Z*)-5-Benzylidenedihydrofuran-2(3*H*)-one, 18e.[60] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50 °C for 72 h. Compound **18e** was obtained as white powder after purification by flash chromatography (24.4 mg, 70%).

m.p. 88-91 °C ($CHCl_3$)(Lit.[63] 91-93 ºC).

^{1}H NMR ($CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 2H, H_{arom}), 7.33 (t, *J* = 7.5 Hz, 2H, H_{arom}), 7.21 (t, *J* = 7.3 Hz, 1H, H_{arom}), 5.55 (s, 1H, H-5), 3.12-2.93 (m, 2H, H-2), 2.81-2.62 (m, 2H, H-3).

^{13}C NMR ($CDCl_3$): δ 174.9 (C-1), 148.1 (C-4), 133.9 (qC_{arom}), 128.5, 128.3, 126.7 (C_{arom}), 104.9 (C-5), 27.0 (C-2), 26.3 (C-3).

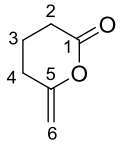


5-Methylfuran-2(3*H*)-one, 18f.[68] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 90°C for 24 h. Compound **18f** was obtained as a colorless oil (19.3 mg, 96%).

[68] N. Nebra, J. Monot, R. Shaw, B. Martin-Vaca, D. Bourissou *ACS Catal.* **2013**, *3*, 2930.

^{1}H NMR ($CDCl_3$) δ 5.11 (td, *J* = 3.3, 2.0 Hz, 1H, H-3), 3.20-3.09 (m, 2H, H-2), 1.99 (d, *J* = 2.0, 3H, H-5).

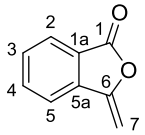
^{13}C NMR ($CDCl_3$) δ 176.9 (C-1), 153.3 (C-4), 99.0 (C-3), 34.1 (C-2), 14.0 (C-5).



6-Methylenetetrahydro-2*H*-pyran-2-one, 18g.[60] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 90 °C for 24 h. Compound **18g** was obtained as a colorless oil (23.9 mg, 98%).

^{1}H NMR ($CDCl_3$) δ 4.64 (s, 1H, H-6a/H-6b), 4.29 (s, 1H, H-6a/H-6b), 2.63 (t, *J* = 6.8 Hz, 2H, H-2), 2.48 (t, *J* = 6.5 Hz, 2H, H-4), 1.93-1.81 (m, 2H, H-3).

^{13}C NMR ($CDCl_3$) δ 168.1 (C-1), 155.3 (C-5), 93.7 (C-6), 30.3 (C-2), 26.7 (C-4), 18.6 (C-3).

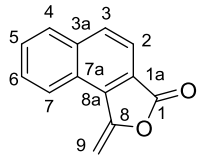


3-Methyleneisobenzofuran-1(3*H*)-one, 18h.[68] The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50 °C for 24 h. Compound **18h** was obtained as a white powder (30 mg, 94%).

m.p. 50-53 °C ($CHCl_3$)(Lit.[69] 55-57 ºC).

^{1}H NMR (MeOD) δ 7.90 (t, *J* = 7.5 Hz, 1H, H-2/H-5), 7.85 (t, *J* = 7.5 Hz, 1H, H-2/H-5), 7.79 (td, *J* = 7.5, 1.1 Hz, 1H, H_{arom}), 7.64 (td, *J* = 7.4, 1.0 Hz, 1H, H_{arom}), 5.40 (d, *J* = 3.0 Hz, 1H, H-7a/H-7b), 5.22 (d, *J* = 3.0 Hz, 1H, H-7a/H-7b).

^{13}C NMR (MeOD) δ 166.9 (C-1), 152.0 (C-6), 138.9 (qC_{arom}), 134.6, 130.4 (C_{arom}), 124.6 (qC_{arom}), 124.5, 120.7 (C_{arom}), 90.4 (C-7).



1-Methylenenaphtho[1,2-*c*]furan-3(1*H*)-one, 18i. The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50°C for 24 h. Compound **18i** was obtained as a white powder after purification by flash chromatography (29.8 mg, 76%).

[69] H. Yamamoto, G. Pandey, Y. Asai, M. Nakano, A. Kinoshita, K. Namba, H. Imagawa, M. Nishizawa *Org. Lett.* **2007**, *9*, 4029.

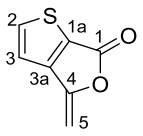
m.p. 90-93 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.37-8.25 (m, 1H, H_{arom}), 8.06-7.94 (m, 2H, H_{arom}), 7.84 (d, *J* = 8.4 Hz, 1H, H_{arom}), 7.78-7.65 (m, 2H, H_{arom}), 5.71 (d, *J* = 3.3 Hz, 1H, H-9a/H-9b), 5.57 (d, *J* = 3.3 Hz, 1H, H-9a/H-9b).

^{13}C NMR ($CDCl_3$) δ 167.1 (C-1), 152.5 (C-8), 136.6, 136.0 (qC_{arom}), 132.2, 129.9, 128.9, 128.8 (C_{arom}), 126.9, 124.7(qC_{arom}), 124.1, 120.0 (C_{arom}), 96.7 (C-9).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_{13}H_9O_2$: 197.0603; found: 197.0596.

IR (ATR) υ_{max} 3619, 2965, 2926, 2857, 1759, 1289, 1063, 991, 962, 754 cm^{-1}.



4-Methylenethieno[2,3-*c*]furan-6(4*H*)-one, 18j. The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 90 °C for 24 h. Compound **18j** was obtained as an orange powder (30 mg, 98%).

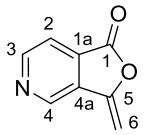
m.p. 85-88 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J* = 4.9 Hz, 1H, H-2), 7.25 (d, *J* = 4.9 Hz, 1H, H-3), 5.17 (d, *J* = 3.1 Hz, 1H, H-5a/H-5b), 5.00 (d, *J* = 3.1 Hz, 1H, H-5a/H-5b).

^{13}C NMR ($CDCl_3$) δ 161.2 (C-1), 153.2 (C-4), 149.1 (C-1a), 140.6 (C-2), 130.2 (C-3a), 118.9 (C-3), 92.60 (C-5).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_7H_5O_2S$: 153.0010; found: 153.0004.

IR (ATR) υ_{max} 3091, 2951, 2922, 2915, 1763, 1662, 1289, 991, 941, 776 cm^{-1}.



3-Methylenefuro[3,4-*c*]pyridin-1(3*H*)-one, 18k. The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50°C for 24 h. Compound **18k** was obtained as a white powder (27.9 mg, 95%).

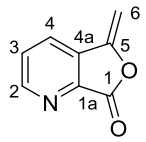
m.p. 99-102 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 9.17 (s, 1H, H-4), 8.89 (d, *J* = 5.0 Hz, 1H, H-3), 7.80 (d, *J* = 5.0 Hz, 1H, H-2), 5.41 (s, 2H, H-6).

^{13}C NMR ($CDCl_3$) δ 165.2 (C-1), 150.7 (C-4), 149.8 (C-5), 143.8 (C-3), 133.2 (C-1a), 130.0 (C-4a), 118.2 (C-2), 93.9 (C-6).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_8H_6NO_2$: 148.0399; found: 148.0389.

IR (ATR) υ_{max} 3105, 3001, 2930, 2847, 1788, 1432, 1285, 1001, 951, 682 cm^{-1}.



5-Methylenefuro[3,4-*b*]pyridin-7(5*H*)-one, 18l. The general procedure for cycloisomerization was followed, and the reaction mixture was heated at 50°C for 24 h. Compound **18l** was obtained as a white powder (27.4 mg, 93%).

m.p. 129-132 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.93 (dd, *J* = 4.7, 1.3 Hz, 1H, H-2), 8.09 (dd, *J* = 8.0, 1.3 Hz, 1H, H-4), 7.63 (dd, *J* = 8.0, 4.7 Hz, 1H, H-3), 5.44-5.36 (m, 1H, H-6a/H-6b), 5.36-5.27 (m, 1H, H-6a/H-6b).

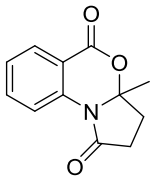
^{13}C NMR ($CDCl_3$) δ 164.3 (C-1), 153.5 (C-2), 149.2 (C-5), 143.7 (C-1a), 133.5 (C-4a), 129.0 (C-4), 127.7 (C-3), 94.2 (C-6).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_8H_6NO_2$: 148.0396; found: 148.0391.

IR (ATR) υ_{max} 2962, 2919, 2875, 2851, 1784, 1257, 1095, 1009, 811, 689 cm^{-1}.

4.4. General procedure for NNC pincer complex 1-catalyzed cascade reaction.

A solution of the aminoaromatic compound **19** (0.2 mmol), alkynoic acid **17** (0.3 mmol), NNC pincer **1** (50 μL of a $7 \cdot 10^{-5}$ M solution in $CHCl_3$, $2x10^{-5}$ mmol), and $FeBr_2$ (30 μL of a $1 \cdot 10^{-6}$ M solution in $CHCl_3$, $2x10^{-5}$ mmol) in $CHCl_3$ (0.5 M) was added to a screw-crabbed tube. The tube was sealed and the mixture was heated in an oil bath at 120 ºC for 96hours. After cooling, the mixture was purified by flash silica gel column chromatography using hexane/ethyl acetate as eluent to afford the desired compounds **20**.



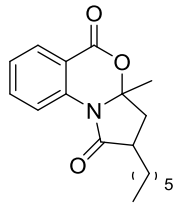
3a-Methyl-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione, 20a.[70] The general procedure was followed, and compound **20a** was obtained as colorless prims (40.4 mg, 93%).

m.p. 143-147 °C ($CHCl_3$)(Lit.[70] 165-167 ºC);

^{1}H NMR ($CDCl_3$) δ 8.12-8.05 (m, 2H, H_{arom}), 7.71-7.65 (m, 1H, H_{arom}), 7.34 (t, J = 7.7 Hz, 1H, H_{arom}), 2.84-2.37 (m, 4H, CH_2), 1.70 (s, 3H, CH_3).

[70] E. Feng, Y. Zhou, D. Zhang, L. Zhang, H. Sun, H. Jiang, H. Liu *J. Org. Chem.* **2010**, *75*, 3274.

^{13}C NMR ($CDCl_3$) δ 171.6 (N*C*O), 161.6 (*C*OO), 136.2 (qC_{arom}), 135.5, 130.4, 125.8, 121.1 (C_{arom}), 116.3 (qC_{arom}), 95.34 (qC), 32.3 (CH_2), 29.4 (CH_2), 24.8 (CH_3).



2-Hexyl-3a-methyl-3,3a-dihydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione, 20b.[70] The general procedure was followed, and compound **20b** was obtained as mixture of diasteroisomers (3:1) which were separated by flash column chromatograpy.

Diasteroisomer 20ba, colorless oil (36.3 mg, 70%).

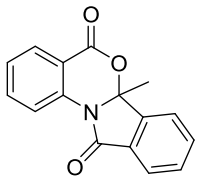
^{1}H NMR ($CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.09 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{arom}), 7.67 (td, *J* = 8.2, 1.5 Hz, 1H, H_{arom}), 7.38-7.20 (m, 1H, H_{arom}), 2.75-2.52 (m, 2H, CH_2), 2.19-2.27 (m, 1H, CH), 2.07-1.91 (m, 1H, CH_2), 1.67 (s, 3H, C*H*$_3$), 1.41-1.25 (m, 9H, H_{alkil}), 0.87 (m, 3H, C*H*$_3$).

^{13}C NMR ($CDCl_3$) δ 173.2 (N*C*O), 161.5 (*C*OO), 136.2 (qC_{arom}), 135.5, 130.4, 125.3, 120.3 (C_{arom}), 115.6 (qC_{arom}), 93.4 (qC), 40.7 (CH_2), 39.2 (*C*H), 31.5 (CH_2), 30.4 (CH_2), 29.0 (CH_2), 26.8 (CH_2), 24.3 (CH_2), 22.5 (CH_3), 13.9 (CH_3).

Diasteroisomer 20bb, yellow oil (12.7 mg, 20%).

^{1}H NMR ($CDCl_3$) δ 8.10 (dd, *J* = 7.8, 1.3 Hz, 1H, H_{arom}), 7.85 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.69 (td, *J* = 8.0, 1.5 Hz, 1H, H_{arom}), 7.35 (td, *J* = 7.7, 1.0 Hz, 1H, H_{arom}), 2.88-2.71 (m, 2H, H_{arom}), 2.09-2.08 (m, 1H, C*H*), 2.04-1.89 (m, 1H, CH_2), 1.71 (s, 3H, CH_3), 1.38-1.25 (m, 9H, H_{alkil}), 0.90 (t, *J* = 6.4 Hz, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ 175.4 (NCO), 162.0 (COO), 136.4 (qC_{arom}), 153.2, 130.2, 126.1, 122.5 (C_{arom}), 117.7 (qC_{arom}), 94.6 (qC), 40.6 (*C*H_2), 38.2 (*C*H), 31.8 (*C*H_2), 31.6 (*C*H_2), 28.9 (*C*H_2), 27.1 (*C*H_2), 26.2 (*C*H_2), 22.5 (*C*H_3), 14.0 (*C*H_3).



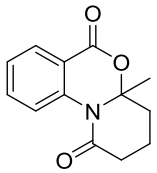
6a-Methyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-dione, 20c.[71] The general procedure was followed, and compound **20c** was obtained as a yellow powder (46.1 mg,87%).

m.p. 138-142 °C ($CHCl_3$)(Lit.[71] 145-148 ºC).

^{1}H NMR ($CDCl_3$) δ 8.16 (dd, *J* = 7.9, 1.3 Hz, 1H, H_{arom}), 8.12 (d, *J* = 8.2 Hz, 1H, H_{arom}), 7.96 (d, *J* = 7.5 Hz, 1H, H_{arom}), 7.81-7.71 (m, 3H, H_{arom}), 7.68-7.61 (m, 1H, H_{arom}), 7.40-7.35 (m, 1H, H_{arom}), 1.95 (s, 3H, CH_3).

[71] P. Aeberli, W. J. Houlihan *J. Org. Chem*. **1968**, *33*, 2402.

^{13}C-NMR ($CDCl_3$) δ 164.7 (N*C*O), 162.0 (*C*OO), 144.20, 136.2 (qC_{arom}), 135.8, 133.9, 130.9, 130.6 (C_{arom}), 130.0 (qC_{arom}), 125.5, 124.7, 122. 5, 121.4 (C_{arom}), 115.6 (qC_{arom}), 92.6 (qC), 24.3 (*C*H3).

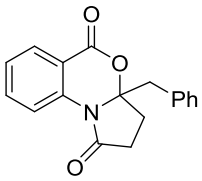


4a-Methyl-2,3,4,4a-tetrahydro-1*H*,6*H*-benzo[d]pyrido[2,1-*b*][1,3]oxazine-1,6-dione, 20d.[70] The general procedure was followed, and compound **20d** was obtained as a white powder (28.8mg, 61%).

m.p. 182-184 °C ($CHCl_3$)(Lit.[70] 201-203 ºC).

^{1}H NMR ($CDCl_3$) δ 8.06 (dd, *J* = 7.8, 1.5 Hz, 1H, H_{arom}), 7.78 (dd, *J* = 8.0, 0.9 Hz, 1H, H_{arom}), 7.64 (td, *J* = 7.8, 1.5 Hz, 1H, H_{arom}), 7.35 (td, *J* = 8.0, 0.9 Hz, 1H, H_{arom}), 2.72-2.53 (m, 2H, CH_2), 2.49-2.35 (m, 1H, CH_2), 2.21-2.01 (m, 2H, CH_2), 1.96-1.79 (m, 1H, CH_2), 1.62 (s, 3H, CH_3)

^{13}C NMR ($CDCl_3$) δ 169.2 (N*C*O), 162.5 (*C*OO), 138.6 (qC_{arom}), 134.1, 129.3, 126.2, 126.1 (C_{arom}), 120.3 (qC_{arom}), 92.4 (qC), 36.0 (*C*H_2), 33.4 (*C*H_2), 26.7 (*C*H_2), 16.6 (*C*H_3).



3a-Benzyl-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione, 20e. The general procedure was followed, and compound **20e** was obtained as colorless cristals (43.9 mg, 75%).

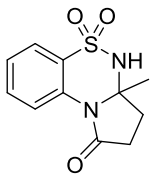
m.p. 142-146 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 1H, H_{arom}), 8.14 (dd, *J* = 7.8, 1.4 Hz, 1H, H_{arom}), 7.77 (td, *J* = 8.2, 1.5 Hz, 1H, H_{arom}), 7.37 (td, *J* = 7.8, 0.9 Hz, 1H, H_{arom}), 7.28 (dd, *J* = 6.6, 3.9 Hz, 3H, H_{arom}), 7.04 (dd, *J* = 6.5, 2.9 Hz, 2H, H_{arom}), 3.36 (d, *J* = 13.8 Hz, 1H, CH_2), 3.11 (d, *J* = 13.7 Hz, 1H, C*H*$_2$), 2.65-2.29 (m, 3H, C*H*$_2$), 1.73-1.50 (m, 1H, C*H*$_2$).

^{13}C NMR ($CDCl_3$) δ 172.0 (N*C*O), 161.4 (*C*OO), 136.3 (qC_{arom}), 135.9 (C_{arom}), 133.0 (qC_{arom}), 130.6, 129.9, 128.9, 127.9, 125.8, 120.7 (C_{arom}), 116.3 (qC_{arom}), 96.8 (qC), 42.6 (*C*H$_2$), 30.2 (*C*H$_2$), 29.5 (*C*H$_2$).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_{18}H_{16}NO_3$: 294.1130; found: 294.1129.

IR (ATR) υ_{max} 2919, 2855, 1716, 1605, 1482, 1372, 751, 707 cm^{-1}.



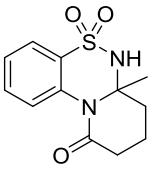
3a-Methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*e*]pyrrolo[2,1-*c*][1,2,4]thiadiazin-1-one 5,5-dioxide, 20f.[52] The general procedure was followed, and compound **20f** was obtained as colorless cristals (47.4 mg, 94%).

m.p. 189-192 °C ($CHCl_3$)(Lit.[52] 230-235 ºC).

^{1}H NMR (DMSO) 8.55 (s, 1H, N*H*), 8.28 (dd, J = 8.4, 0.8 Hz, 1H, H_{arom}), 7.81 (dd, J = 7.9, 1.4 Hz, 1H, H_{arom}), 7.73 – 7.55 (m, 1H, , H_{arom}), 7.38 (td, J = 7.8, 1.0 Hz, 1H**,** , H_{arom}), 2.77 (dt, J = 17.2, 10.0 Hz, 1H, CH_2), 2.31 – 2.18 (m, 3H, CH_2), 1.58 (s, 3H, CH_3).

^{13}C NMR (DMSO) δ 172.3 (N*C*O), 133.6 (C_{arom}), 132.9, 127.9 (qC_{arom}), 125.6, 124.7, 122.2 (C_{arom}), 78.1 (qC), 33.2 (*C*H_2), 29.6 (*C*H_2), 24.5 (*C*H_3).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_{11}H_{13}N_2O_3S$: 253.0647; found: 253.0640.



6a-Methyl-6a,7,8,9-tetrahydrobenzo[*e*]pyrido[2,1-*c*][1,2,4]thiadiazin-10(6*H*)-one 5,5-dioxide, 20g. The general procedure was followed, and compound **20g** was obtained as yellow crystals (33.5 mg, 63%).

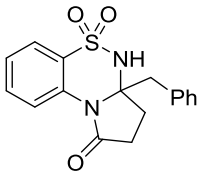
m.p. 196-199 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 1H, H_{arom}), 7.58 (d, *J* = 3.7 Hz, 2H, H_{arom}), 7.44-7.36 (m, 1H, H_{arom}), 5.17 (bs, 1H, N*H*), 2.62 (t, *J* = 6.3 Hz, 2H, CH_2), 2.23-2.06 (m, 3H, CH_2), 1.95-1.80 (m, 1H, CH_2), 1.52 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 170.0 (N*C*O), 135.4, 134.5 (qC_{arom}), 132.4, 129.3, 127.0, 123.4 (C_{arom}), 76.1 (qC), 38.1, 33.3 (*C*H_2), 27.6 (*C*H_3), 16.2 (*C*H_2).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_{15}H_{15}N_2O_3S$: 267.0803; found: 267.0802.

IR (ATR) υ_{max} 2962, 2922, 2851, 1655, 1472, 1339, 1267, 1163, 736 cm^{-1}.



3a-Benzyl-2,3,3a,4-tetrahydro-1*H*-benzo[*e*]pyrrolo[2,1-*c*][1,2,4]thiadiazin-1-one 5,5-dioxide, 20h. The general procedure was followed, and compound **20h** was obtained as a white powder (47.9 mg, 73%).

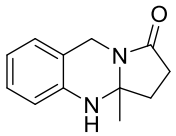
m.p. 194-196 °C ($CHCl_3$).

^{1}H NMR ($CDCl_3$) δ 8.32 (d, *J* = 8.4 Hz, 1H, H_{arom}), 7.80 (d, *J* = 7.9 Hz, 1H, H_{arom}), 7.61 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.26-7.30 (m, 4H, H_{arom}), 7.04-7.07 (m, 2H, H_{arom}), 5.77 (bs, 1H, N*H*), 3.54 (d, *J* = 14.1 Hz, 1H, CH_2), 3.06 (d, *J* = 14.1 Hz, 1H, CH_2), 2.55-2.46 (m, 1H, CH_2), 2.24-1.99 (m, 2H, CH_2), 1.46-1.31 (m, 1H, CH_2).

^{13}C NMR (CDCl3) δ 172.4 (N*C*O), 133.7 (C_{arom}), 132.5 (qC_{arom}), 130.1, 128.9 (C_{arom}), 127.9 (qC_{arom}), 127.8, 125.8, 124.7, 122.8 (C_{arom}), 80.3 (qC), 42.1 (*C*H_2), 31.3 (*C*H_2), 29.6 (*C*H_2).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_{17}H_{17}N_2O_3S$: 329.0960; found: 329.0957.

IR (ATR) υ_{max} 3238, 1695, 1472, 1361, 1332, 1260, 1156, 725, 700 cm^{-1}.



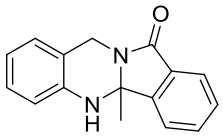
3a-Methyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one, 20i.[72] The general procedure was followed, and compound **20i** was obtained as yellow crystals (38.4 mg, 95%).

m.p. 131-134 °C ($CHCl_3$)(Lit.[72] 138-140 ºC).

^{1}H NMR ($CDCl_3$) δ 7.10-6.96 (m, 2H, H_{arom}), 6.78 (t, *J* = 7.4 Hz, 1H, H_{arom}), 6.56 (d, *J* = 8.0 Hz, 1H, H_{arom}), 5.02 (d, *J* = 16.9 Hz, 1H, CH_2), 4.17 (d, *J* = 16.8 Hz, 1H, CH_2), 3.83 (bs, 1H, N*H*), 2.59-2.48 (m, 2H, CH_2), 2.25-1.97 (m, 2H, CH_2), 1.54 (s, 3H, CH_3).

[72] N. T. Patil, A. K. Mutyala, P. G. V. V. Lakshmi, B. Gajula, B. Sridhar, G. R. Pottireddygari, T. P. Rao *J. Org. Chem.* **2010**, *75*, 5963.

^{13}C NMR ($CDCl_3$) δ 174.2 (N*C*O), 141.8 (qC_{arom}), 127.6, 126.9, 119.3 (C_{arom}), 117.4 (qC_{arom}), 116.4 (C_{arom}), 71.9 (qC), 38.6 (*C*H_2), 32.9 (*C*H_2), 29.5 (*C*H_2), 25.6 (*C*H_3).



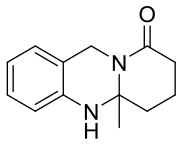
4b-Methyl-5,10-dihydroisoindolo[1,2-*b*]quinazolin-12(4b*H*)-one, 20j.[72]

The general procedure was followed, and compound **20j** was obtained as a brown powder (41.0 mg, 82%).

m.p. 190-194 °C ($CHCl_3$)(Lit.[72] 222-224 ºC).

^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J* = 7.4 Hz, 2H, H_{arom}), 7.63 (d, *J* = 4.0 Hz, 2H, H_{arom}), 7.58-7.48 (m, 1H, H_{arom}), 7.15-7.09 (m, 2H, H_{arom}), 6.88 (t, *J* = 7.4 Hz, 1H, H_{arom}), 6.69 (d, *J* = 8.0 Hz, 1H, H_{arom}), 5.32 (d, *J* = 16.9 Hz, 1H, C*H*$_2$), 4.45 (d, *J* = 17.0 Hz, 1H, C*H*$_2$), 1.71 (s, 3H, C*H*$_3$).

^{13}C NMR ($CDCl_3$) δ 165.7 (N*C*O), 147.7, 140.0 (qC_{arom}), 132.2 (C_{arom}), 131.3 (qC_{arom}), 129.5, 127.8, 127.1, 124.3, 120.5, 120.3 (C_{arom}), 118.6 (qC_{arom}), 118.0 (C_{arom}), 71.4 (qC), 37.9 (*C*H_2), 23.8 (*C*H_3).

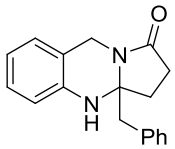


5a-Methyl-5,5a,6,7,8,11-hexahydro-9*H*-pyrido[2,1-*b*]quinazolin-9-one, 20k.[72] The general procedure was followed, and compound **20k** was obtained as a yellow powder (24.6 mg, 57%).

m.p. 135-138 °C ($CHCl_3$)(Lit.[72] 156-158 ºC).

^{1}H NMR ($CDCl_3$) δ 7.05 (d, *J* = 7.8 Hz, 2H, H_{arom}), 6.79 (t, *J* = 7.4 Hz, 1H, H_{arom}), 6.60 (d, *J* = 7.8 Hz, 1H, H_{arom}), 5.48 (d, *J* = 17.3 Hz, 1H, CH_2), 4.18 (d, *J* = 17.3 Hz, 1H, CH_2), 2.60-2.29 (m, 2H, CH_2), 2.09-1.86 (m, 3H, CH_2), 1.84-1.68 (m, 1H, CH_2), 1.53 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$) δ 169.0 (N*C*O), 141.0 (qC_{arom}), 127.4, 126.8, 119.3 (C_{arom}), 118.9 (qC_{arom}), 116.1 (C_{arom}), 68.3 (qC), 39.8 (*C*H_2), 37.4 (*C*H_2), 32.9 (*C*H_2), 26.9 (*C*H_2), 16.8 (*C*H_3).



3a-Benzyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one, 20l. The general procedure was followed, and compound **20l** was obtained as an orange oil (45.0 mg, 81%).

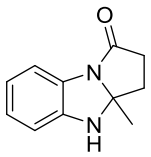
^{1}H NMR ($CDCl_3$) δ 7.26-7.35 (m, 3H, H_{arom}), 7.17-7.03 (m, 4H, H_{arom}), 6.83 (t, *J* = 7.4 Hz, 1H, H_{arom}), 6.59 (d, *J* = 7.8 Hz, 1H, H_{arom}), 5.11 (d, *J* =

17.1 Hz, 1H, CH_2), 4.34 (d, *J* = 17.1 Hz, 1H, CH_2), 4.04 (bs, 1H, N*H*), 3.22 (d, *J* = 13.1 Hz, 1H, CH_2), 2.90 (d, *J* = 13.1 Hz, 1H, CH_2), 2.54-2.18 (m, 3H, CH_2), 1.84-1.62 (m, 1H, CH_2).

^{13}C NMR ($CDCl_3$) δ 174.6 (N*C*O), 141.4 (qC_{arom}), 135.5 (qC_{arom}), 130.1, 128.7, 127.9, 127.3, 127.1, 119.4 (C_{arom}), 117.5 (qC_{arom}), 116.3 (C_{arom}), 74.1 (qC), 42.5 (*C*H_2), 39.1 (*C*H_2), 30.5 (*C*H_2), 29.3 (*C*H_2).

HRMS (*m/z*): $[M+H]^+$ calc. for $C_{18}H_{19}N_2O$: 279.1497; found: 279.1498.

IR (ATR) υ_{max} 3310, 3023, 2922, 2861, 1684, 1482, 1451, 1393, 1264, 739, 703 cm^{-1}.

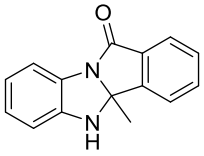


3a-Methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one, 20m.[73] The general procedure was followed, and compound **20m** was obtained as a brown oil (27.8 mg, 74%).

^{1}H NMR ($CDCl_3$) δ 7.45 (dd, *J* = 7.6, 0.8 Hz, 1H, H_{arom}), 6.98 (td, *J* = 7.7, 1.2 Hz, 1H, H_{arom}), 6.84 (td, *J* = 7.6, 1.1 Hz, 1H, H_{arom}), 6.70 (dd, *J* = 7.7, 0.6 Hz, 1H, H_{arom}), 4.20 (bs, 1H, N*H*), 2.87-2.74 (m, 1H, CH_2), 2.61-2.47 (m, 1H, CH_2), 2.45-2.36 (m, 2H, CH_2), 1.53 (s, 3H, CH_3).

[73] S. Caccamese, G. Principato, A. Chimirri, S. Grasso *Tetrahedron*, **1996**, *7*, 2577.

^{13}C NMR ($CDCl_3$) δ 173.7 (N*C*O), 142.7, 128.6 (qC_{arom}), 125.2, 120.1, 115.4, 110.6 (C_{arom}), 85.6 (qC), 37.7 (*C*H_2), 33.6 (*C*H_2), 26.2 (*C*H_3).

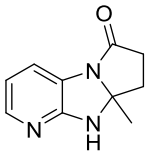


4b-Methyl-4b,5-dihydro-11*H*-benzo[4,5]imidazo[2,1-*a*]isoindol-11-one, 20n.[72] The general procedure was followed, and compound **20n** was obtained as a yellow powder (41.5 mg, 75%).

m.p. 146-149 °C ($CHCl_3$)(Lit.[72] 186-188 ºC).

^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 1H, H_{arom}), 7.63 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.57-7.47 (m, 3H, H_{arom}), 7.03-6.87 (m, 2H, H_{arom}), 6.74 (d, *J* = 7.7 Hz, 1H, H_{arom}), 4.24 (s, 1H, N*H*), 1.83 (s, 3H, C*H*$_3$).

^{13}C NMR ($CDCl_3$) δ 170.6 (N*C*O), 149.5, 145.0 (qC_{arom}), 133.4 (C_{arom}), 132.1, 130.7 (qC_{arom}), 129.6, 125.3, 125.1, 121.8, 121.1, 117.2, 111.5 (C_{arom}), 86.0 (qC), 26.8 (*C*H_3).



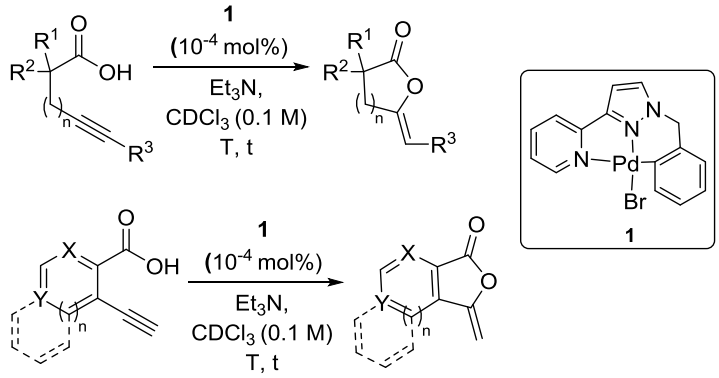
8a-Methyl-7,8,8a,9-tetrahydro-6*H*-pyrrolo[1',2':1,2]imidazo[4,5-*b*]pyridin-6-one, 20o.[73] The general procedure was followed, and compound **20o** was obtained as a brown oil (34.0 mg, 90%).

^{1}H NMR ($CDCl_3$) δ 7.75 (dd, *J* = 5.4, 1.2 Hz, 1H, H_{arom}), 7.52 (dd, *J* = 7.4, 1.4 Hz, 1H, H_{arom}), 6.66 (dd, *J* = 7.4, 5.5 Hz, 1H, H_{arom}), 5.84 (bs, 1H, N*H*), 2.87-2.65 (m, 1H, CH_2), 2.60-2.38 (m, 3H, CH_2), 1.58 (s, 3H, CH_3).

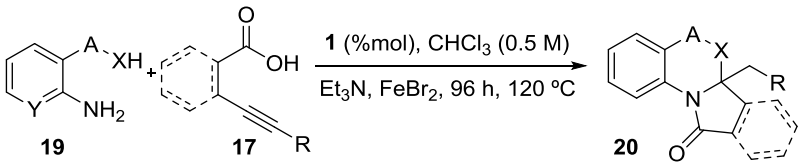
^{13}C NMR ($CDCl_3$) δ 174.9 (N*C*O), 156.6 (qC_{arom}), 142.8 (C_{arom}), 122.5 (qC_{arom}), 120.6, 114.5 (C_{arom}), 83.3 (qC), 38.2 (*C*H_2), 32.5 (*C*H_2), 26.7 (*C*H_3)

5. CONCLUSIONS

- γ- alkylidene lactones can be easily obtained through the cycloisomerization of the corresponding acetylenic acid in the presence of very low amounts (10^{-4} mol%) of palladium pincer complex **1**. This procedure shows tolerance to a variety of functional groups on both the α and γ positions of the acetylenic acids.



- The knowledge gained in the above transformation can be applied to a facile and practical entry to a number of relatively complex tri- and tetracyclic systems (pyrrolo-, indolo- and pyridobenzooxazinediones, pyrido-quinazolinones and benzo pyridothiadiazinones *inter alia*).
- The above cascade reaction from alkynoic acids and dinucleophiles takes place in the presence of a low loading of palladium pincer complex **1** and an iron co-catalyst, thereby forming three new bonds in a very convenient tandem process.



19 **17** **20**

A= CH, CO, SO_2; X= N, O; Y= N

- Mechanistic and kinetics assays suggest the participation of homogeneous catalytic species for both protocols.

IV

Dynamic Kinetic Resolution of allylic alcohols

1. INTRODUCTION

The importance of chirality is well recognised, mainly in connection with the fact that a large number of natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. Indeed, the use of chiral drugs in enantiopure form is now a standard requirement for many chemical entities and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies, as well as an important and challenging area of contemporary synthetic organic chemistry.[1]

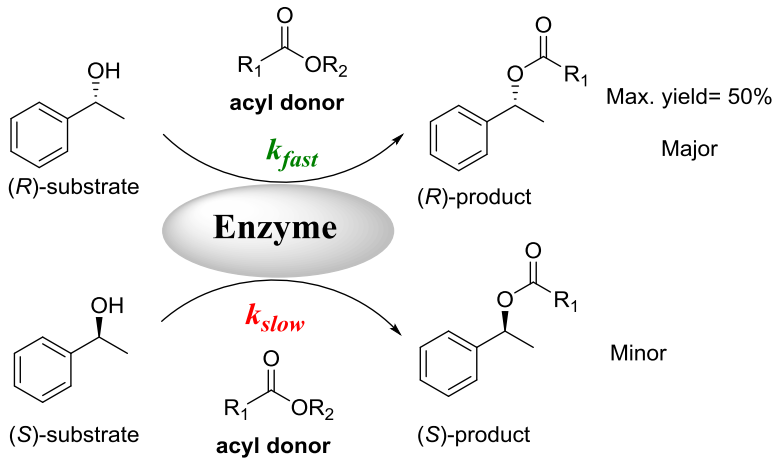
1.1. Enzymatic kinetic resolution

Enzymatic kinetic resolution (KR) of racemic mixtures is a common way for the access to enantiomerically pure alcohols and amines on an industrial scale, due to its high performance in terms of activity and selectivity.[2] Lipases and proteases have been exploited in the field of KR due to their enantioselectively to catalyze transterification and hydrolysis reactions. In this process, the two enantiomers react with different reaction rates in a chemical reaction with a biocatalyst that enantioselectively converts one of the enantiomer of the racemic mixture into an enantiomerically pure

[1] a) N. Nogradi in *Stereoselective Synthesis*, Wiley-VCH, Weinheim, **1995**; b) B. S. Sekhon *J. Mod. Med. Chem.* **2013**, *1*, 10.

[2] a) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kesseler, R. Stürmer, T. Zelinski *Angew. Chem. Int. Ed.* **2004**, *43*, 788; b) C. Kim, J. Park, M.-J. Kim, in *Comprehensive Catalysis* (Eds.: E. M. Carreira, H. Yamamoto), Elsevier, Italy, **2012**.

product. This allows to separate the product and the substrate from each other by conventional purification techniques (Scheme 4.1).



Scheme 4.1. Example of lipase catalyzed KR of a *sec*-alcohol.

In the ideal case, the employed enzyme is fully selective for one enantiomer. In that case, the racemic mixture would be resolved into two different compounds, both having an enantiomeric excess (*ee*) close to 100%. However, this does not happen usually, since the enzyme often catalyzes the conversion of the other enantiomer as well, but at a slower rate. Therefore, the resolution must be stopped before the conversion reaches 50%, in order to achieve high *ee* of the acylated product. In contrast, if the aim is to obtain the substrate in high *ee*, the reaction must proceed beyond 50% conversion. In acylation reactions running under kinetic resolution conditions, the acyl group being transferred to the substrate by the enzyme comes from an acyl donor, which is added to the reaction in at least equimolar amounts in regard to the substrate. Since this transesterification process is fully reversible, it is

necessary the employment of highly activated esters or enol esters as acyl donors. In that way the reaction will be pushed toward the formation of the acylated product.[3]

Unfortunately, enzymatic KR, as all other resolution methods, suffers from the limitation that the maximum theoretical yield is only 50%.

In order to quantify the enantioselectivity of an enzyme-catalyzed reaction, "Enantiomeric Ratio" (*E* value) dimensionless parameter has been developed. The *E* value expresses the ratio of the rate constants of the two enantiomers k_{fast}/k_{slow} and is a constant that is unaffected by the conversion. The resolution benefits from a large *E* value, which means that the selectivity for the wanted enantiomer is high.[4]

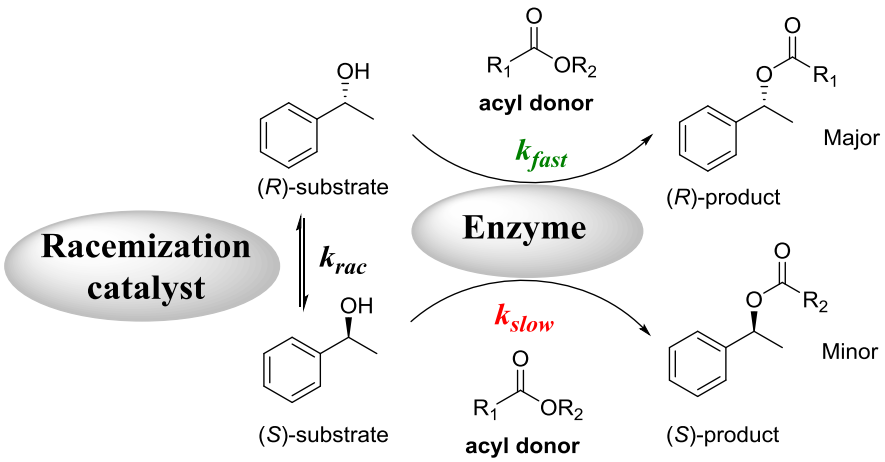
1.2. Dynamic kinetic resolution

Many efforts have been devoted to overcome the above limitation of KR and to afford compounds with the same high enantiomeric purity, but with much improved yields. It is a combination of these two goals that has led to the evolution of classical kinetic resolution into dynamic kinetic resolution (DKR). In this process, it is possible, in principle, to obtain a quantitative yield of one of the enantiomers, by the introduction of an *in situ*

[3] a) Y.-F. Wang, C. -H. Wong *J. Org. Chem.* **1988**, *53*, 3127; b) [3] Y. -F. Wang, J.J. Lalonde, M. Momongan, D. E. Bergbreiter, C.-H. Wong *J. Am. Chem. Soc.* **1998**, *110*, 7200; c) G. Xu, Y. Chen, J. Wu, Y. Cheng, L. Yang *Tetrahedron: Asymmetry* **2011**, *22*, 1373.

[4] C. S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih *J. Am. Chem. Soc*. **1982**, *104*, 7294.

racemization catalyst that keeps the substrate racemic throughout the reaction (Scheme 4.2).



Scheme 4.2. (*R*)-selective DKR of a *sec*-alcohols.

Depending on the compound (substrate) that needs to be racemized, there are different methods available. The follows are some examples: i) thermal racemization, ii) base and acid-catalyzed racemization, iii) racemization *via* Schiff-base intermediates, iv) racemization *via* reduction-oxidation (redox) reactions, and v) enzyme-catalyzed racemization.[5]

1.2.1. Racemization catalysts

In the last years numerous metal complexes of ruthenium, iridium, palladium and rhodium have been developed as catalyst to perform the

[5] a) E. J. Ebbers, G. J. A. Ariaams, J. P.M. Houbiers, A. Bruggink, B. Zwanenburg *Tetrahedron* **1997**, *53*, 9417; b) K. Faber *Chem. Eur. J.* **2001**, *7*, 5004;

hydrogen transfer reaction which is necessary to achieve racemization.[6] However, not all of them are suitable for a successful DKR, since to get it the following requirements must be fulfilled:

(i) The KR must display a sufficient enantioselectivity (E value = $k_{fast}/k_{slow} \geq 20$).[4]

(ii) The enzyme and the racemization catalyst must be compatible with one another.

(iii) The rate of racemization (k_{rac}) must be at least 10 times faster than the enzyme-catalyzed reaction of the slow reacting enantiomer (k_{slow}).

(iv) the racemization catalyst must not react with the product formed from the resolution.

Among these requirements, the compatibility between the enzyme and racemization catalyst is generally the critical issue, due to the fact that the latter often need different reaction conditions to operate optimally. It is also common that the racemization catalyst interferes with the enzymatic resolution or that the enzyme and its accompanying additives (e.g., surfactants and stabilizers) have an inhibitory effect on the racemization catalyst. As a result of this compatibility issue, the identification of reaction

[6] a) J. Troch-Grimshaw, H. B. Henbest *Chem. Commun*. **1967**, 544; b) R. L. Chowdhury, J. -E. Bäckvall *J. Chem. Soc.* **1991**, 16, 1063; c) J. -E. Bäckvall *J. Organometal. Chem.* **2002**, *652*, 105; d) J. S. Samec, J. -E. Bäckvall, P. G. Andersson, P. Brandt *Chem. Soc. Rev*. **2006**, *35*, 237; e) O. Saidi, J. M. J. Williams *Top. Organomet. Chem.* **2011**, *34*, 77.

conditions that enable both high enantioselectivity of the KR and efficient racemization has been a recurring challenge within the field of DKR. [7]

In that context, a few racemization catalysts which fulfill those criteria have been developed (Figure 4.1).[8] The first example was reported by William and co-workers, who achieved racemization employing rhodium(II) acetate, although they only obtained moderate yields for the DKR (60%).[9] Shortly after Bäckvall's group published a DKR with high yield and excellent *ee*, employing the Shvo catalyst **35** for racemization.[10] Further improvement of the DKR was possible after the development of the monomeric catalysts **32-34**, which were easier to combine with the enzymes due to their higher activity at room temperature.[11] Catalyst **32** will be discussed in more detail since it was used in this thesis.

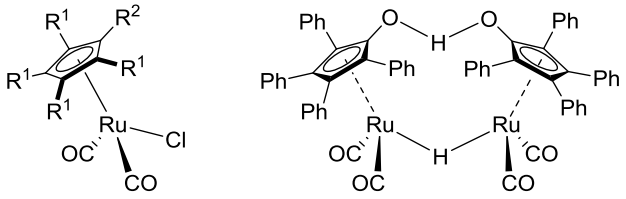
[7] a) B. Martín-Matute, J. -E. Bäckvall, *J. Curr. Opin. Chem. Biol.* **2007**, *11*, 226; b) *Multi-Step Enzyme Catalysis: Biotransformations and Chemoenzymatic Synthesis*, (Ed.: E. Garcia-Junceda), Wiley-VCH, Weinheim, **2008**, Ch. 1; c) M. Warner; J.-E. Bäckvall *Acc. Chem. Res.* **2013**, *46*, 2545.

[8] a) J. Steinreiber, K. Faber, H. Griengl *Chem. Eur. J*. **2008**, *14*, 8060; b) K. Faber *Chem. Eur. J*. **2001**, *7*, 5004; c) *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*, (Ed.: R. Peters), Wiley-VCH, Weinheim, **2015**.

[9] P. M. Dinh, J. A. Howarth, A. R. Hudnott, J. M. J. Williams, W. Harris *Tetrahedron Lett.* **1996**, *37*, 7623.

[10] A. L. E. Larsson, B. A. Persson, J. -E. Bäckvall *Angew. Chem. Int. Ed*. **1997**, *36*, 1211.

[11] a) G. Csjernyk, K. Bogar, J. -E. Bäckvall *Tetrahedron Lett.* **2004**, *45*, 6799; b) B. Martin-Matute, M. Edin, K. Bogar, J. -E. Bäckvall *Angew. Chem. Int. Ed*. **2004**, *43*, 6535.



32, $R^1 = R^2 = Ph$

33, $R^1 = R^2 = Bn$

34, $R^1 = Ph$, $R^2 = NH^iPr$

35

Figure 4.1. Example of homogeneous, enzyme compatible racemization catalysts.

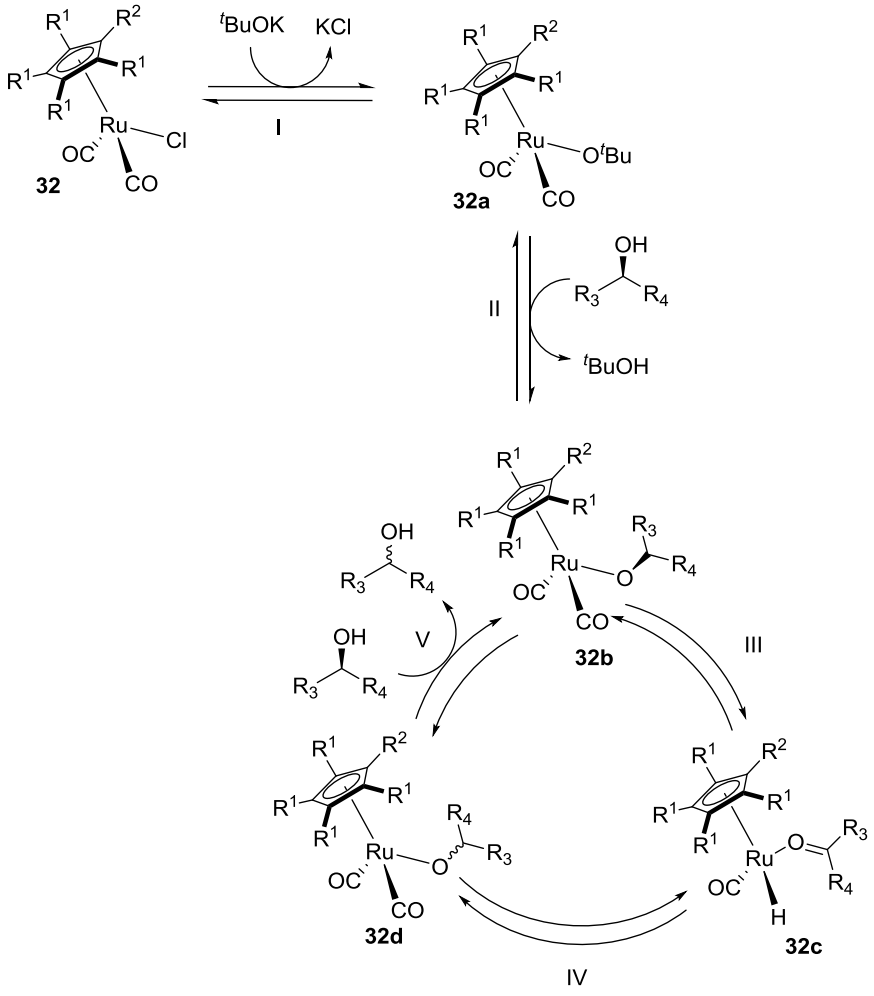
1.2.2. Racemization catalyst **32**

Catalyst **32** is an 18-electron ruthenium complex which has demonstrated to be able to racemize 1-phenylethanol completely in 10 minutes at room temperature.[11] Furthermore, it has been successfully used in many DKR processes of *sec*-alcohols.[12] The proposed racemization mechanism is shown in Scheme 4.3.[13] The active species, **32a** is obtained after nucleophilic displacement of the chloride ligand by *tert*-butoxide anion (Scheme 4.3, step I). This activation is easy to see during the performance of the reaction, as the mixture immediately changes its color from yellow to orange after the addition of KO^{t}Bu. Then, alcohol-alkoxide exchange

[12] Selected examples: a) B. Martin- Matute, M. Edin, K. Bogar, F. B. Kaynak, J. -E. Bäckvall *J. Am. Chem. Soc.* **2005**, *127*, 8817; b) M. Warner, A. Nagendiran, K. Bogar, J. -E. Bäckvall *Org. Lett.* **2012**, *14*, 5094; c) M. Warner, G. A. Shevchenko, S. Jouda, K. Bogar, J. -E. Bäckvall *Chem. Eur. J.* **2013**, *19*, 13859.

[13] a) B. Martin- Matute, J. B. Åberg, M. Edin, J. -E. Bäckvall *Chem. Eur. J.* **2007**, *13*, 6063; b) J. B. Åberg, J. Nyhlén, B. Martin-Matute, T. Privalov, J. -E. Bäckvall *J. Am. Chem. Soc.* **2009**, *131*, 9500; c) , J. Nyhlén, T. Privalov, J. -E. Bäckvall *Chem. Eur. J.* **2009**, *15*, 5220; d) M. C. Warner, O. Verho, J. -E. Bäckvall *J. Am. Chem. Soc.* **2011**, *133*, 2820.

happens forming the ruthenium *sec*-alkoxide complex **32b** (step II). The substrate stays coordinated to the metal while CO dissociation enables a β-hydride elimination to obtain ketone intermediate **32c** (step III).



Scheme 4.3. Proposed catalytic cycle for the racemization of *sec*- alcohols by **32**.

This is followed by insertion of the ketone into the Ru-hydride bond which to form alkoxide **32d** (step IV). The re-addition of the above hydride can occur at either face of the ketone intermediate, thereby leading to racemization of the alcohol. After a ligand exchange, the *rac*- alcohol is exchanged by another molecule of enantiomerically pure *sec*-alcohol and the cycle can start all over again (step V).

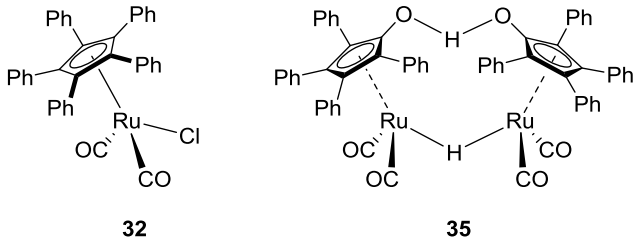
1.2.3. General concerns regarding DKR

A typical problem when performing a chemoenzymatic reaction is to come upon an optimal rate for both the enzymatic process and racemization. The adjustment of the solvent and its water content would be one of the most straightforward methods to modify the rate and the enantioselectivity of the enzyme-catalyzed reactions. Nevertheless, because of the demands of the racemization catalyst, these changes are not always possible in DKR. For example, catalyst **32** is air-stable and can be stored at room temperature, but its activated catalytic species generated during catalysis are highly sensitive to water and oxygen. Because of this, the reactions require an inert atmosphere and dry, non-polar solvents in order to achieve a well functioning racemization.

1.3. Background of the research group

Although the development of a protocol of DKR is not trivial, the research group of Prof. Bäckvall has a long experience in this area, having carried out numerous synthesis of chiral secondary alcohols and amines. In fact, as mentioned above, Bäckvall's group has been very active in the development

of new racemization catalysts. For instance, they have synthesized several ruthenium-based catalysts shown in Figure 4.2.[14,15]



32 **35**

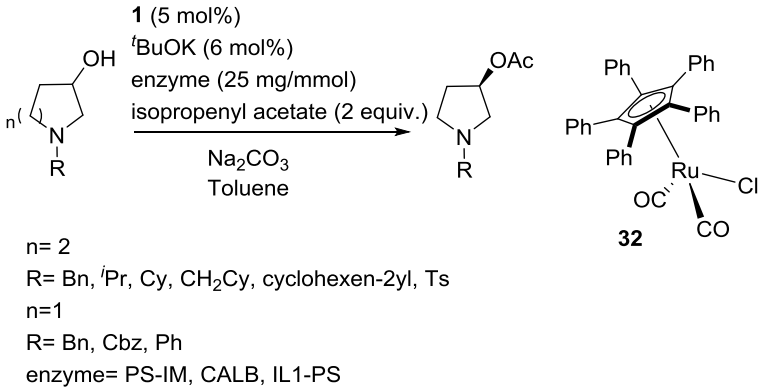
Figure 4.2. Racemization catalysts developed by the group.

Besides the synthesis of those catalysts, they have employed them for the obtainment of both chiral secondary alcohol and amines.[14,15] In this context, they applied DKR successfully to a number of vicinal amino alcohols with a 3-hydroxypyrrolidine or -piperidine structure using racemization catalyst **1**. Furthermore, the developed method allowed the use of a variety of electron-

[14] a) R. Marcos, B. Martín-Matute *M. Isr. J. Chem.* **2012**, *52*, 639; b) J. H. Lee, K. Han, M. -J. Kim, J. Park *Eur. J. Org. Chem.* **2010**, *6*, 999; c) I. Hussain, J. -E. Bäckvall in *Enzyme Catalysis in Organic Synthesis, 3rd ed.;* (Eds.: K. Drauz, H. Gröger, O. May), Wiley-VCH, Weinheim, **2012**.

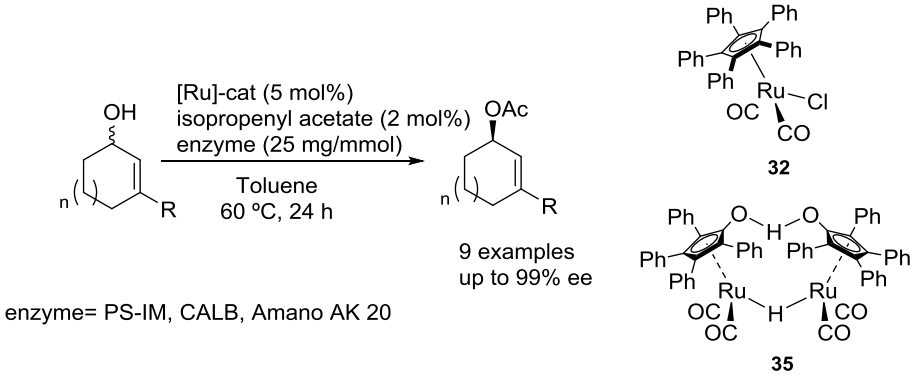
[15] a) J. H. Choi, Y. K. Choi, Y. H. Kim, E. S. Park, E. J. Kim, M.-J. Kim, J. Park, *J. Org. Chem.***2004**, *69*, 1972; b) H. Kim, Y. K. Choi, J. Lee, E. Lee, J. Park, M.-J. Kim *Angew.Chem., Int. Ed.* **2011**, *50*, 10944; c) K. Leijondahl, L. Borén, R. Braun, J.-E. Bäckvall *J. Org. Chem*. **2009**, *74*, 1988; d) C. Kim, J. Lee, J. Cho, Y. Oh, Y. K. Choi, E. Choi, J. Park, M.-J. Kim *J. Org. Chem* .**2013**, *78*, 2571; e) R. Lihammar, R. Millet, J.-E. Bäckvall *Adv. Synth. Catal.* **2011**, *353*, 2321; f) R. Lihammar, R.Millet, J.-E. Bäckvall *J. Org. Chem.* **2013**, *78*, 12114; g) J. Paetzold, J.-E. Bäckvall *J. Am. Chem. Soc.* **2005**, *127*, 17620.

withdrawing and electron-donating substituents on the cyclic amine (Scheme 4.4).[15e]



Scheme 4.4. General conditions for DKR of vicinal amino alcohols.

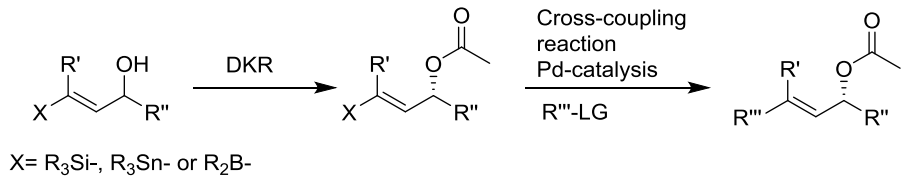
In that context, they also described an efficient protocol of DKR for cyclic allylic alcohols. Both catalyst **32** and **35** turned out to be effective for the stereocontrolled formation of (*R*)-allyl alcohols, as shown in Scheme 4.5.[16]



Scheme 4.5. General conditions for DKR of allylic alcohols.

[16] R. Lihammar, R. Millet, J. -E. Bäckvall *J. Org. Chem.* **2013**, *78*, 12114.

Considering the experience of the group in the field of DKR and the possibility of its employment to obtain of cyclic allylic alcohols, they decided to develop a new methodology to prepare acyclic chiral secondary alcohols. Moreover, chemoenzymatic DKR would be used for the synthesis of chiral secondary alcohols containing functional groups applicable to cross coupling reactions. In particular, vinylstannanes, vinylsilanes and vinylboranes would be explored. The first two mentioned functional groups are reported to be tolerated in transesterification reactions by a lipase. However, to the best of our knowledge, they have not been used in a DKR.[17] So, the project would focus on combining commercially available enzymes and metal racemization catalyst **32** to create a DKR protocol on the functionalized allylic alcohols shown in Scheme 4.6. A successful DKR would provide access to highly desirable and useful building blocks.[18] These building blocks could be used in subsequent cross-coupling reactions for the preparation of a variety of allylic alcohols.



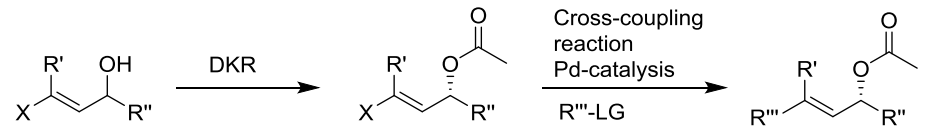
Scheme 4.6. Outline of the key steps in the project.

[17] a) R. T. Beresis, J. S. Solomon, M. G. Yang, N. F. Jain, J. S. Panek *Org. Synth.* **1998**, *75*, 78; b) T. Lee, S. Kim *Tetrahedron: Asymmetry* **2003**, *14*, 1951.

[18] a) P. Espinet, A. M. Echavarren *Angew. Chem. Int. Ed*. **2004**, *43*, 4704; b) Y. Nakao, T. Hiyama *Chem. Soc. Rev*. **2011**, *40*, 4893; c) A. J. J. Lennox, G.C. Lloyd-Jones *Chem. Soc. Rev*. **2014**, *43*, 412.

2. AIMS AND OBJECTIVES

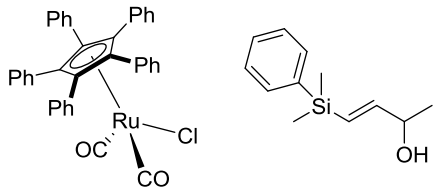
Taking into account the issues mentioned before and the experience of the research group in this area, the aims of this work will be the development of a protocol of chemoenzymatic DKR for the synthesis of chiral secondary acyclic alcohols containing functional groups applicable in cross coupling reactions.



X= R_3Si-, R_3Sn- or R_2B-

For that purpose the following points should be performed:

- Synthesis of the allylic alcohol 4-(dimethylphenylsilyl)-but-3-yn-2-ol **36** and ruthenium-based recemization catalyst **32**.



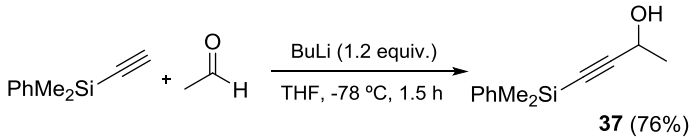
32 **36**

- Optimization of KR for **36** employing different enzymes and of racemization processes using catalyst **32**.
- If successful, a suitable DKR protocol would be developed.
- Subsequent cross-coupling reactions would be carried out on allylic alcohol **36** in an enantioriched form.

3. RESULTS AND DISCUSSION

3.1. Preparation of starting materials

The synthesis of (*E*)-4-(dimethylphenylsilyl)-but-3-en-2-ol **36** was accomplished in two steps starting from commercially available dimethyl(phenyl)silylacetylene (Scheme 4.7). Following the synthesis developed by Jung and co-workers,[19] the treatment of the acetylide anion with acetaldehyde in THF at -78 ºC afforded the desired propargyl alcohol **37** with very good yield (76%).



Scheme 4.7. Preparation of silylated propargyl alcohol **37**.

After the homologation, propargyl alcohol **37** was selectively reduced using Red-Al in diethyl ether at 0 ºC for 4 hours by a procedure reported by Woerpel and co-workers (Scheme 4.8).[20] Target compound (*E*)-4-(dimethylphenylsilyl)-but-3-en-2-ol **36** was quantitatively achieved as a colorless oil. Thereby, the synthesis of the allylic alcohol **36** was performed with an overall yield of 75% in just two steps.

[19] M. E. Jung, G.Piizzi *J. Org. Chem.* **2002,** *67*, 3911.

[20] J. H. Smitrovich, K. A. Woerpel *J. Org. Chem.* **2000**, *65*, 1601.

Scheme 4.8. Reduction of propargyl alcohol **37**.

3.2. Optimization of KR and racemization processes

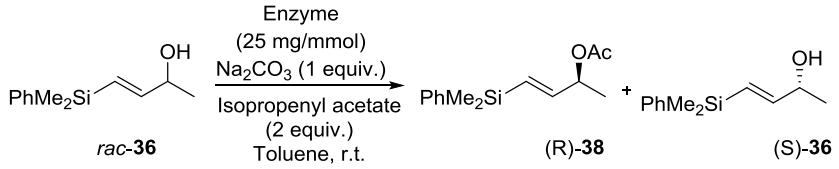
KR and racemization were studied separately before being combined in a DKR. In non-aqueous media (*e.g.*, toluene), lipases catalyze transesterification of a wide range of substrates such as carboxylic acids, alcohols, amines, or esters. The reaction usually proceeds with high regio- and/or enantioselectivity, and as a result, lipases have attracted considerable attention. In agreement with Kazlauskas' rule,[21] lipases display (*R*)-selectivity in transesterification reactions, whereas serine proteases (e.g., Subtilisin Carlsberg) display (*S*)-selectivity.

The study started with a screening of lipases to find the most suitable enzyme for the KR. Four immobilized enzymes were tested for the transesterification of (*E*)-4-(dimethylphenylsilyl)-but-3-en-2-ol **36** employing isopropenyl acetate as acyl donor and toluene as solvent. Although *Candida antarctica* lipase B (CALB) showed high activity affording the corresponding acetate **38** in 50% (Table 4.1, entry 1), no enantioselectivity was observed. On the other hand, lipase PS from

[21] a) R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport, L. A. Cuccia *J. Org. Chem*. **1991**, *56*, 2656; b) R. J. Kazlauskas, A. N. E. Weissfloch *J. Mol. Catal. B: Enzym.* **1997**, *3*, 65.

Burkholderia cepacia (previously named *Pseudomonas cepacia*) immobilized on Celite (PS-IM) was found to work slower in comparison with CALB, since after 4 hours only a 23% of acetate was obtained (Table 4.1, entry 2). Furthermore, in this case a poor enantioselectivity was observed. Regarding to lipase AK Amano 20 and PS immobilized on ceramics (PS-C1), they delivered the acetate with a poor conversion rate, but in the case of AK Amano 20 the enantioselectivity was relatively high (entry 3). Taking into account these results, the assayed conditions were not considered suitable for further studies, so we decided to repeat the KR assays changing both the solvent and acyl donor (Table 4.2).

Table 4.1. Screening of lipases.



rac-**36** (R)-**38** (S)-**36**

	Enzyme	Time/h	Conv. (%)[b]	ee_{OAc} (%)[c]	*E* value[d]
1	CALB	4	50	nd	nd
2	PS-IM	4	23	34	2.24
3	AK Amano 20	4	18	85	14.8
4	PS-C1	4	3	37	12.7

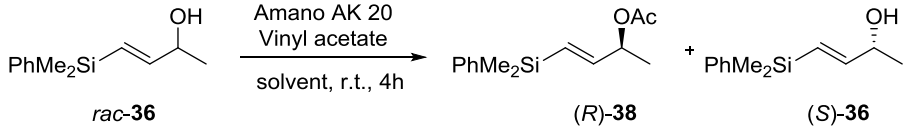
[a]Reaction conditions: **5** (0.2 mmol), isopropenyl acetate (2 equiv), Na_2CO_3 (1 equiv), and enzyme (25 mg/mmol) stirred in dry toluene (0.8 mL) at room temperature. [b]Determined by ^{1}H NMR [c]Determined by GC. [d]Calculated by ee_{OH} and ee_{OAc} according to formula. [22]

[22] E = $k_{fas}t/k_{slow}$. The *E* value can be calculated according to the formulas presented in: C. S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih *J. Am. Chem. Soc.* **1982**, *104*, 7294. *E* = ln

AK Amano 20 was chosen for the following assays, as it was the enzyme which had shown the highest enantioselectivity. Different solvents and acyl donors were tried varying the amount of enzyme and acyl donor, as it can be seen in Table 4.2. Pentane, MTBE and diisiopropyl ether were found to be suitable solvents for KR when vinyl acetate was used as the acyl donor (entries 2,3,8,9). Not only they showed high activity and enantioselectivity but also gave an *E* value >200.[22] Once again, when isopropenyl acetate and PhMe were combined in the presence of CALB enzyme (entry 5), although high activity was observed no enantioselectivity was achieved. On the other hand, when PhMe, THF or the mixture of Pentane:PhMe were employed, in the acylation with vinyl acetate the desired acetate was obtained with a very low conversion rate and without enantioselectivity (entries 4,6,7), so those conditions were directly discarded. As it is displayed in entry 1, hexane was also tried using isopropenyl acetate as acyl donor, providing a low conversion with a moderate enantioselectivity. Even so, it was not appropriate to further studies since the reaction was not fast enough. All in all, we considered that the conditions displayed in entry 3 were the best for KR even if using MTBE and disiisopropyl ether similar results were obtained.

$[(ee_{OA}c\cdot(1 - ee_{OH})/(ee_{OAc} + ee_{OH})]/\ln[ee_{OAc}\cdot(1 + ee_{OH}) /(ee_{OAc} + ee_{OH}) = \ln(1 - (conv\cdot(1 + ee_{OAc})))/\ln(1 - (conv\cdot(1 - ee_{OAc})))$ and $E = \ln[(ee_{OAc}\cdot(1 - ee_{OH}))/(ee_{OAc} + ee_{OH})]/\ln[(ee_{OAc}\cdot(1 + ee_{OH}))/(ee_{OAc} + ee_{OH})]$.

Table 4.2. Optimization of KR process.



rac-**36** (*R*)-**38** (*S*)-**36**

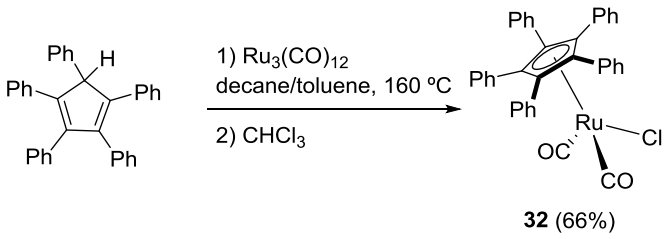
	Enzyme amount	Solvent	Acyl donor (equiv.)	Conv. (%)[b]	ee_{OAc} (%)[c]	*E* value[d]
1[e]	50% wt.	Hexane	2	9	64	2.25
2	50% wt	Pentane	2.8	46	>99	>200
3	50% wt	Dry pentane	2.8	48	>99	>200
4	25 mg/mmol	PhMe	2.8	4	nd	nd
5[e,f]	25 mg/mmol	PhMe	2	51	nd	nd
6	50% wt	THF	2.8	18	nd	nd
7	50% wt	Pentane:PhMe (1:1)	2.8	11	nd	nd
8	50% wt	MTBE	2.8	48	>99	>200
9	50% wt	Diisopropyl ether	2.8	50	>99	>200

[a]Reaction conditions: *rac*-**36** (0.2 mmol), Na_2CO_3 (1 equiv), and AK Amano 20 stirred at room temperature for 4h. [b]Determined by ^{1}H NMR [c]Determined by GC. [d]Calculated by ee_{OH} and ee_{OAc} according to formula.[e] The employed acyl donor was isopropenyl acetate [f] The employed enzyme CALB and reaction time 2.5h.

Dry pentane was selected since, after the dehydratation process, the content of water traces is usually higher in the latter ethers, and as it has been mentioned in the introduction DKR requires anhydrous reaction media.

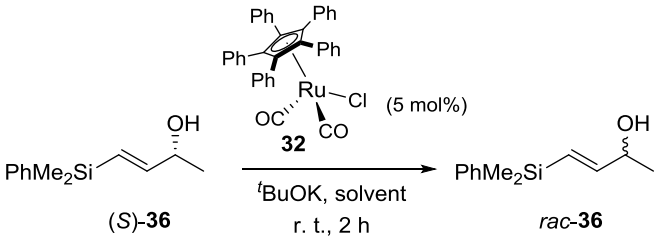
Before starting with the optimization of the racemization process, we proceeded to the synthesis of ruthenium-based catalyst **32**. For that purpose

we employed the optimized conditions by the group,[11b] based on the reaction of 1,2,3,4,5-pentaphenylcyclopentadiene and [$Ru_3(CO)_{12}$] in a mixture of decane:toluene (2:1) under reflux for 2.5 days. Once the mixture was cooled, $CHCl_3$ was added and it was heated to 160ºC for 1h. After cooling down to room temperature, pentane was added and a precipitate fell out, which was collected by filtration thus obtaining complex **32** as a greenish powder in 66% yield after purification by flash column chromatography (Scheme 4.9).



Scheme 4.9. Synthesis of ruthenium catalyst **32**.

The racemization of (*S*)-(*E*)-4-(dimethylphenylsilyl)-but-3-en-2-ol was investigated at room temperature in toluene and pentane employing ruthenium complex **32**. From the results it was clear that an elevated temperature was not necessary for an effective racemization in a DKR as (*S*)-allylic alcohol **36** was fully racemized within 2 hours (Scheme 4.10).



Scheme 4.10. Outline of the racemization assays.

From these individual studies it seemed that the optimal conditions for a successful DKR would be to run the reaction at room temperature employing AK Amano 20 for the resolution in pentane. Due to the lack of time the DKR was not carried out at that moment. Even so, the group continued working on that and the DKR has been performed successfully and now, the methodology is going to be applied to another allylic alcohols.

4. EXPERIMENTAL PROCEDURES

4.1. General methods and materials

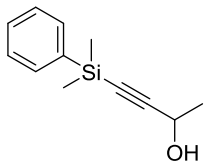
All reactions were carried out using dry conditions in flame-dried glassware. DKR and KR were carried out under dry argon atmosphere using standard Schlenk techniques. Dry solvents were obtained from VAC solvent purifier. Isopropenyl acetate and vynil acetate were dried over $CaCl_2$ and distilled before use. Na_2CO_3 was dried for 1h in vacuo at 220 °C before use. All other chemicals and solvents were used as purchased. The enantiomeric excess of the compounds was determined by chiral HPLC or chiral GC using racemic compounds as references. Racemic acetates 2 were obtained from the corresponding alcohols by standard acylation. Ruthenium-based complex **32**[11b] was synthesized according to literature procedures. CALB (Novozyme 435), PS-IM, AK Amano 20, PS-C1 are commercially available. IL1-PS can be prepared according to literature procedures.[23] Column chromatography was performed with Davisil chromatographic silica media for separation and purification applications (35−70 μm). HPLC samples were analyzed by UV detection. GC samples were run on an IVADEX-1 chiral column with FID detector and N_2 as a carrier gas with a flow of 1.8 mL/min. ^1H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively. ^1H NMR data are presented as follows: chemical shift δ (in ppm) [multiplicity, coupling constant(s) *J*, relative integral]. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the

[23] T. Itoh, Y. Matsushita, Y. Abe, S.-H. Han, S.Wada, S. Hayase, M. Kawatsura, S. Takai, M. Morimoto, Y. Hirose *Chem.Eur. J.* **2006**, *12*, 9228.

$CDCl_3$ "triplet" appearing at δ_C 77.16 were used to reference the ^1H and ^{13}C NMR spectra, respectively.

4.2. Synthesis of (*E*)-4-(dimethylphenylsilyl)-but-3-en-2-ol, 36

***4-(Dimethylphenylsilyl)-but-3-yn-2-ol,* 37.**[19]

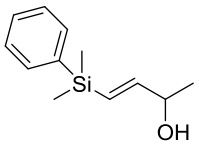


In a flame dried 25mL round bottom flask, ^{n}BuLi (1.1 mL of a 2M solution in hexane, 2.25mmol) was added dropwise to a solution of (dimethylphenyl)acetylene (0.33 mL, 1.87 mmol) in 4 mL THF cooled to -78ºC over 10 min under argon. Then, the reaction was stirred at the same temperature for 20 min, and acetaldehyde (0.26 mL, 4.68 mmol) was added neat *via* syringe. The reaction mixture was stirred at -78ºC for 1.5 hours, and then quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$. Solvent removal under vacuum afforded the desired product as a yellow pale oil that was purified by flash column chromatography using as eluent petroleum ether:EtOAc (9:1) to give the desired alcohol as a colorless oil. (290 mg, 76%).

^{1}H NMR ($CDCl_3$) δ 7.75-7.78 (m, 2H, H_{arom}), 7.48-7.50 (m, 3H, H_{arom}), 4.65 (q, *J* =6.7 Hz, 1H, C*H*), 3.42 (s, 1H, O*H*), 1.57 (d, *J* =6.7 Hz, 3H, CH_3), 0.56 (s, 6H, SiCH_3).

^{13}C NMR ($CDCl_3$) δ 136.8 (qC_{arom}), 133.8 (C_{arom}), 129.6 (C_{arom}), 128.1(C_{arom}), 109.9 (qC), 86.2 (qC), 58.6 (CH), 24.3 (CH_3), -0.7 ($SiCH_3$).

***(E)-4-(Dimethylphenylsilyl)-but-3-en-2-ol*, 36.**[24]



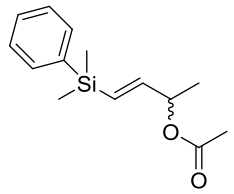
The alcohol **37** (100mg, 0,49 mmol) was dissolved in 5 mL of dry Et_2O and stirred at 0 ºC under argon. A solution of Red-Al (60% wt. toluene, 0.14 mL, 0,73 mmol) was added dropwise over 15 min. The resulting clear solution was stirred for an additional 10 min at the same temperature and for 4h at 20ºC. Then, the reaction was quenched at 0ºC by addition of an aqueous solution of NH_4Cl (0,4 mL) and a white precipitate was formed immediately. The suspension was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with water and dried over $MgSO_4$. Solvent removal under vacuum afforded the desired product **36** as the (*E*)-isomer exclusively as a colorless oil (86.8 mg, 86%)

^{1}H NMR ($CDCl_3$) δ 7.56-7.59 (m, 2H, H_{arom}), 7.40-7.42 (m, 3H, H_{arom}), 6.22 (dd, *J* = 18.8, 4.7 Hz, 1H, =C*H*CHOH), 6.02 (dd, *J* = 18.8, 1.4 Hz, 1H, =C*H*Si), 4.35 (m, 1H, C*H*), 1.99 (bs, 1H, O*H*), 1.31 (d, *J* = 6.7 Hz, 3H, CH_3), 0.41 (s, 6H, SiCH_3).

[24] M. G. McLaughlin, M. J. Cook *Chem. Commun*. **2011**, *47*, 11104.

^{13}C NMR ($CDCl_3$) δ 151.4 (qC_{arom}), 138.5 (=*C*HCHOH), 133.8 (C_{arom}), 129.1 (C_{arom}), 127.8 (C_{arom}), 125.9 (=*C*HSi), 70.4 (CH), 22.9 (CH_3), -2.6 ($SiCH_3$).

4.3. *(E)*-4-(Dimethylphenylsilyl)but-3-en-2-yl acetate, 38.[25]



Acetic anhydride (19 µL, 0.2 mmol) was added to a mixture of alcohol **36** (41.2 mg, 0.2 mmol), 4-(dimethylamino)pyridine (10 mg, 0.08 mmol), and triethylamine (28 µL, 0.2 mmol) in 2 mL of dry dichloromethane. The reaction mixture was stirred for 4 hours and then was poured onto diethyl ether. The organic solution was washed with aqueous solutions of 1M HCl (1 x 5 mL) and saturated sodium bicarbonate (1 x 5 mL). Each separate aqueous layer was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography using as eluent petroleum ether:EtOAc (9:1) gave the desired product **38** as a colorless oil (25.8 mg, 52%).

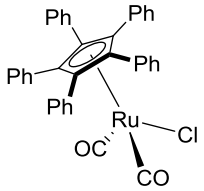
^{1}H NMR ($CDCl_3$) δ 7.53-7.55 (m, 2H, H_{arom}), 7.38-7.40 (m, 3H, H_{arom}), 6.11 (dd, *J* = 18.8, 4.5 Hz, 1H, =C*H*CHOH), 6.00 (dd, *J* = 18.6, 1.7 Hz, 1H,

[25] C. Spino, C.Thibault, S. Gingras *J. Org. Chem.* **1998**, *63*, 5286.

=C*H*Si), 5.40 (m, 1H, C*H*), 2.10 (s, 3H, OCH_3), 1.34 (d, *J* = 6.7 Hz, 3H, CH_3), 0.38 (s, 6H, SiCH_3).

^{13}C NMR ($CDCl_3$) δ 170.3 (CO), 146.6 (qC_{arom}), 138.3 (=*C*HCHOH), 133.8, 129.1, 128.1 (C_{arom}), 127.8 (=*C*HSi), 72.2 (CH), 21.3 (O*C*H_3), 19.8 (CH_3), -2.7 ($SiCH_3$).

4.4. Chlorodicarbonyl(1,2,3,4,5-pentaphenylcyclopenta dienyl)ruthenium (II), 32[12a]



A suspension of 1,2,3,4,5-pentaphenylcyclopentadiene (982.5 mg, 2.2mmol) and [$Ru_3(CO)_{12}$] (473.1 mg, 0.74mmol) in a mixture of 8 mL of decane and 4 mL of toluene was heated at 160ºC in a screw-capped tube for 2.5 days under argon. After cooling to room temperature, 1 mL of $CHCl_3$ was added and the mixture was heated to 160ºC for 1h. After cooling down to room temperature, pentane was added and the resulting yellow power was filtered off. After purification by column chromatography using as eluent pentane:CH_2Cl_2 (3:1) the product was obtained as a yellow solid (918 mg, 66%).

^{1}H NMR ($CDCl_3$) δ 7.27 (tt, *J* = 7.3, 1.3 Hz, 5H, H_{arom}), 7.10 (br t, *J* = 7.8 Hz, 10H, H_{arom}), 7.04-7.02 (m, 10H, H_{arom}).

^{13}C NMR (CDCl3) δ 196.9 (CO), 132.12 (C_{arom}), 129.6 (qC_{arom}), 128.4, 127.8 (C_{arom}), 106.5 (qC_{arom}).

4.5. General procedure for kinetic resolution.

Substrate **36** (41.2 mg, 0.2 mmol), acyl donor (0.4 mmol), lipase (5 mg, 25 mg/mmol), and Na_2CO_3 (21.2 mg, 0.2 mmol) was dissolved in dry toluene (0.8 mL) and stirred at room temperature. Aliquots (50 μL) were taken by syringe at the indicated time and filtered with EtOAc through a Celite plug. After evaporation of the solvent, the enantiomeric excess and conversion were examined by HPLC and ^{1}H-NMR spectroscopy, respectively. HPLC: Chiralcel OJ column, ^{i}hexane/^{i}PrOH, 99:1 for 90 min, 0.5mL/min, 30 ºC, UV at 230 nm, t_{R1}= 17 min (S)-**38**, t_{R2} = 33 min (R)-**38**, t_{R3} = 50 min (S)-**36**, t_{R4} = 54 min (R)-**36**.

4.6. General Procedure for Racemization of (*S*)-36.

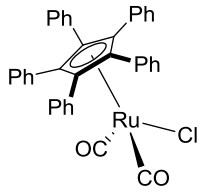
Ruthenium complex **32** (9.5 mg, 0.015 mmol), and Na_2CO_3 (32 mg, 0.3 mmol) were added to a Schlenk tube under argon. Dry solvent (0.3 mL) was added, and the resulting yellow solution was stirred for 5 min. A THF solution of ^{t}BuOK (30 μL, 0.5 M in dry THF, 0.015 mmol) was added to the reaction mixture at room temperature. The reaction turned orange. After approximately 6 min of stirring, a solution of (*S*)-**36** (62 mg, 0.3 mmol) in a dry solvent (0.3 mL) was added to the reaction mixture. Samples for HPLC

analysis were collected with a syringe after 5, 15, 30, 60, and 120 min. HPLC: Chiralcel OJ column, ^{i}hexane/^{i}PrOH, 99:1 for 90 min, 0.5mL/min, 30 ºC, UV at 230 nm, t_{R1} = 50 min (S)-**36**, t_{R2} = 54 min (R)-**36**.

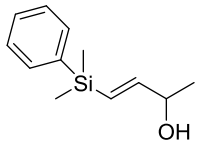
5. CONCLUSIONS

As it has been discussed in the previous section almost all the aims of the project have been achieved.

- The allylic alcohol **36**, 4-(dimethylphenylsilyl)-but-3-yn-2-ol can be prepared with an overall yield of 75% in just two steps. Besides, ruthenium-based racemization catalyst (η^5-Ph_5Cp) $Ru(CO)_2Cl$ **32** previously developed by Bäckvall´s group has been also prepared.



32



36

- Kinetic resolution of 4-(dimethylphenylsilyl)-but-3-yn-ol can be performed by vinyl acetate as acylating agent in the presence of AK Amano 20 lipase if the reaction is performed in dry pentane as solvent.

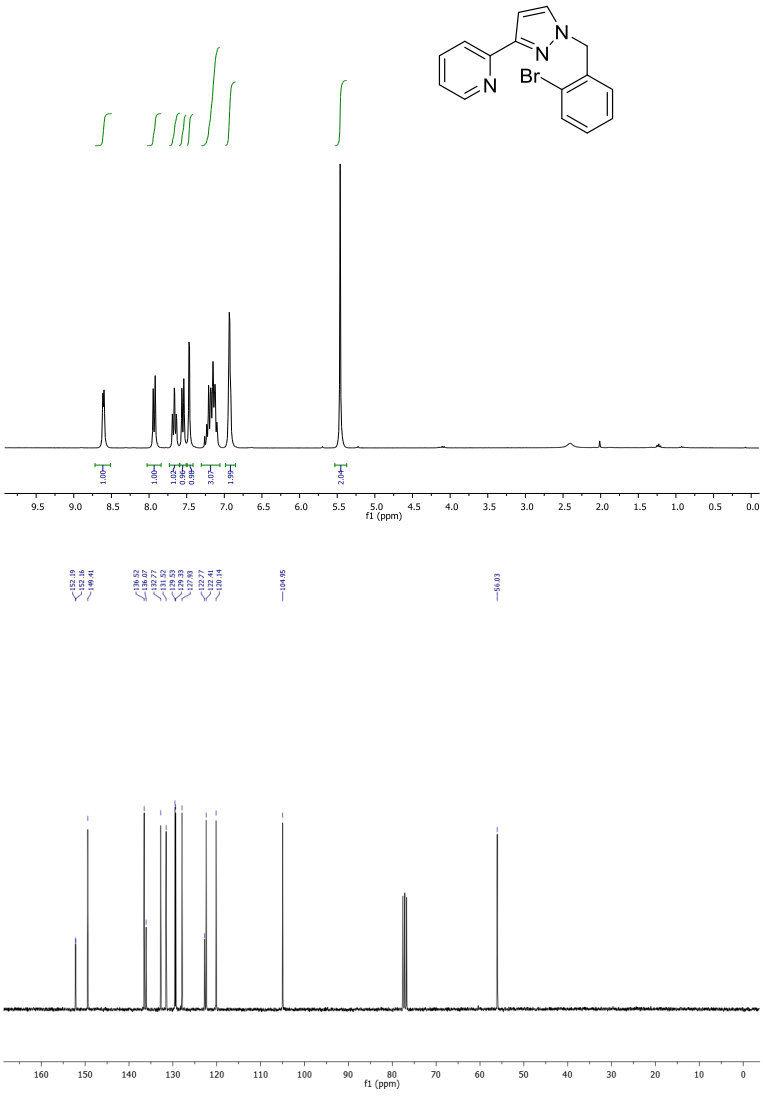
- Racemization of (*S*)-4-(dimethylphenylsilyl)-but-3-yn-ol can be performed by means of (η^5-Ph_5Cp) $Ru(CO)_2Cl$ racemization catalyst.

- The above achievements provide solid support for the development of a DKR protocol for the above silylated allyl alcohol.

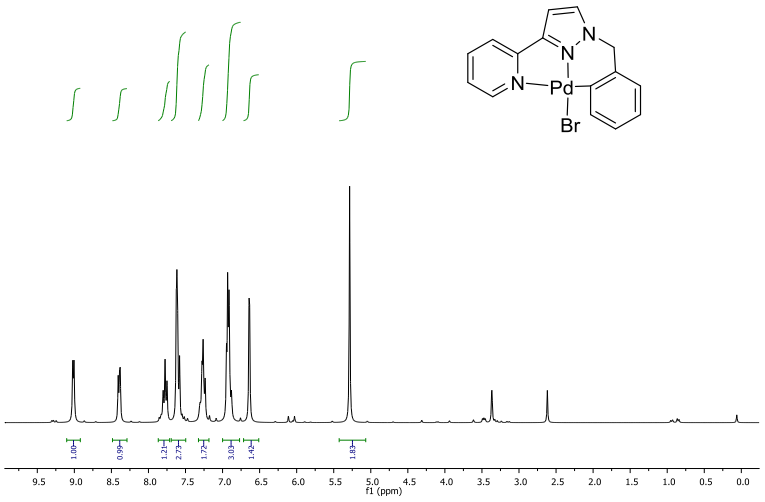
Appendix

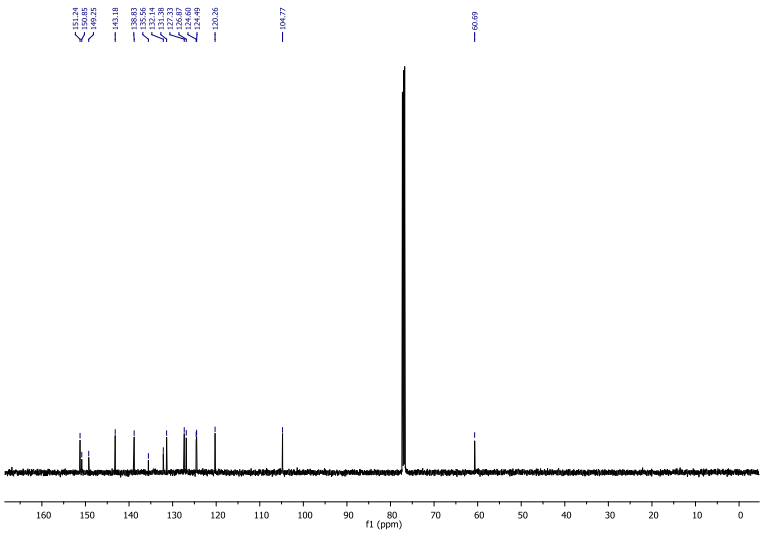
Selection of representative spectra

4: 2-[1-(2-Bromobenzyl)-1*H*-pyrazol-3-yl]pyridine

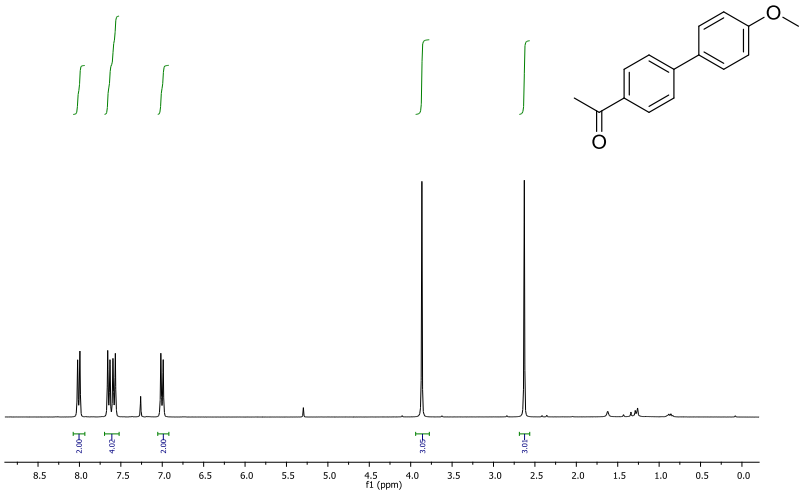


1:[2-[1-[(Phenil-κC2)-methyl]-1*H*-pyrazol-3-yl-κN2]-pyridine-κN-palladium(II) bromide

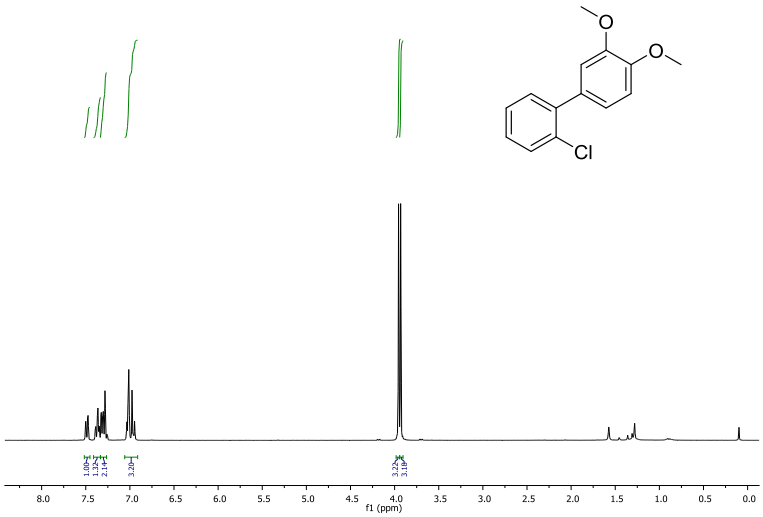




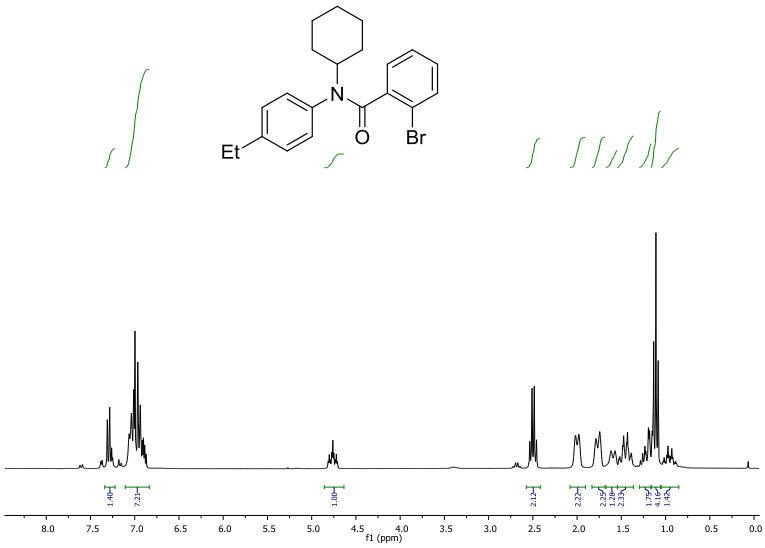
7a: 4-Acetyl-4'-methoxybiphenyl

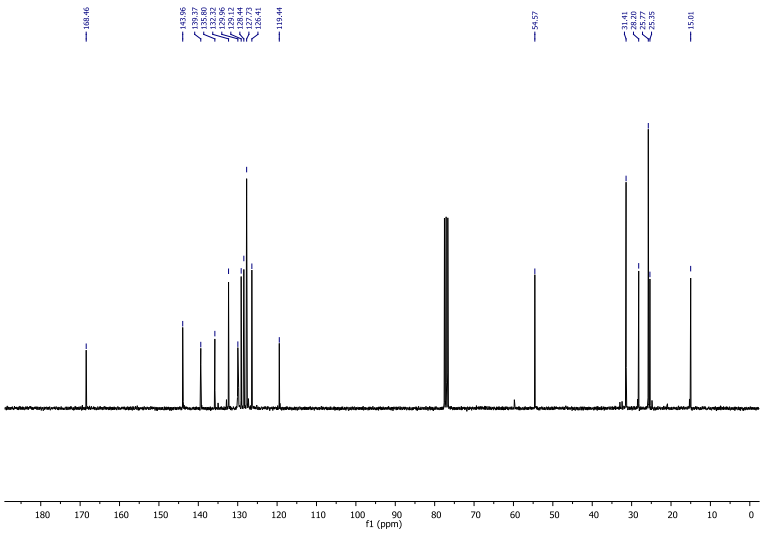


7m: 2-Chloro-3',4'-dimethoxy-1,1'-biphenyl

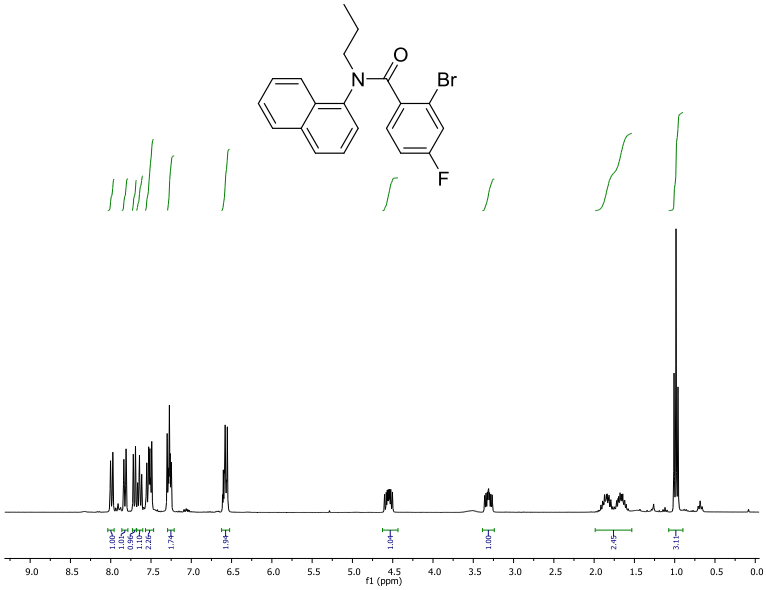


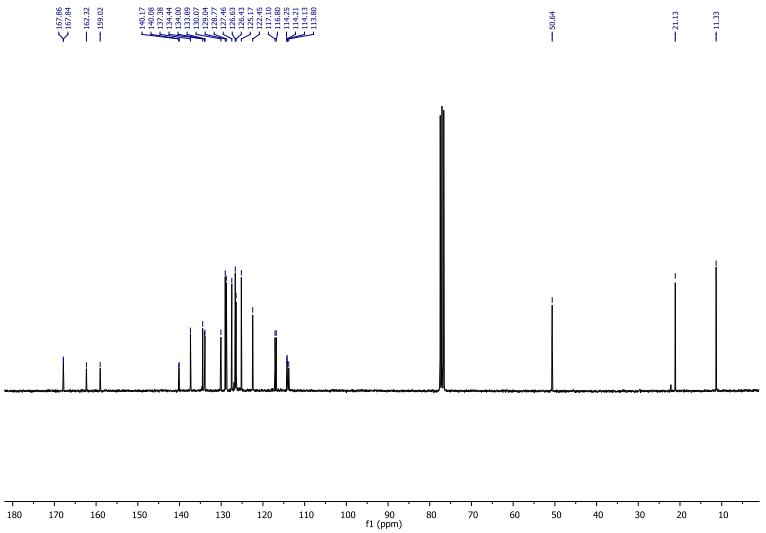
15d: 2-Bromo-*N*-cyclohexyl-*N*-(4-ethylphenyl)benzamide



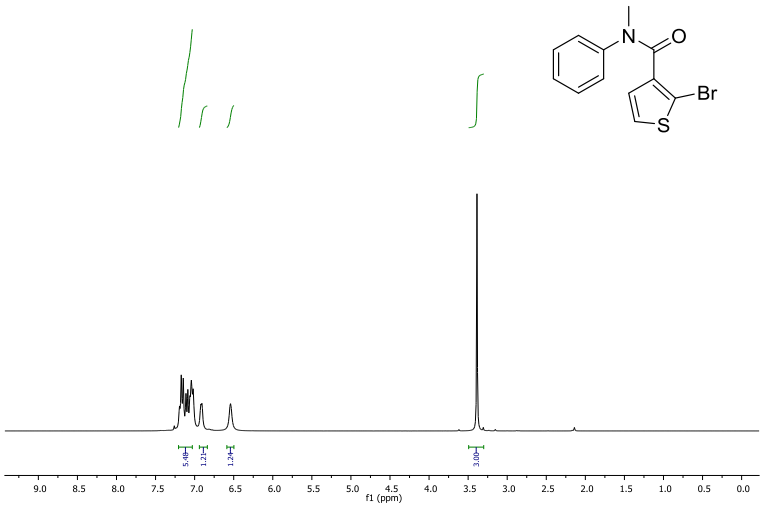


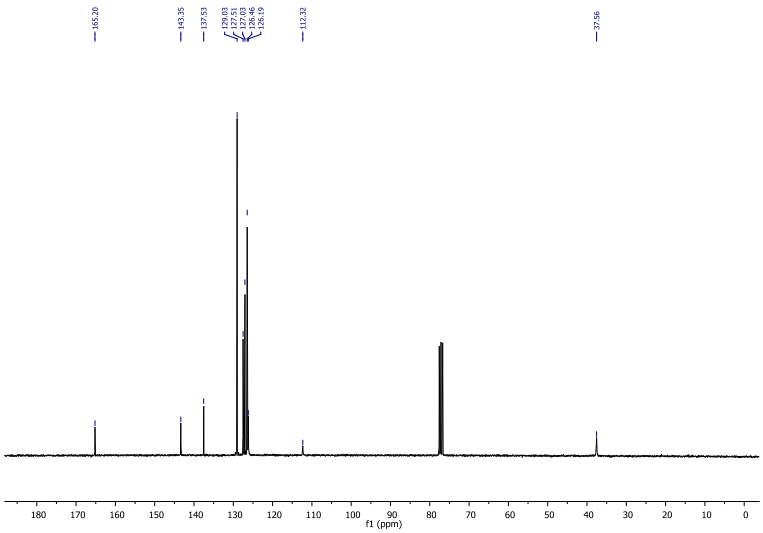
15e: 2-Bromo-3-fluoro-*N*-(1-naphthyl)-*N*-propylbenzamide



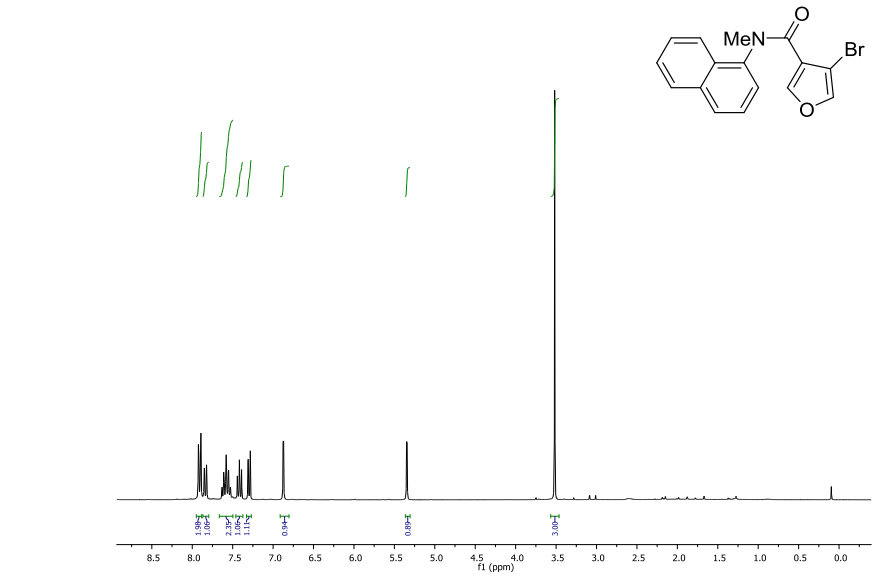


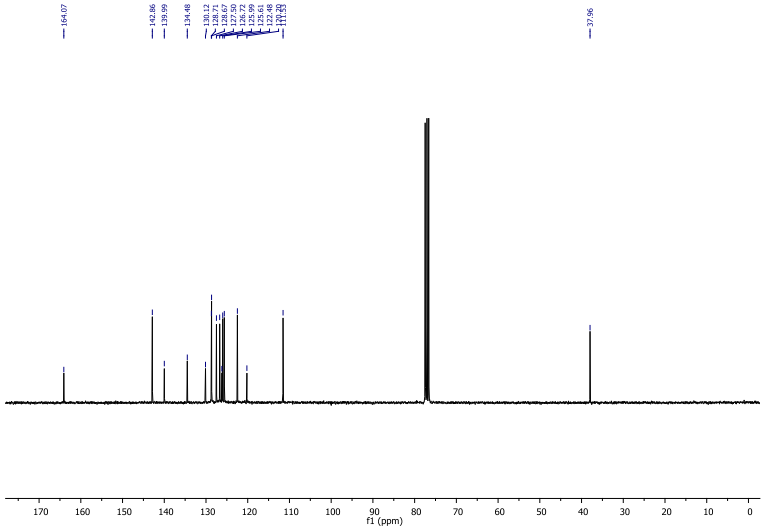
15f: 2-Bromo-*N*-methyl-*N*-phenylthiophene-3-carboxamide



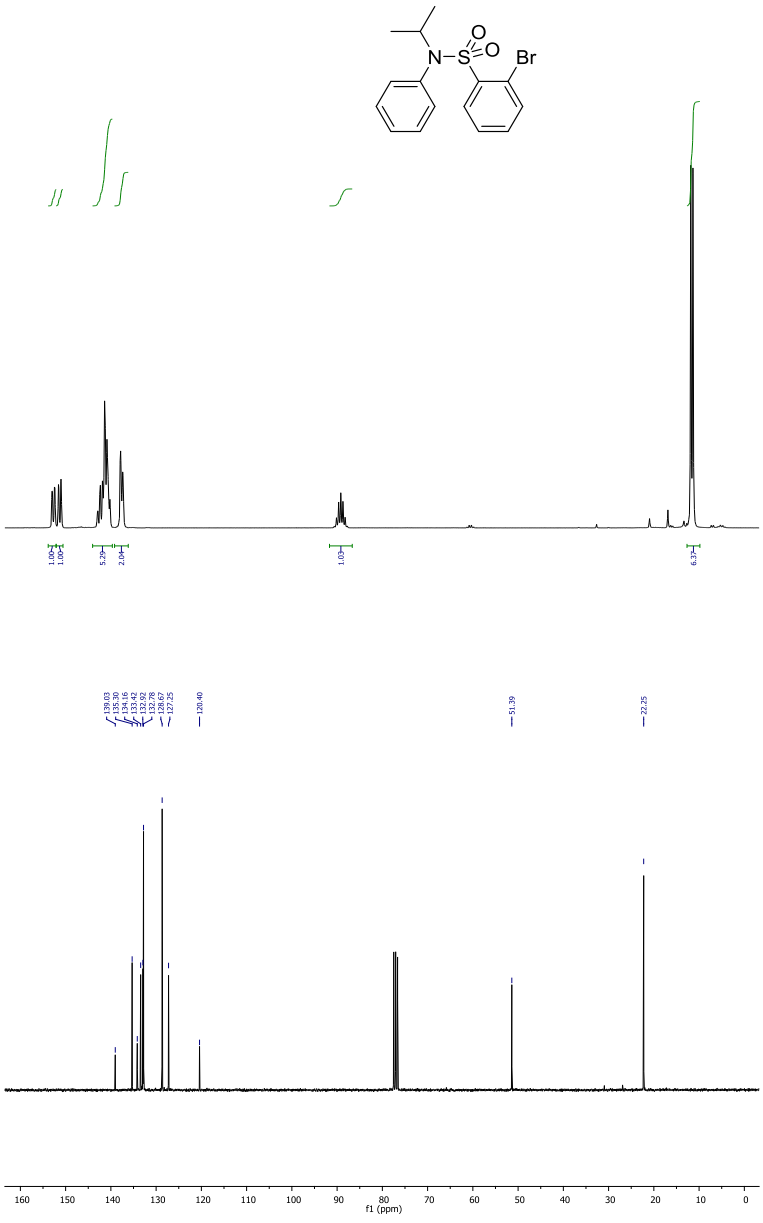


15g: 2-Bromo-*N*-methyl-*N*-(1-naphthyl)furan-3-carboxamide

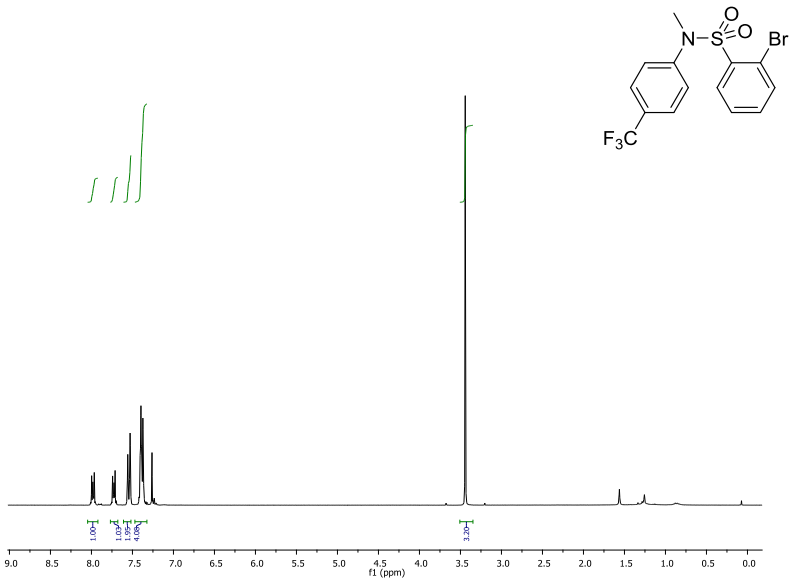


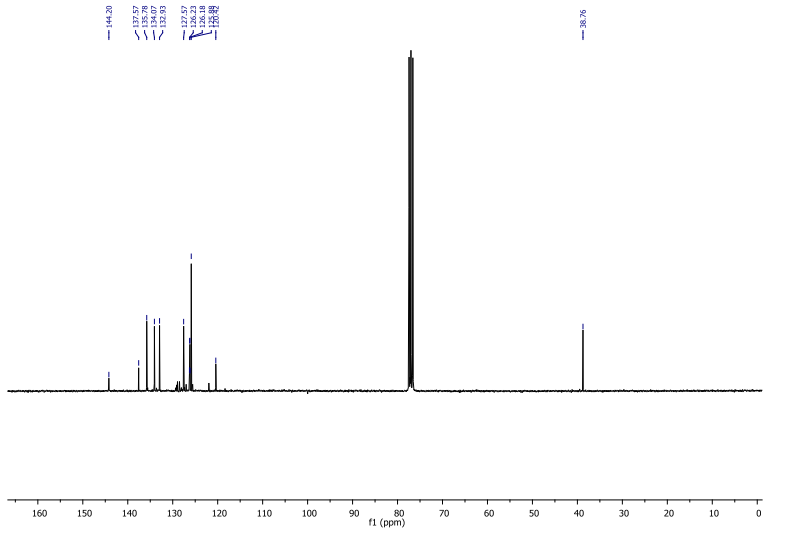


15j: 2-Bromo-*N*-isopropyl-*N*-phenylbenzenesulfonamide

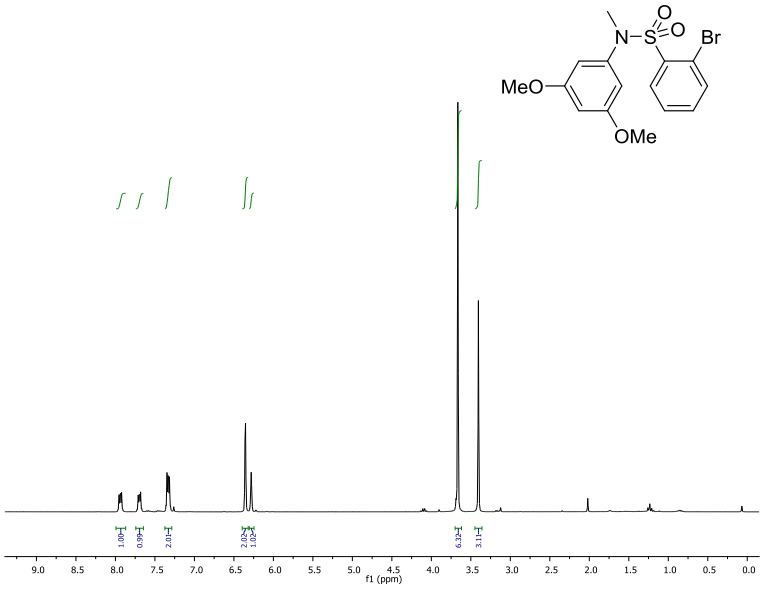


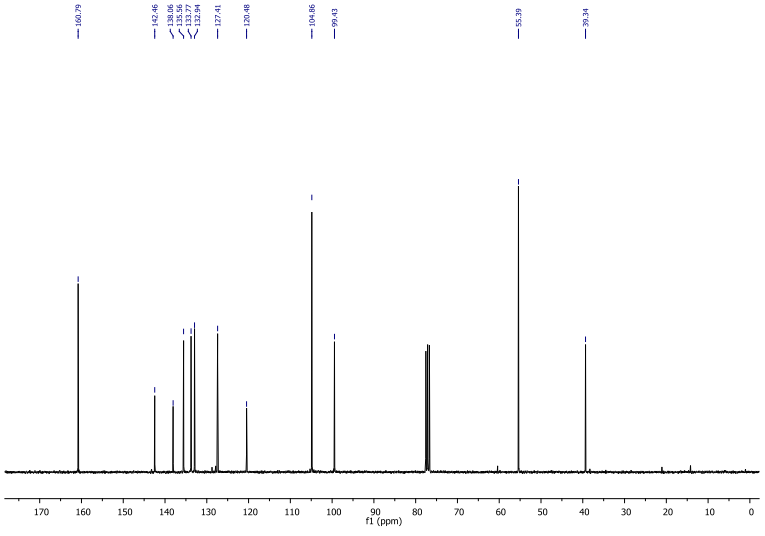
15k: 2-Bromo-*N*-methyl-*N*-(4-trifluoromethylphenyl)benzenesulfonamide



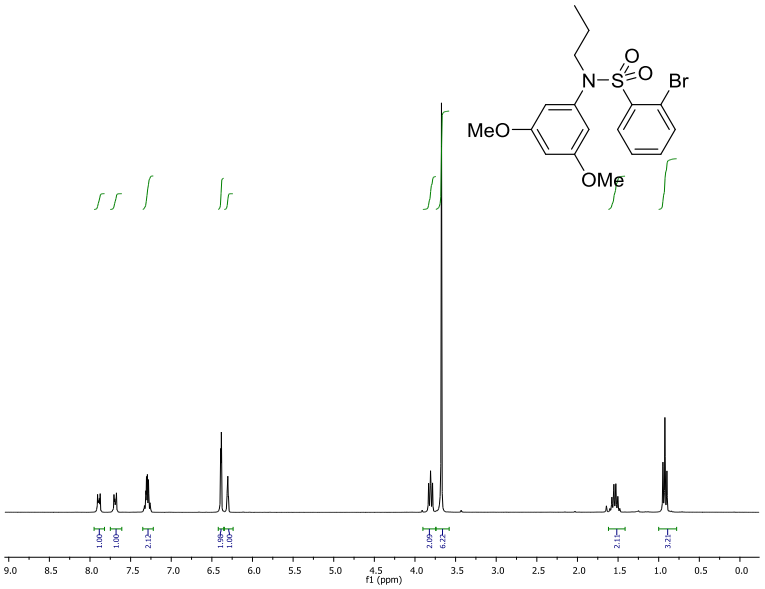


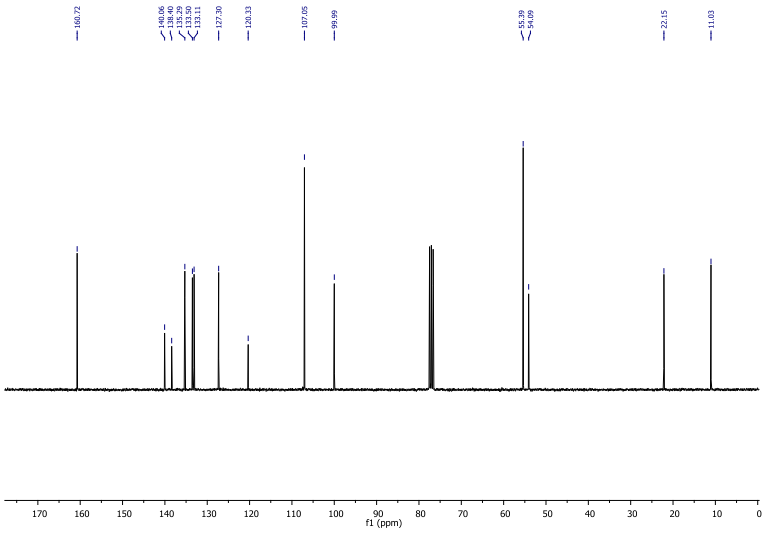
15l: 2-Bromo-*N*-(3,5-dimethoxyphenyl)-*N*-methylbenzenesulfonamide



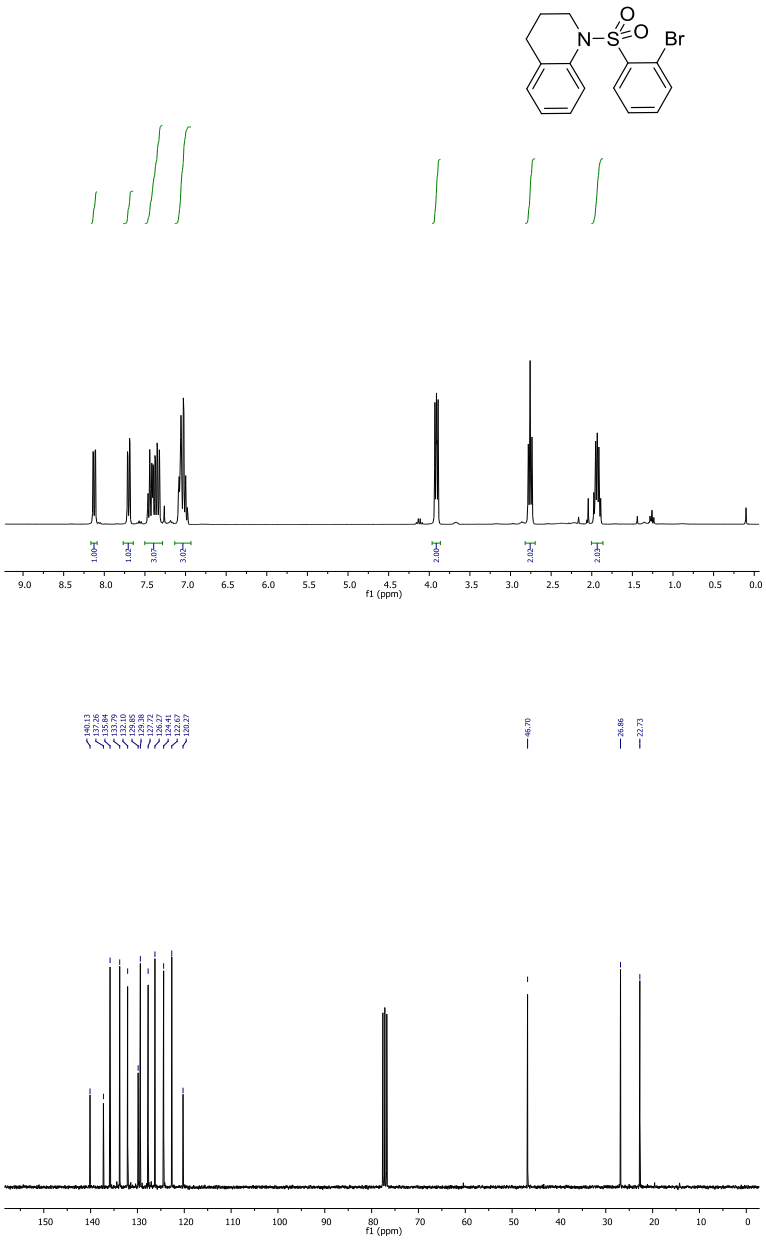


15m: 2-Bromo-*N*-(3,5-dimethoxyphenyl)-*N*-propylbenzenesulfonamide

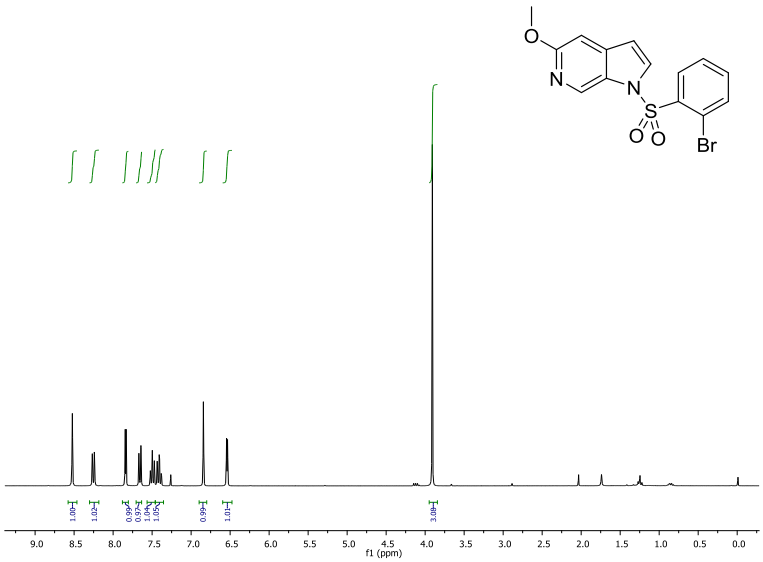


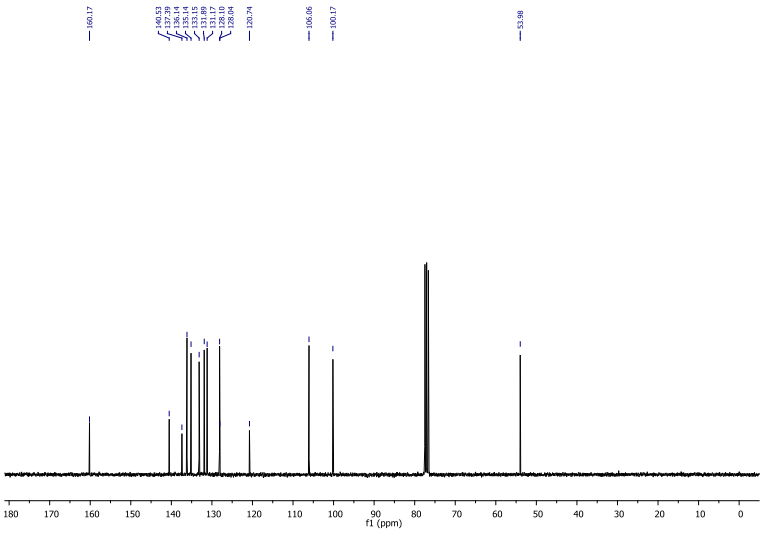


15n: 1-((2-Bromophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline

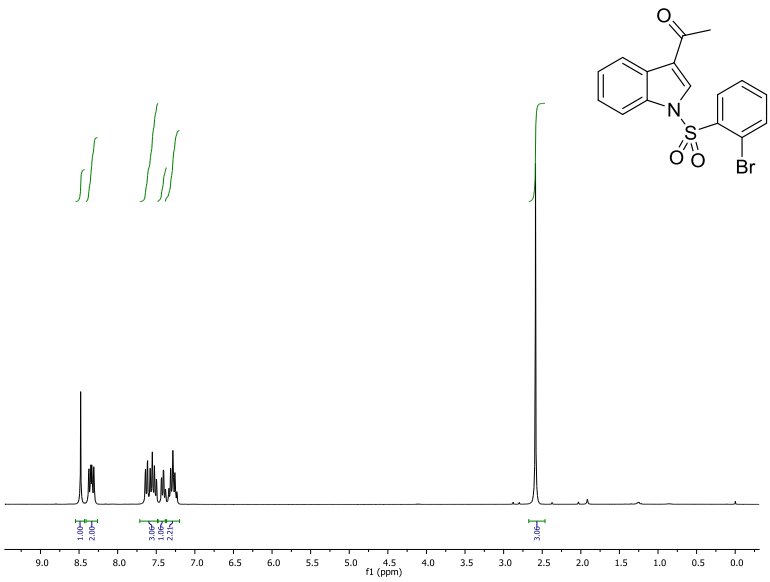


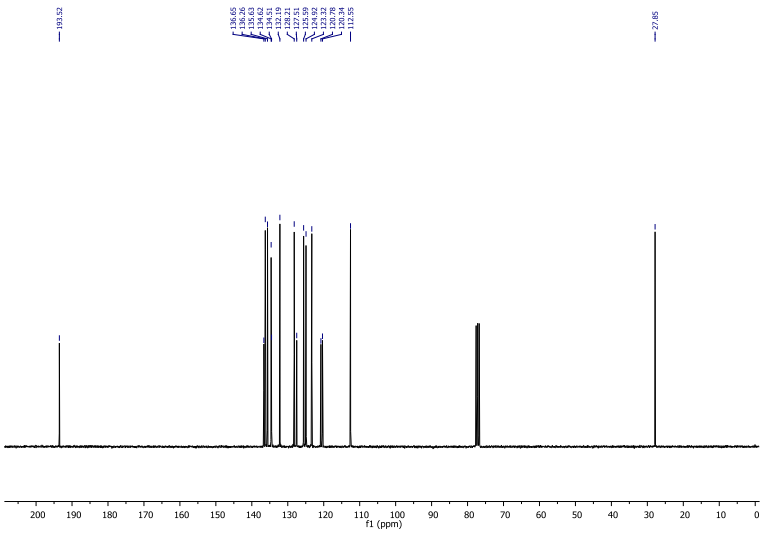
15p: 1-((2-Bromophenyl)sulfonyl)-5-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine



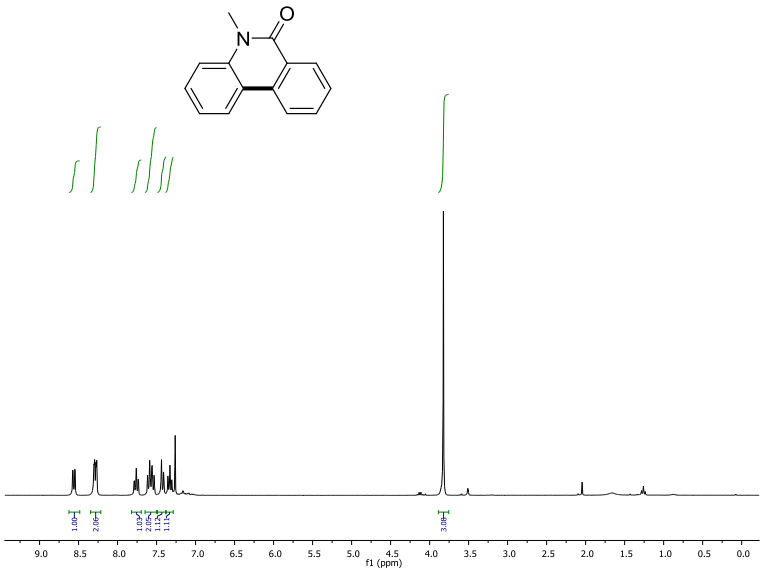


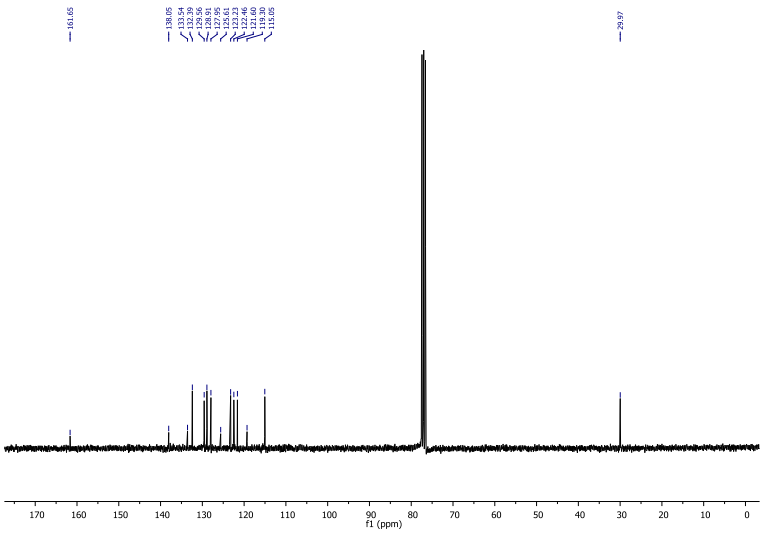
15r: 1-(1-((2-Bromophenyl)sulfonyl)-1*H*-indol-3-yl)ethan-1-one



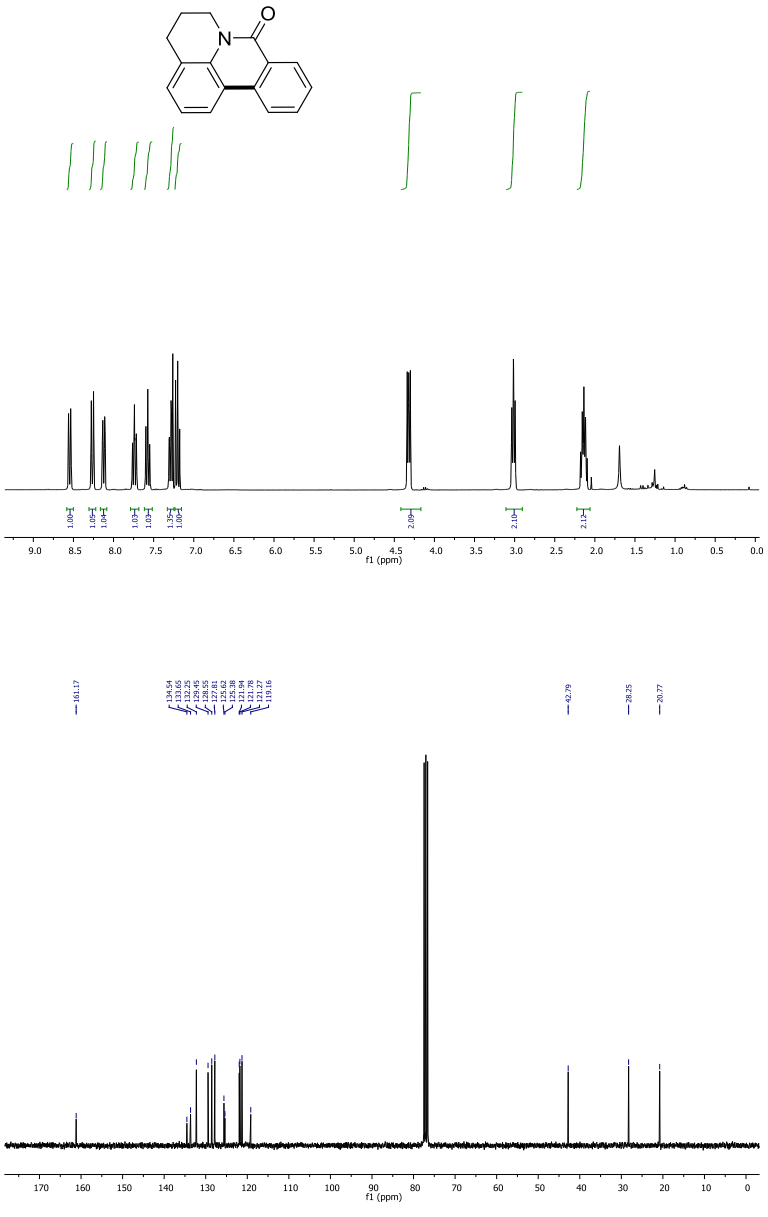


16a: 5-Methylphenanthridin-6(*5H*)-one

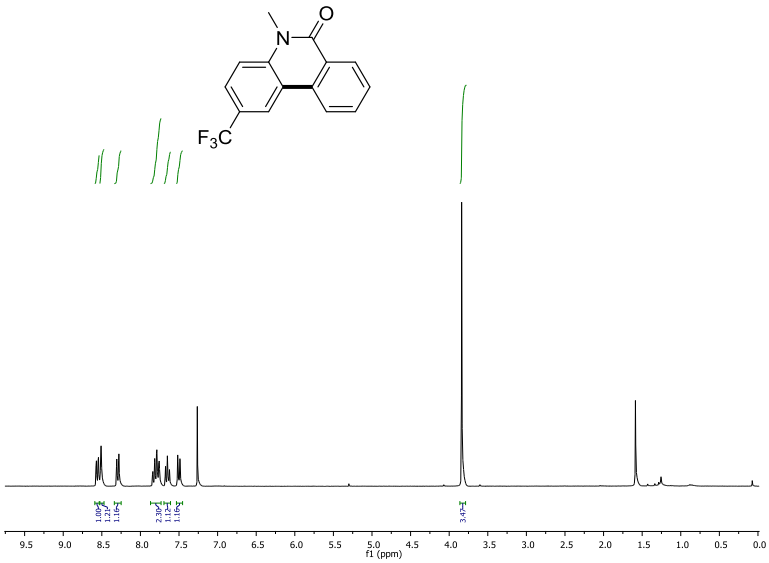


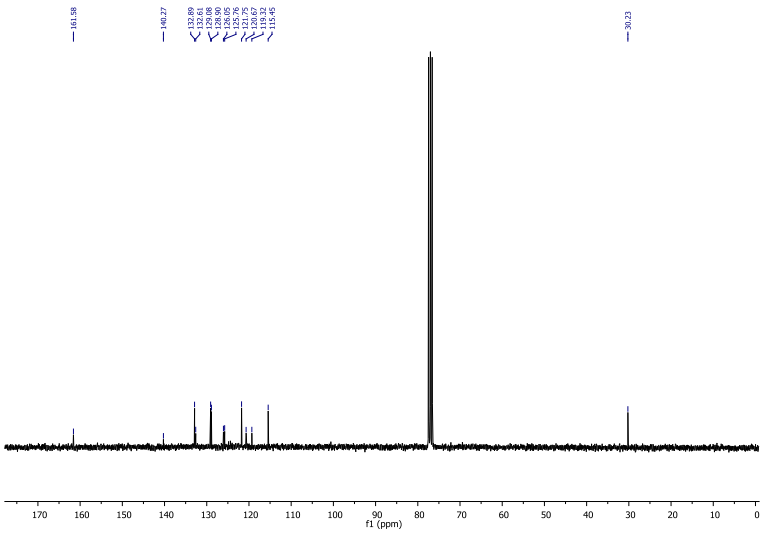


16b: 5,6-Dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridin-8-one

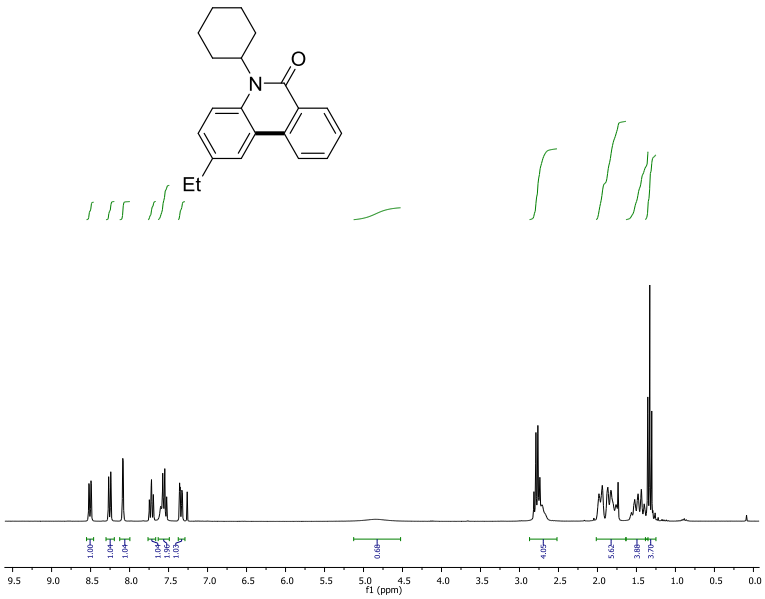


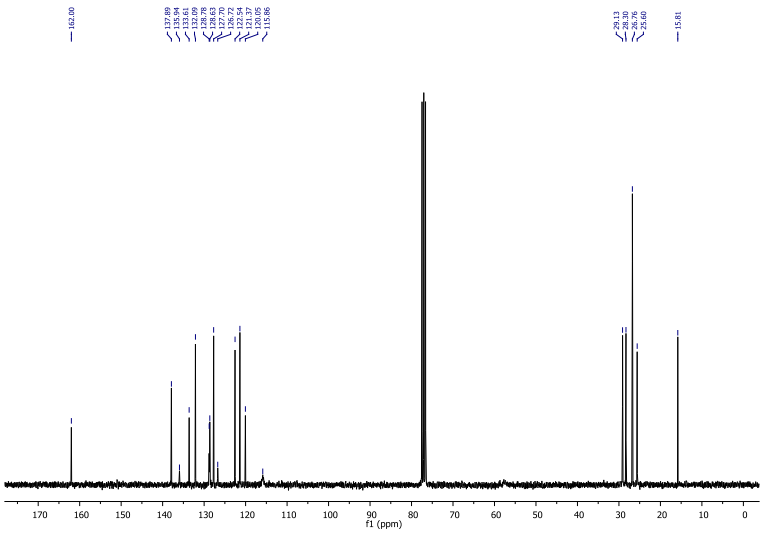
16c: 5-Methyl-2-(trifluoromethyl)phenanthridin-6(5*H*)-one



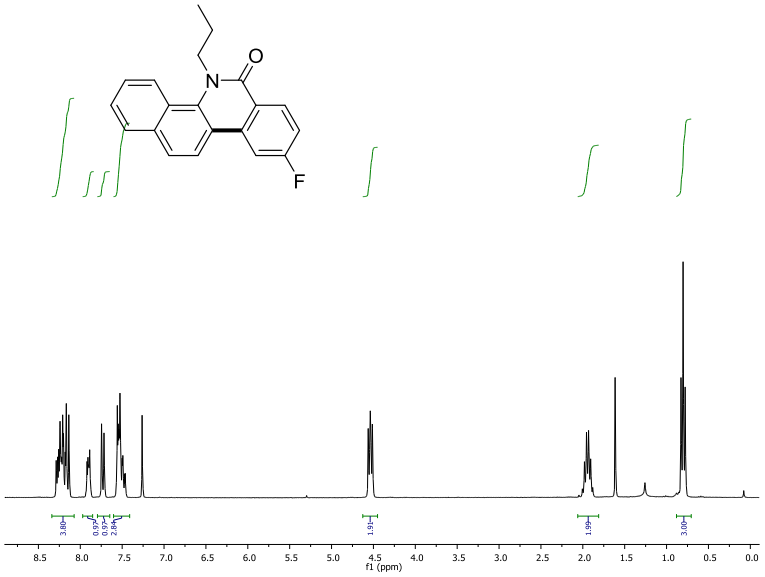


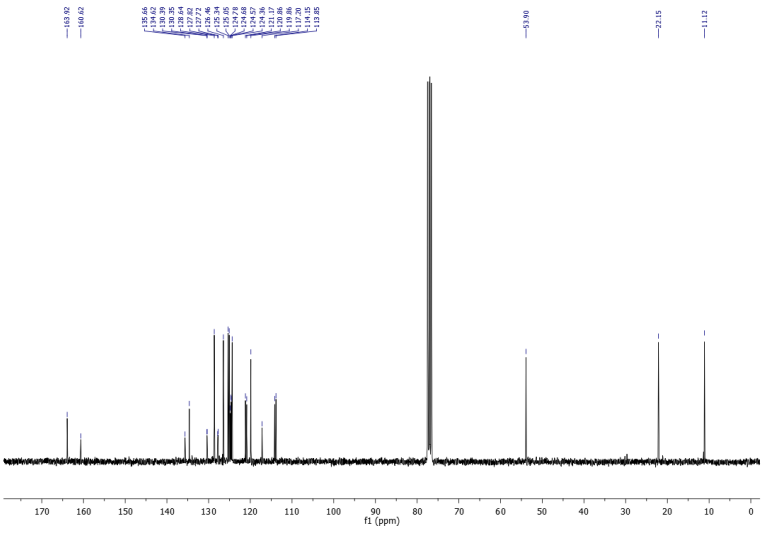
16d: 5-Cyclohexyl-2-ethylphenanthridin-6(*5H*)-one



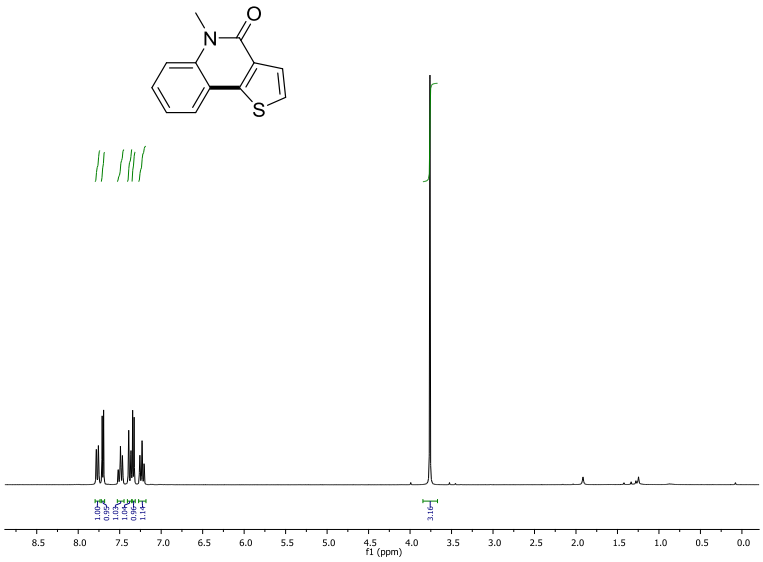


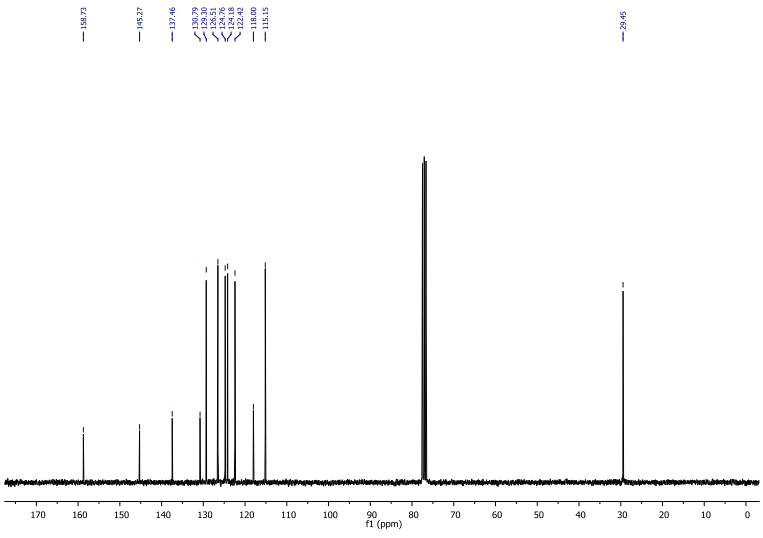
16e: 9-Fluoro-5-propylbenzo[*c*]phenanthridin-6(5*H*)-one



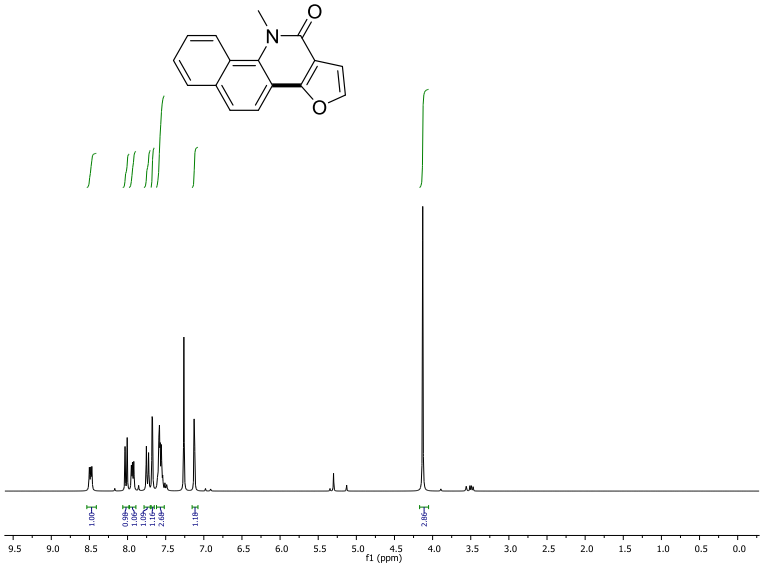


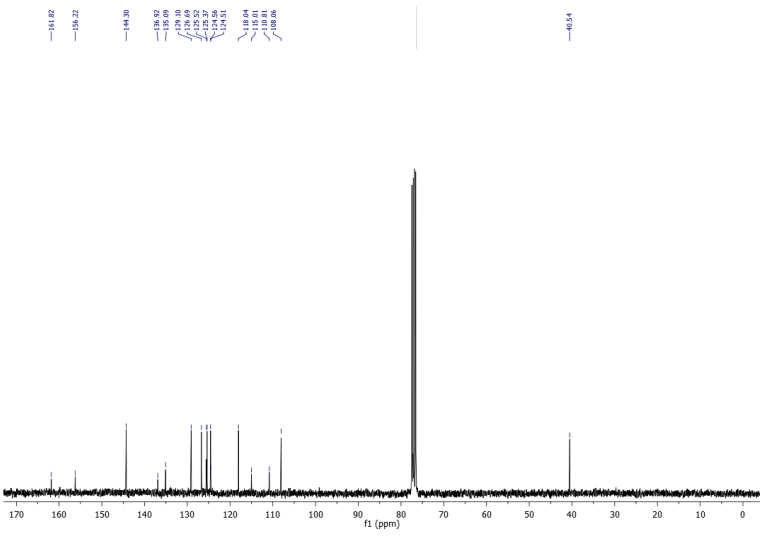
16f: 5-Methylthieno[3,2-*c*]quinolin-4(5*H*)-one



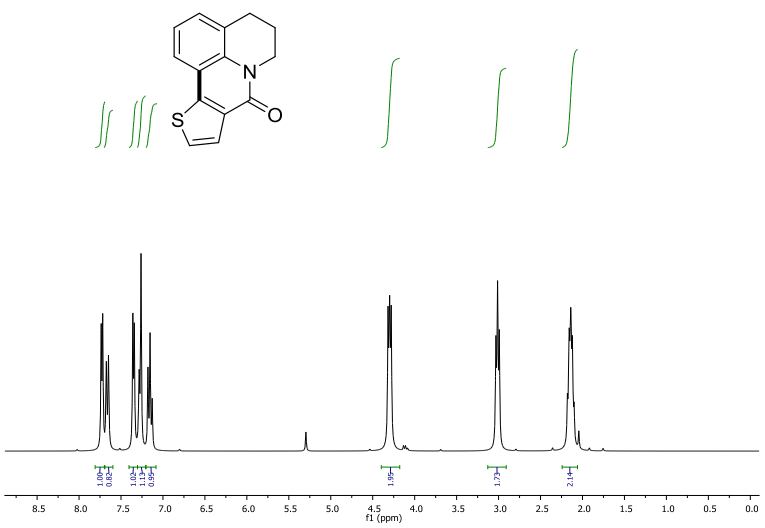


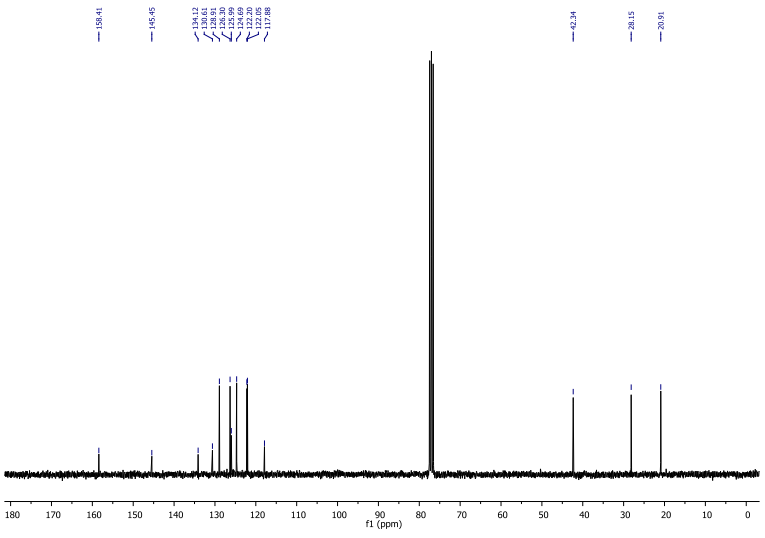
16g: 10-Methylbenzo[*h*]furo[3,2-*c*]quinolin-11(10*H*)-one



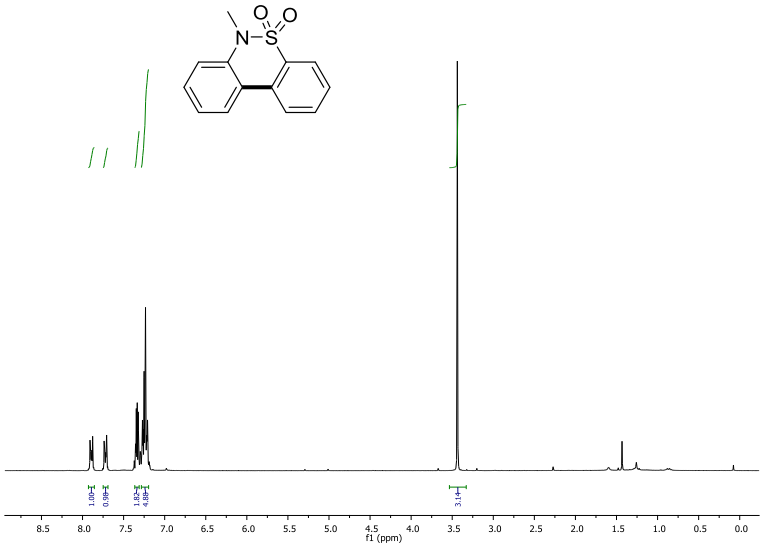


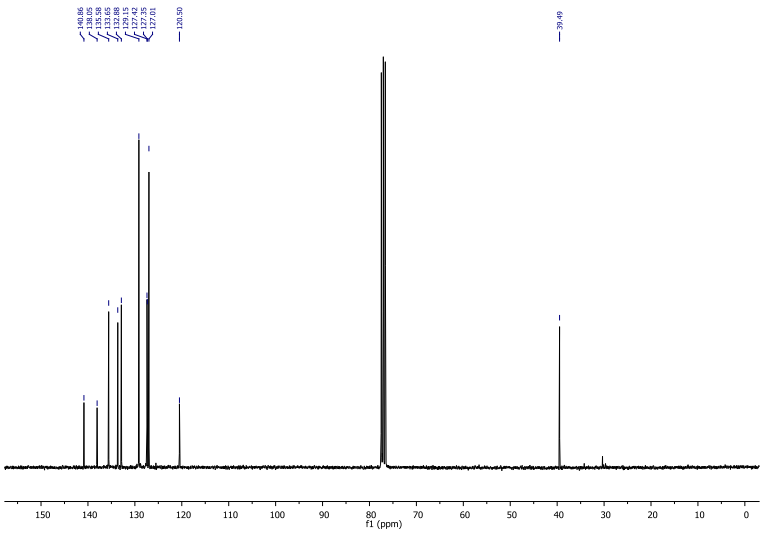
16h: 5,6-Dihydro-4*H*,8*H*-pyrido[3,2,1-*ij*]thieno[3,2-*c*]quinolin-8-one



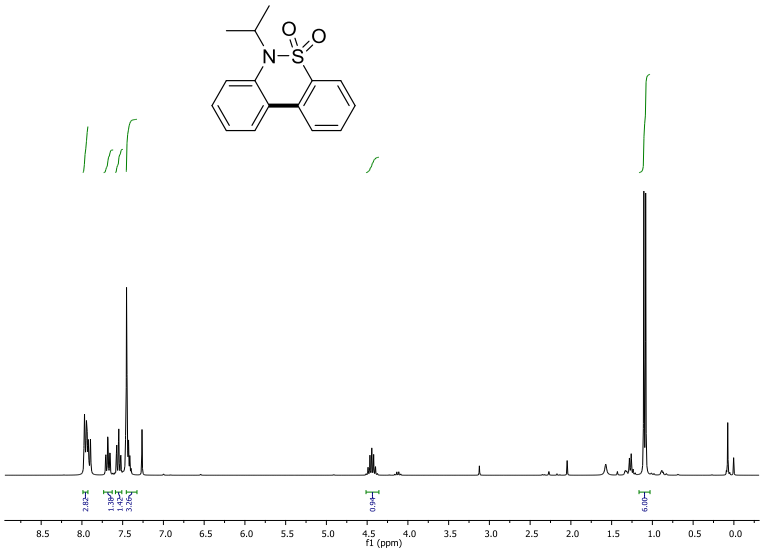


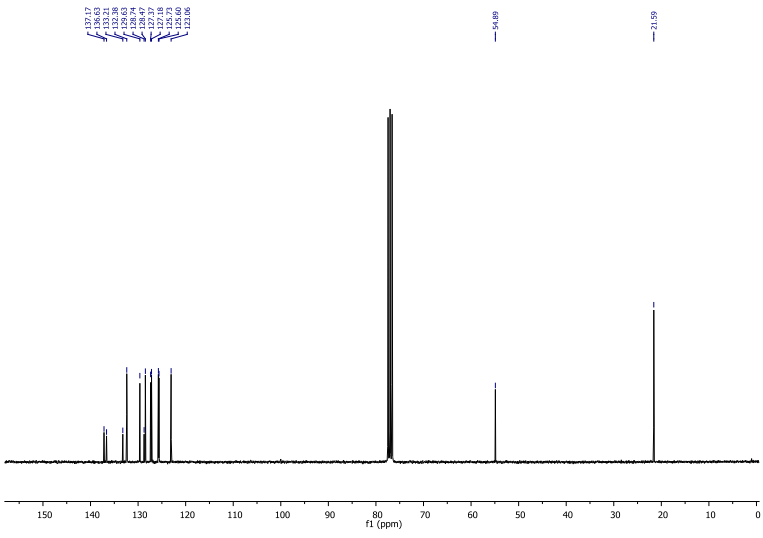
16i: 6-Methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide



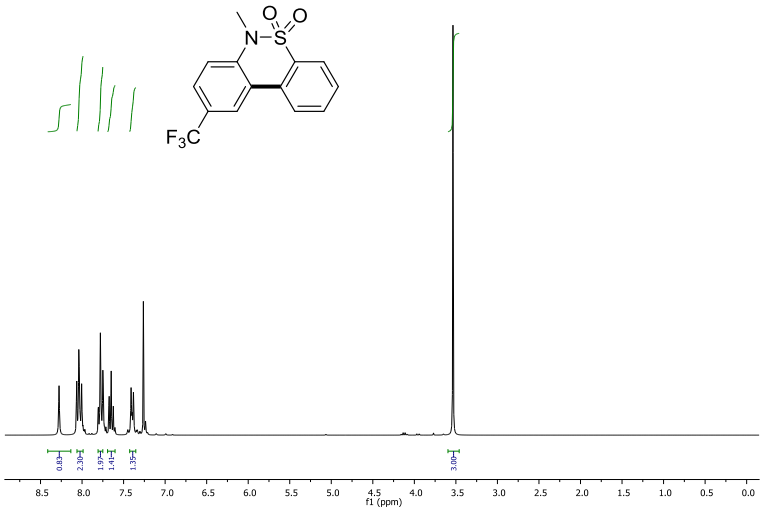


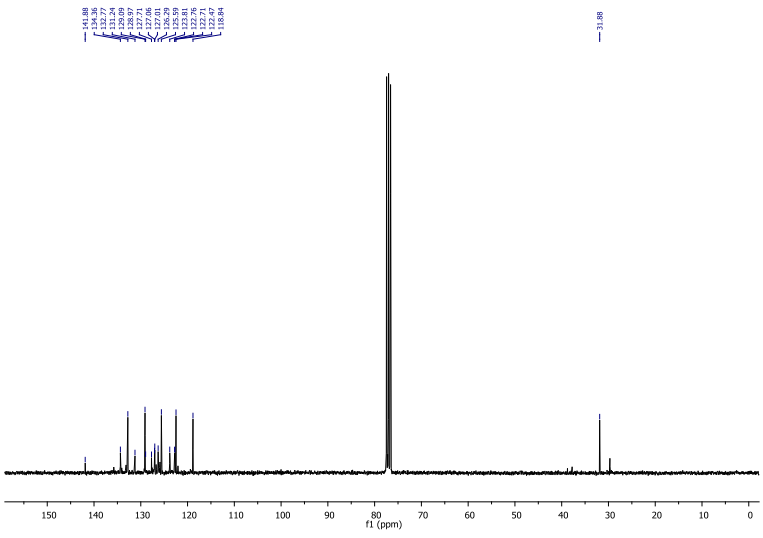
16j: 6-Isopropyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide



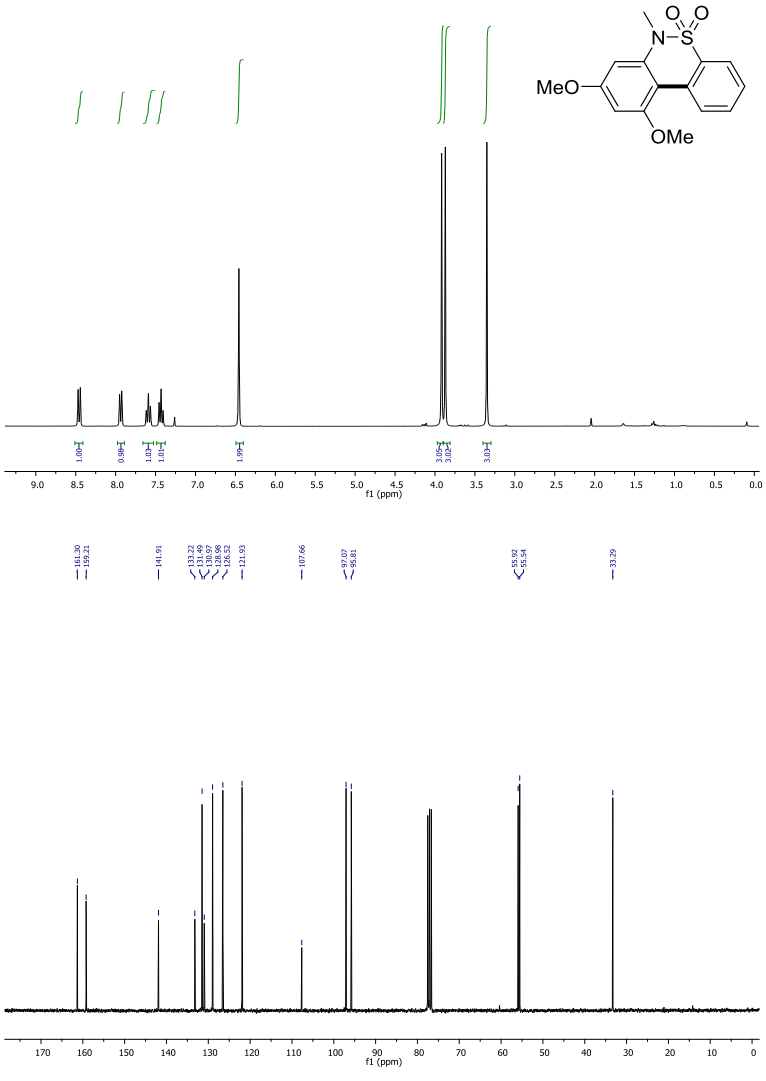


16k: 6-Methyl-9-(trifluoromethyl)-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide

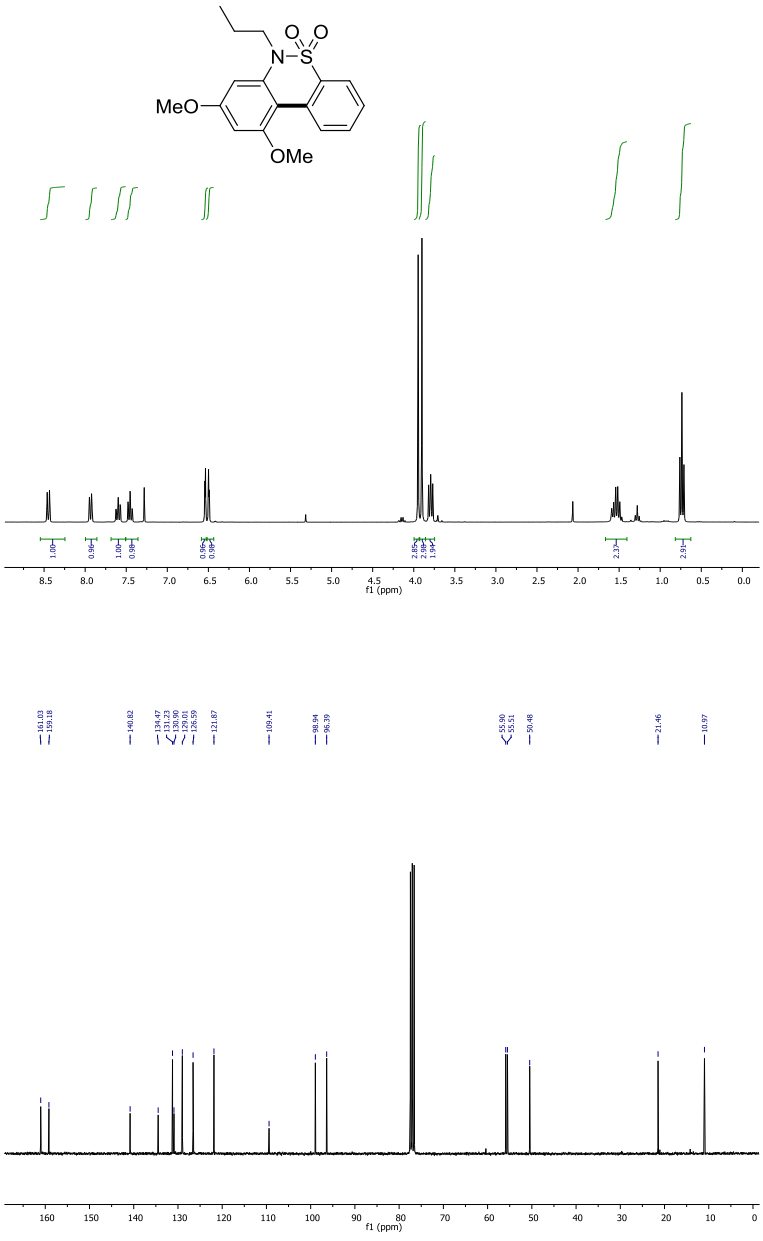




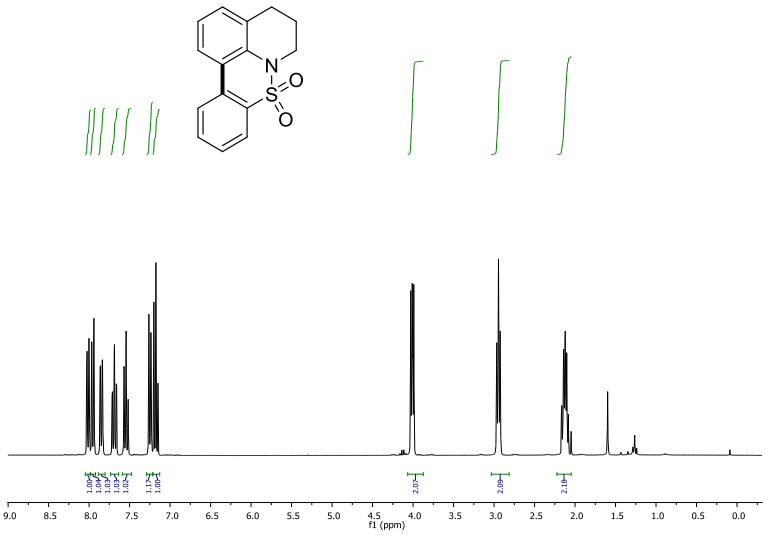
16l: 8,10-Dimethoxy-6-methyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide

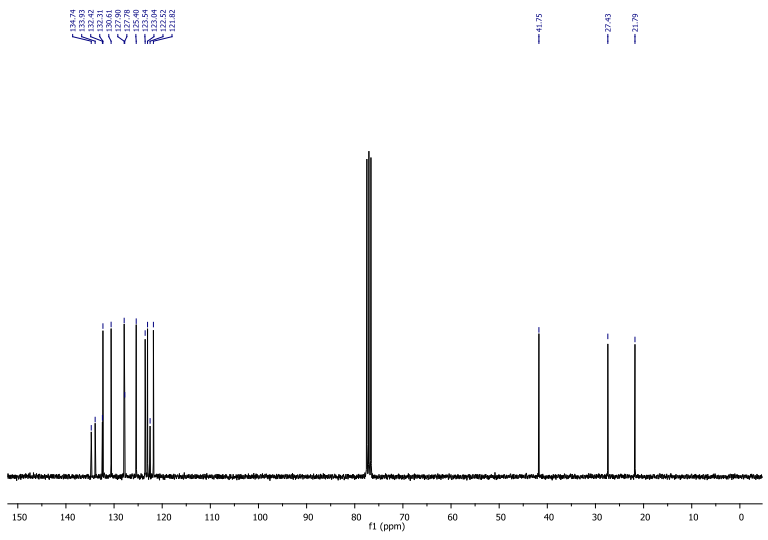


16m: 8,10-Dimethoxy-6-propyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine

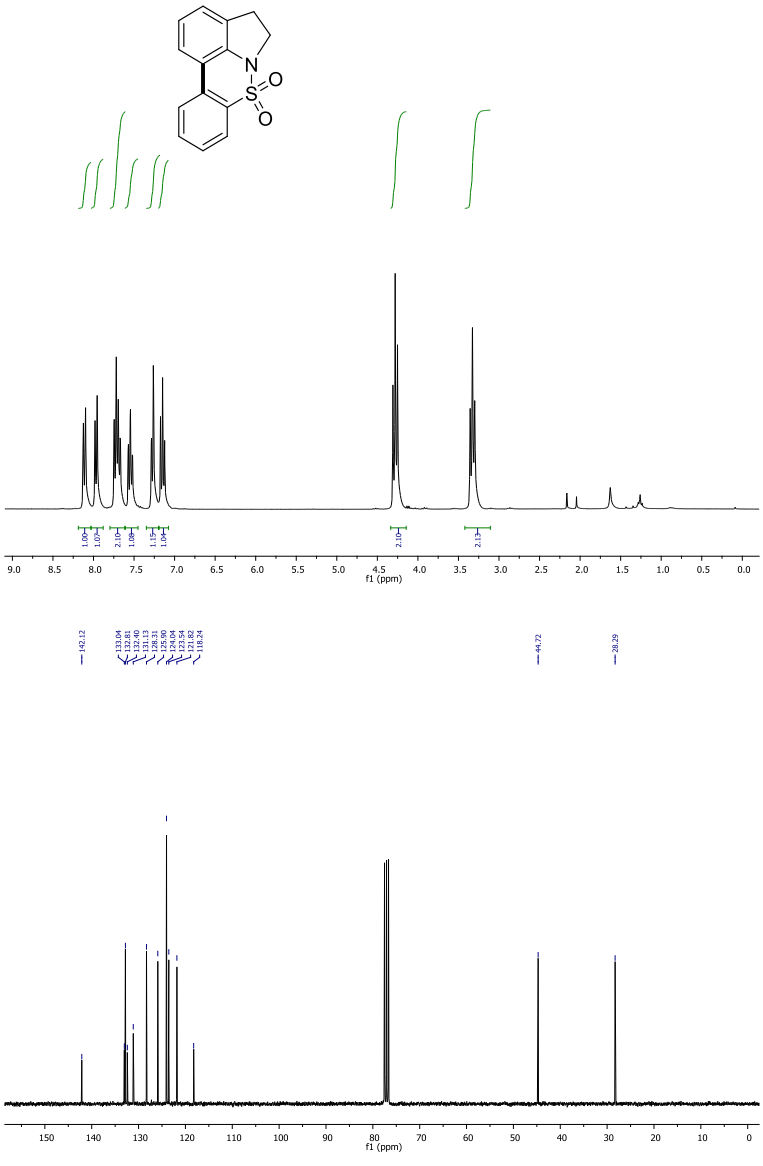


16n: 5,6-Dihydro-4*H*-benzo[5,6][1,2]thiazino[4,3,2-*ij*]quinoline 8,8-dioxide

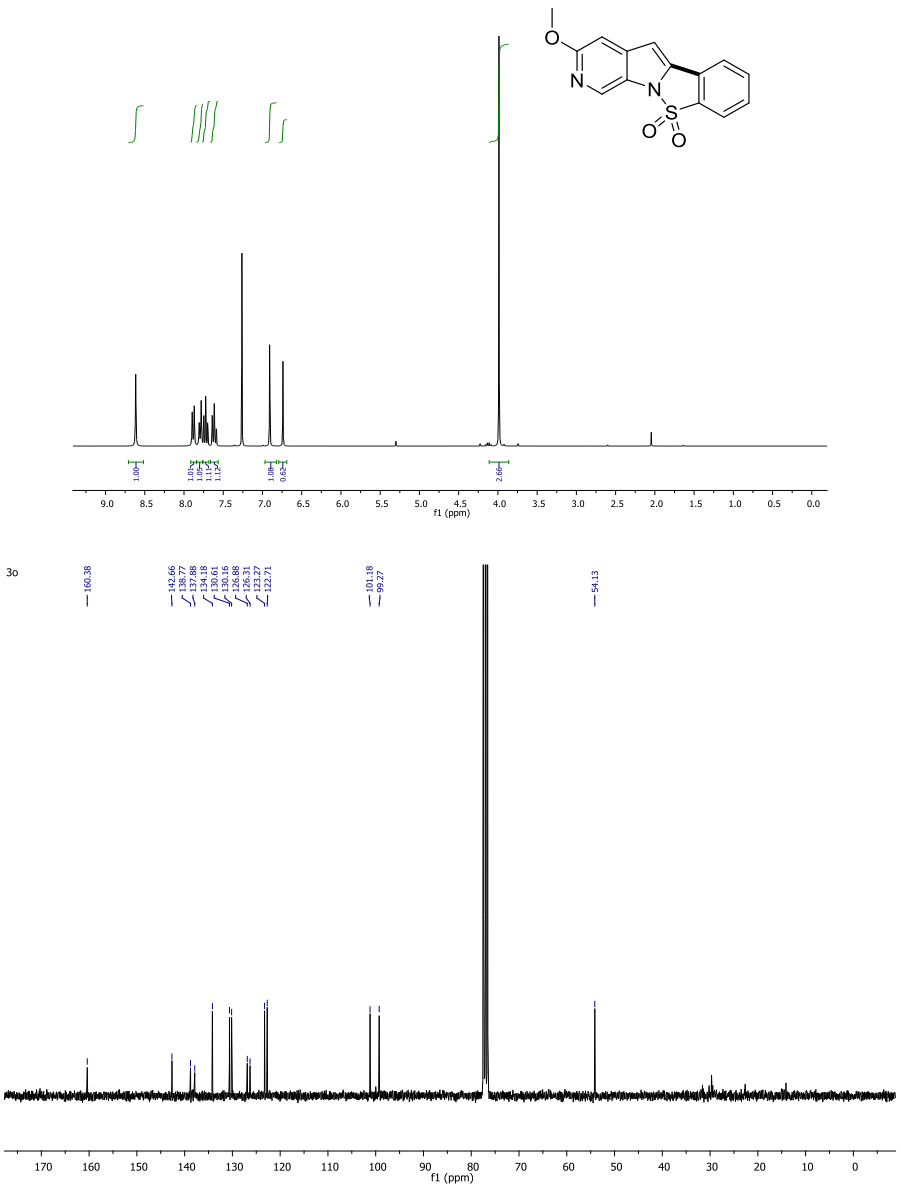




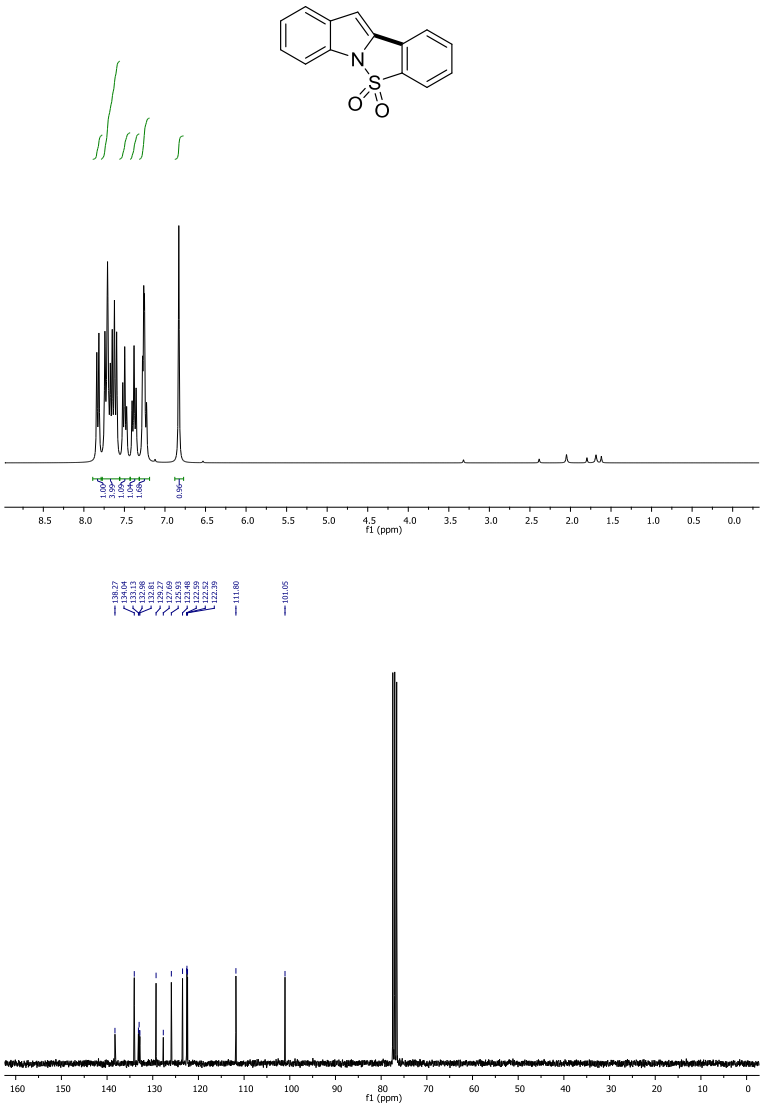
16o: 4,5-Dihydrobenzo[5,6][1,2]thiazino[4,3,2-*hi*]indole 7,7-dioxide



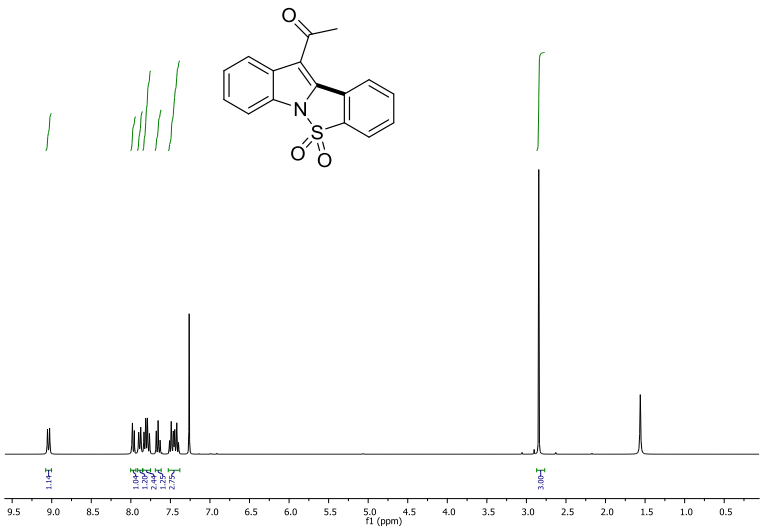
16p: 3-Methoxybenzo[4',5']isothiazolo[2',3':1,5]pyrrolo[2,3-*c*]pyridine 10,10-dioxide

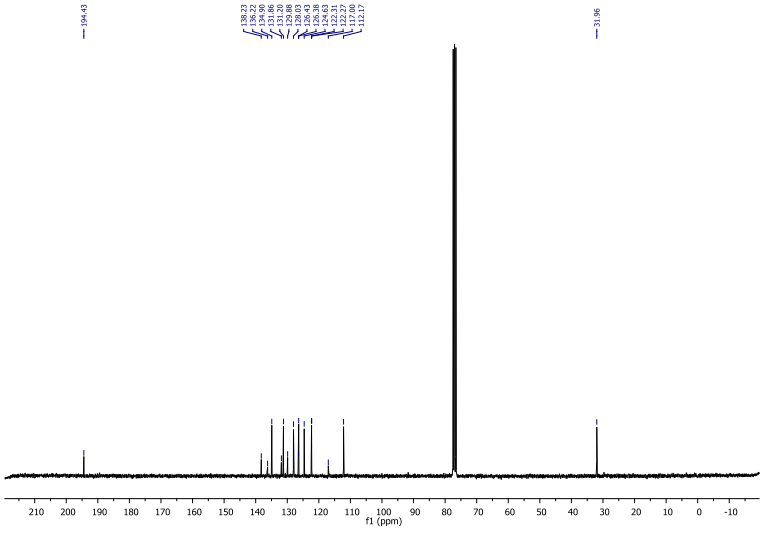


16q: Benzo[4,5]isothiazolo[2,3-*a*]indole 5,5-dioxide

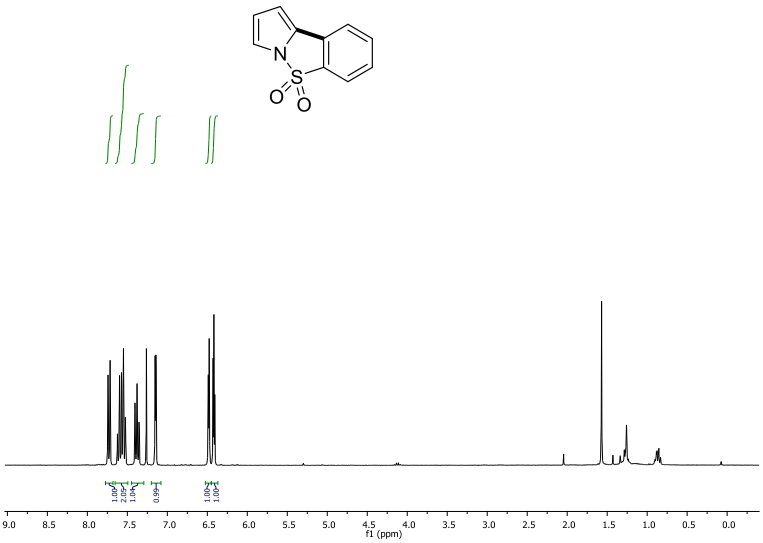


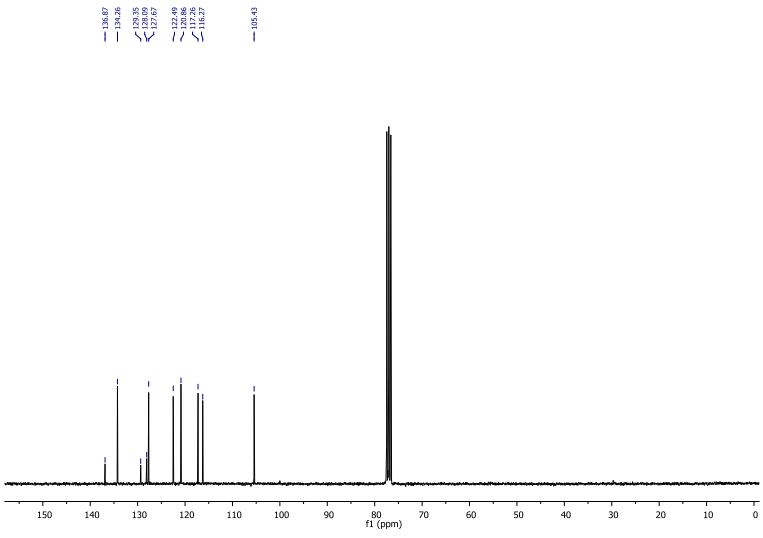
16r: 1-(5,5-Dioxidobenzo[4,5]isothiazolo[2,3-*a*]indol-11-yl)ethan-1-one



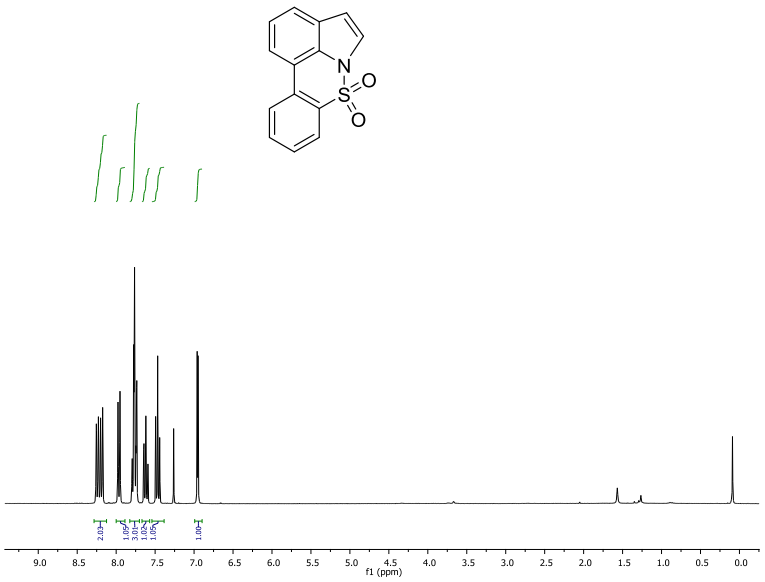


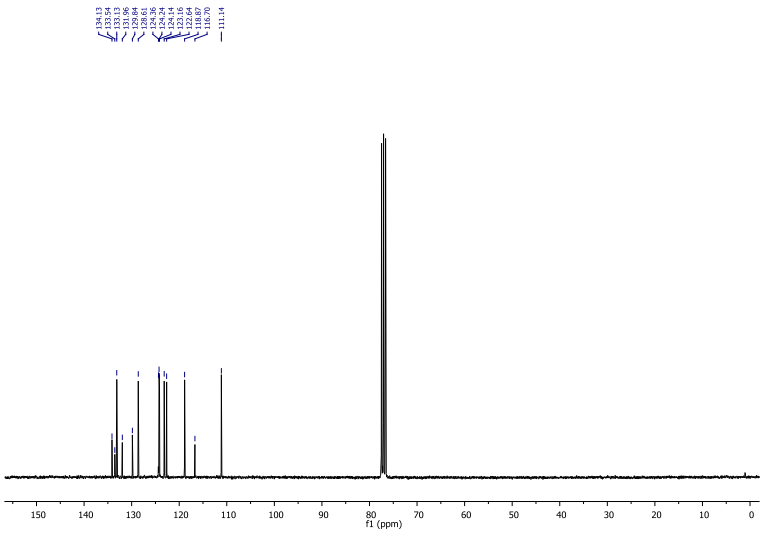
16s: Benzo[*d*]pyrrolo[1,2-*b*]isothiazole 5,5-dioxide



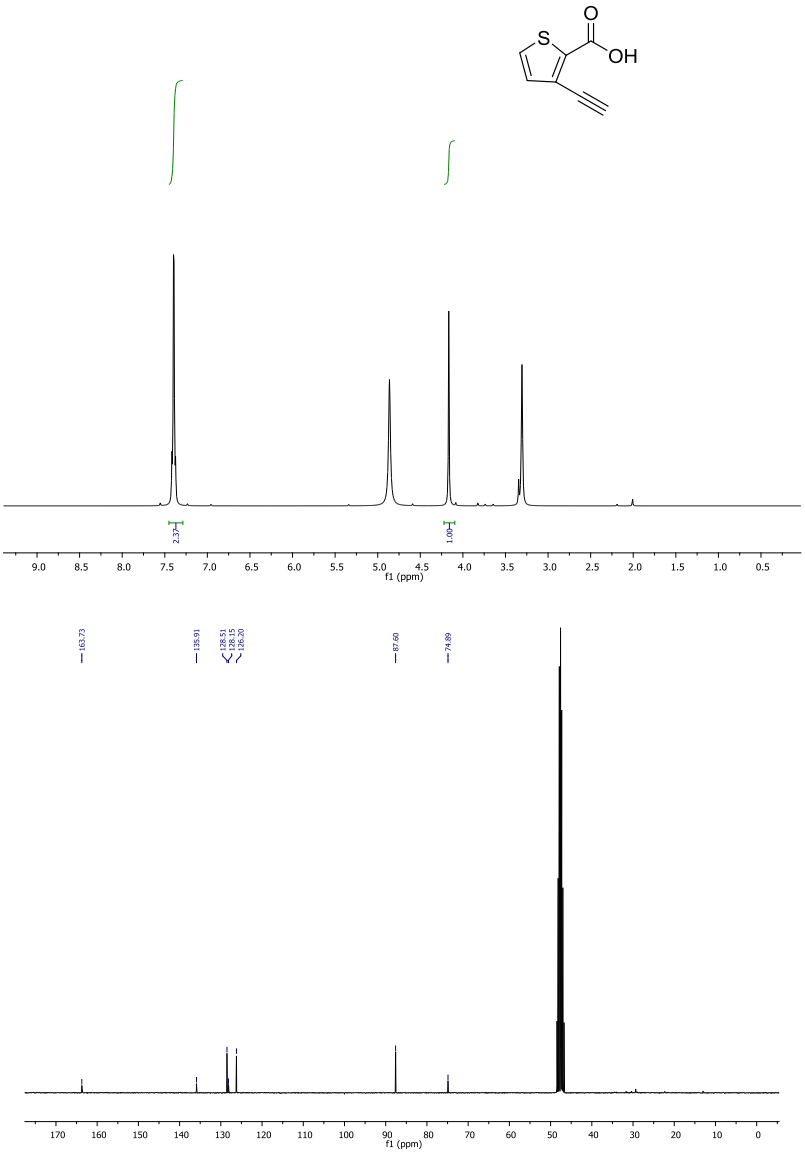


16t: Dihydrobenzothiazinoindole 7,7-dioxide

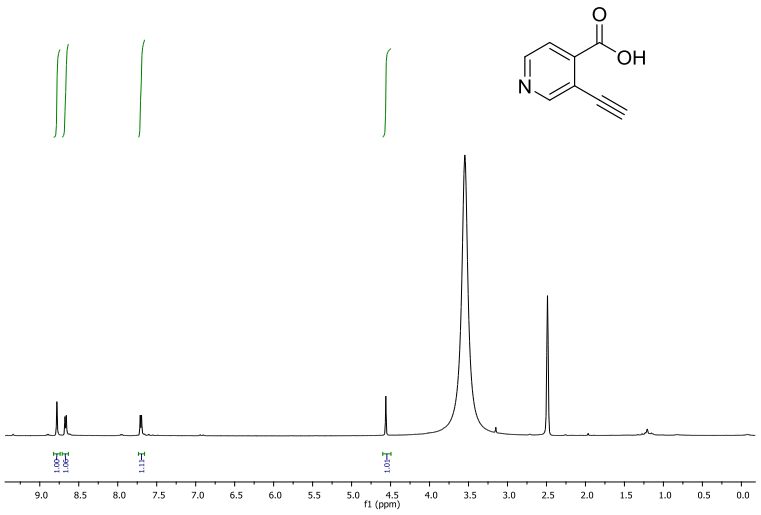


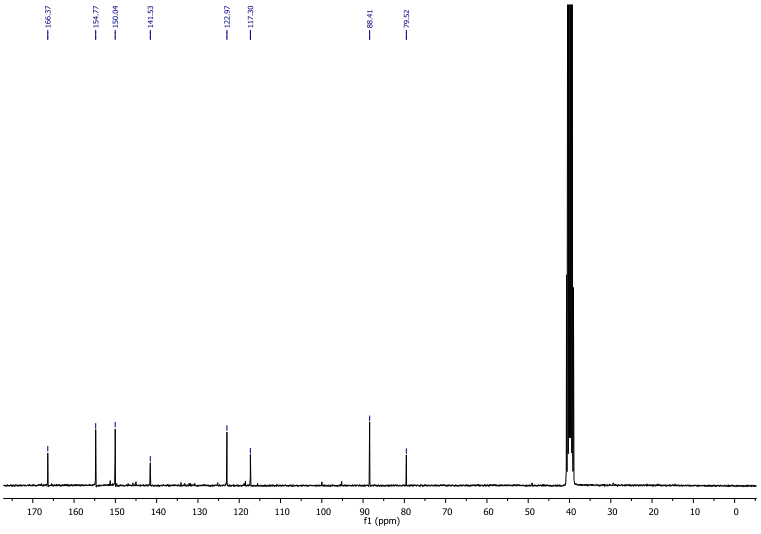


17j: 3-ethynylthiophene-2-carboxylic acid

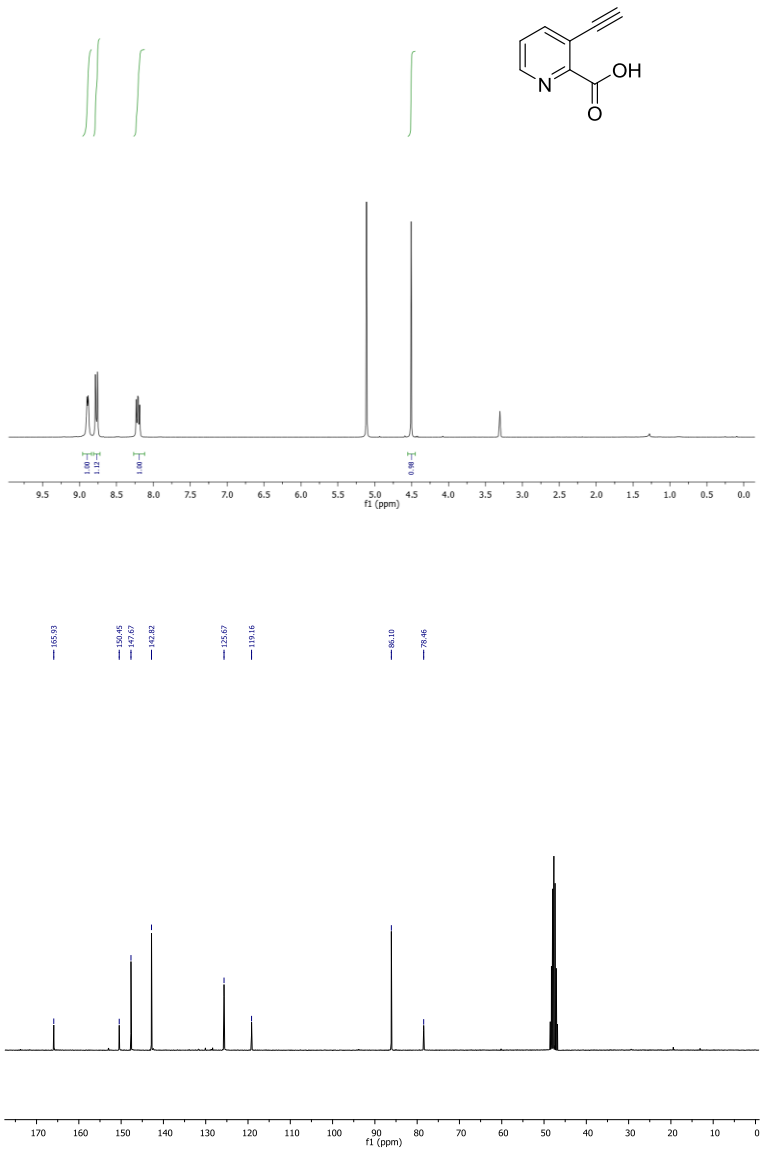


17k: 3-ethynylisonicotinic acid

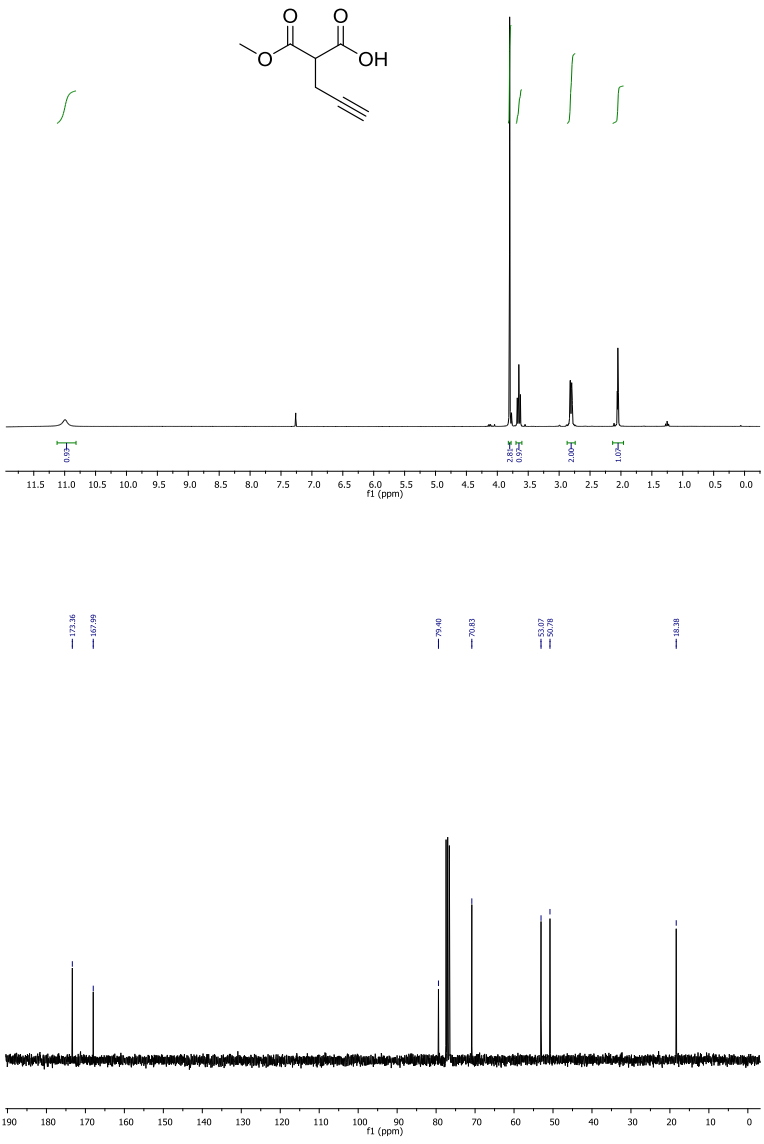




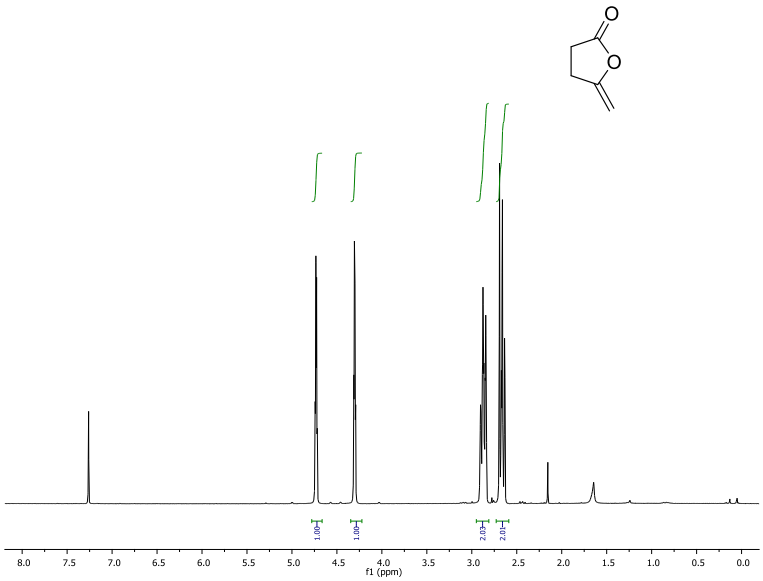
17l: 3-ethynylpicolinic acid

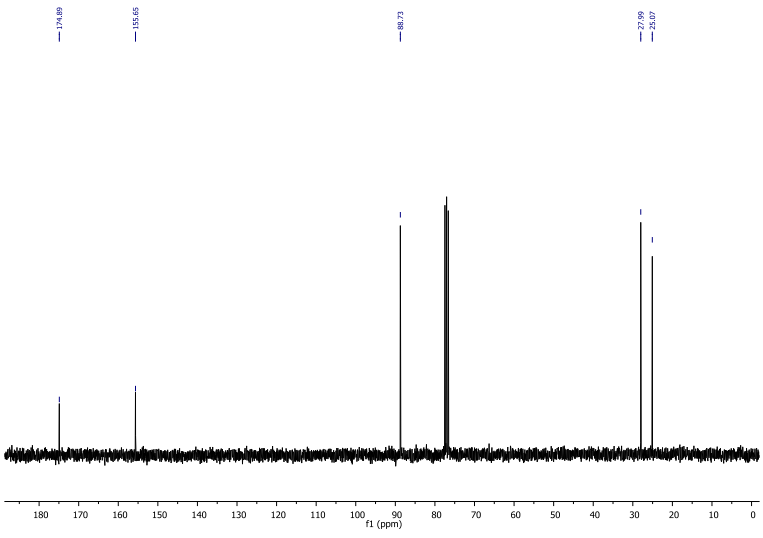


17d: 2-(methoxycarbonyl)pent-4-ynoic acid

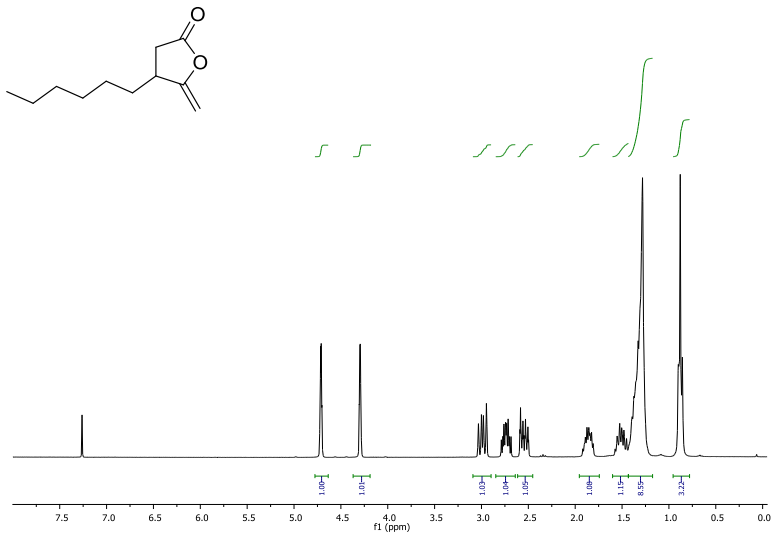


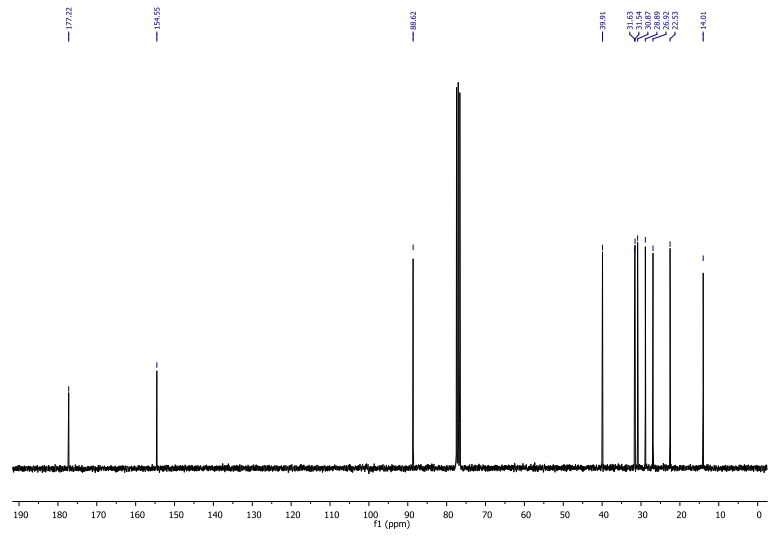
18a: 5-Methylenedihydrofuran-2(3*H*)-one



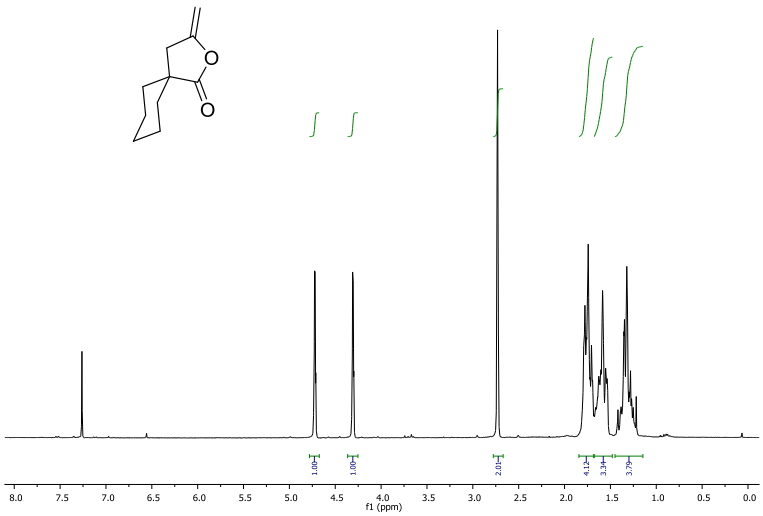


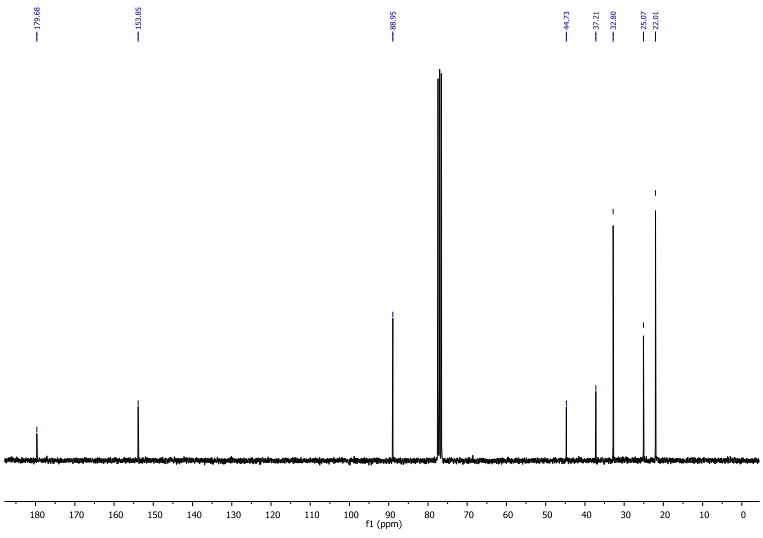
18b: 4-Hexyl-5-methylenedihydrofuran-2(3*H*)-one



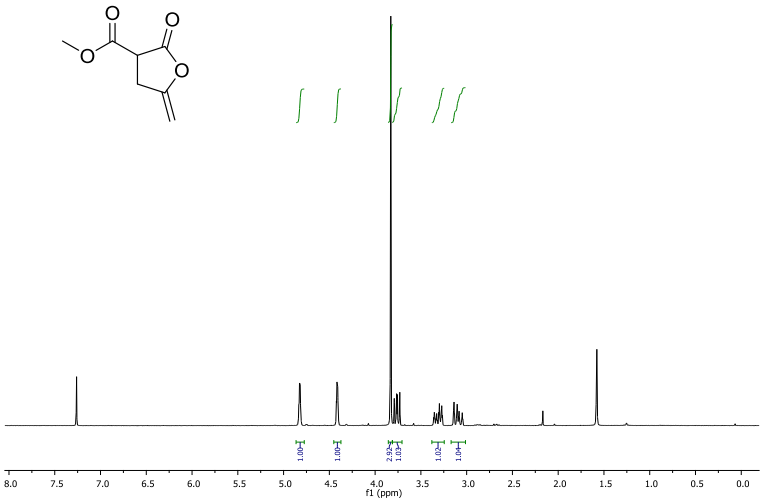


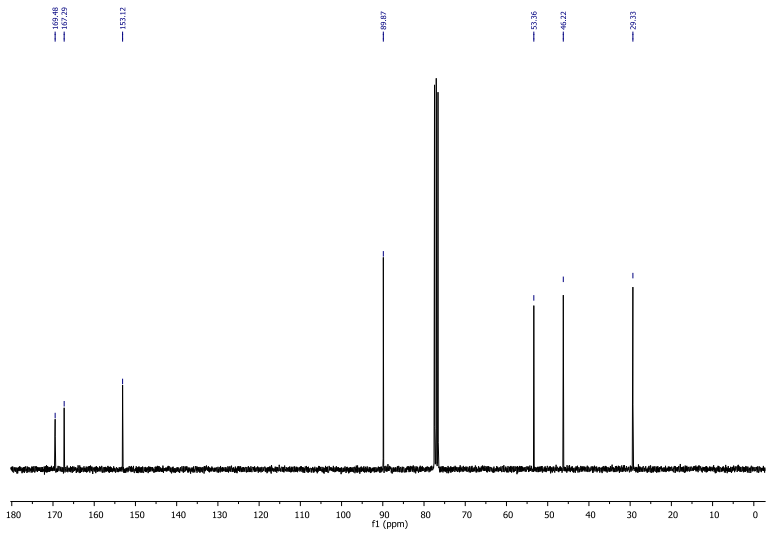
18c: 3-Methylene-2-oxaspiro[4.5]decan-1-one



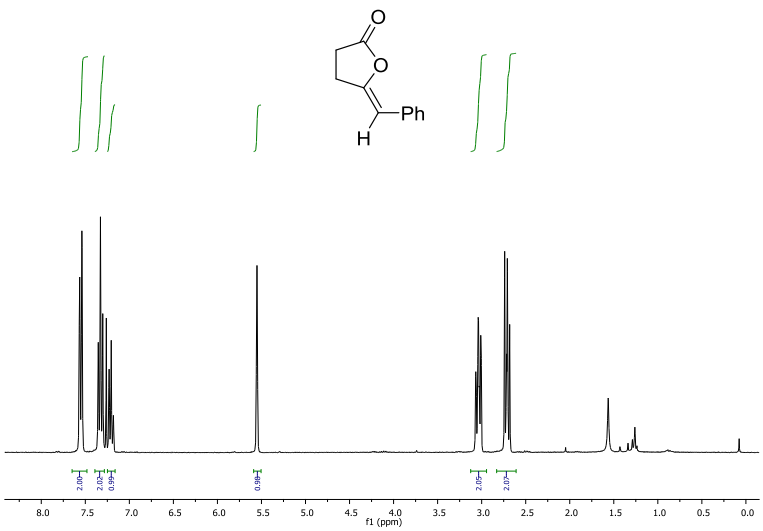


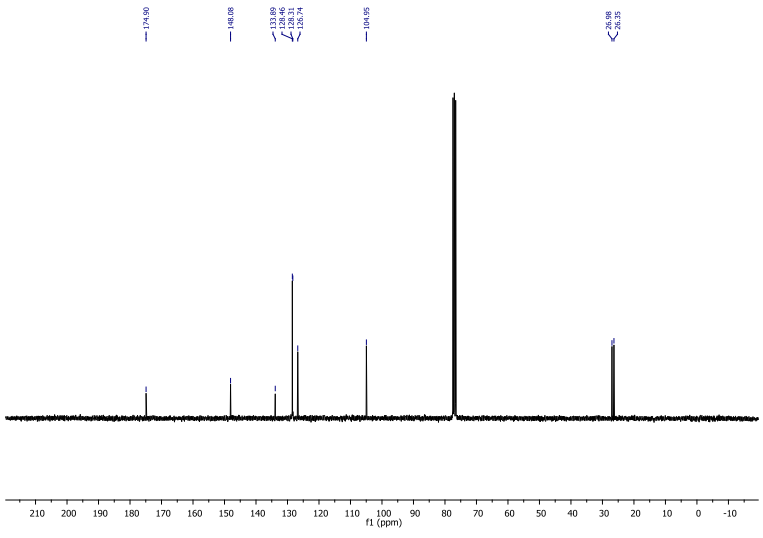
18d: Methyl 5-methylene-2-oxotetrahydrofuran-3-carboxylate



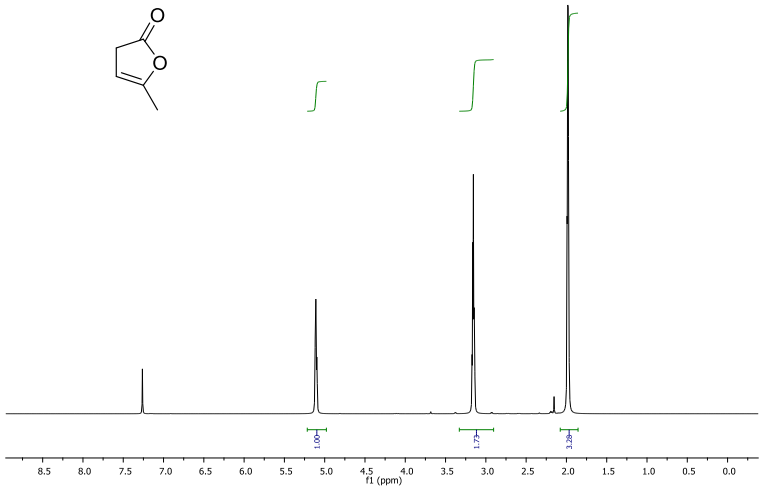


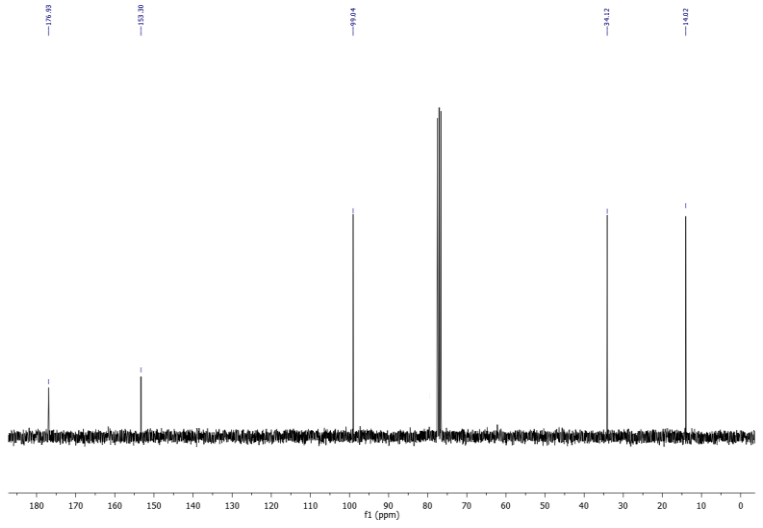
18e: (*Z*)-5-benzylidenedihydrofuran-2(3*H*)-one



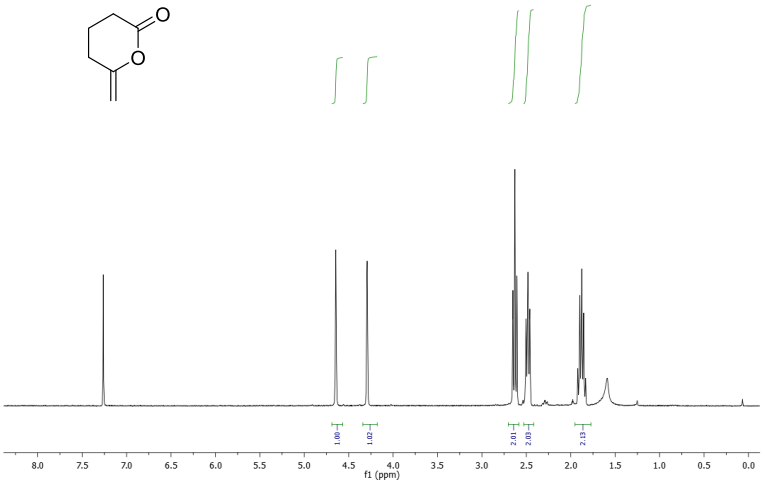


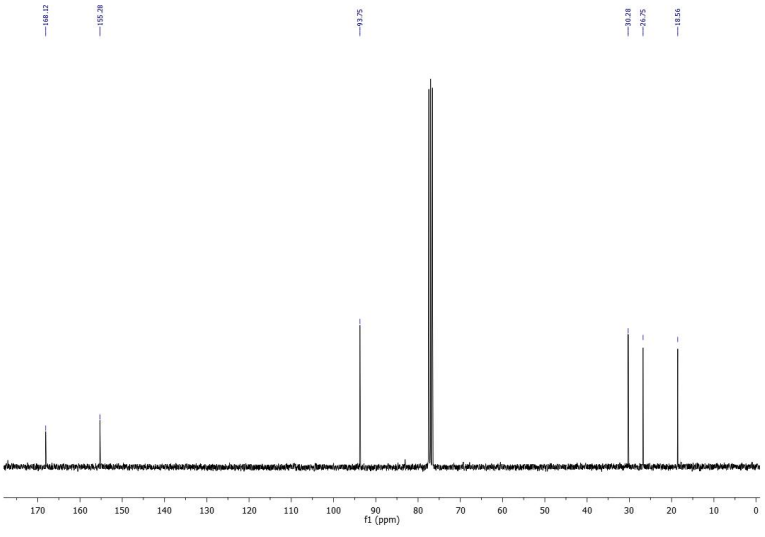
18f: 5-Methylfuran-2(3*H*)-one



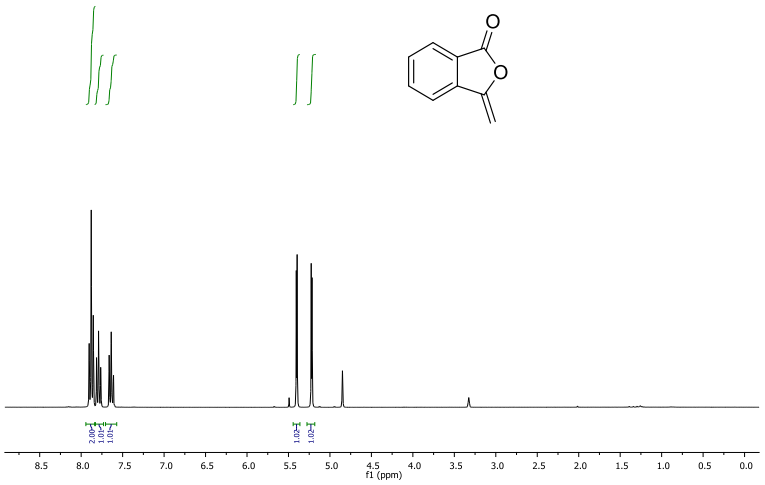


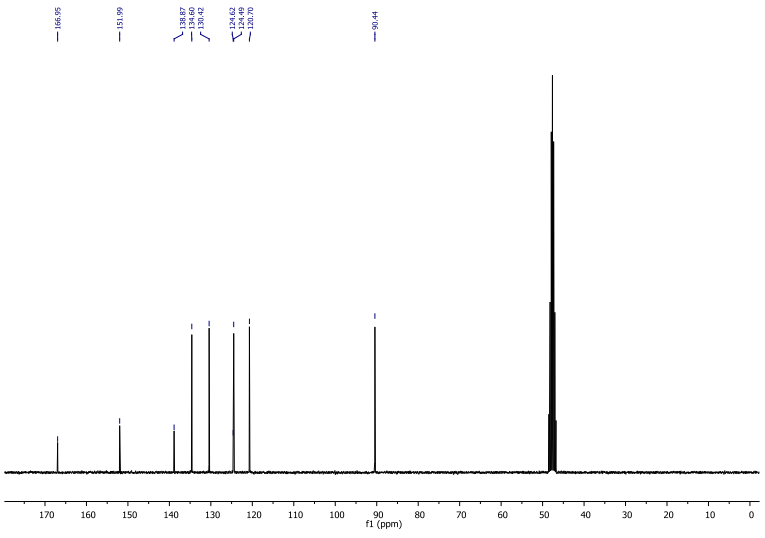
18g: 6-methylenetetrahydro-2*H*-pyran-2-one



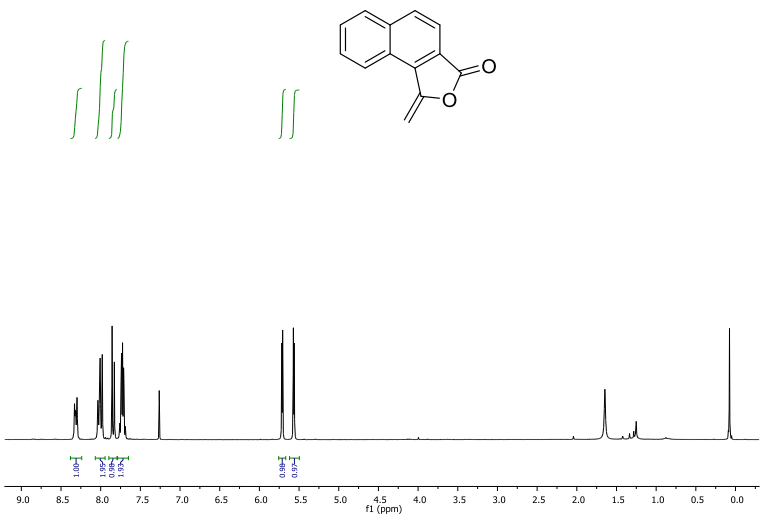


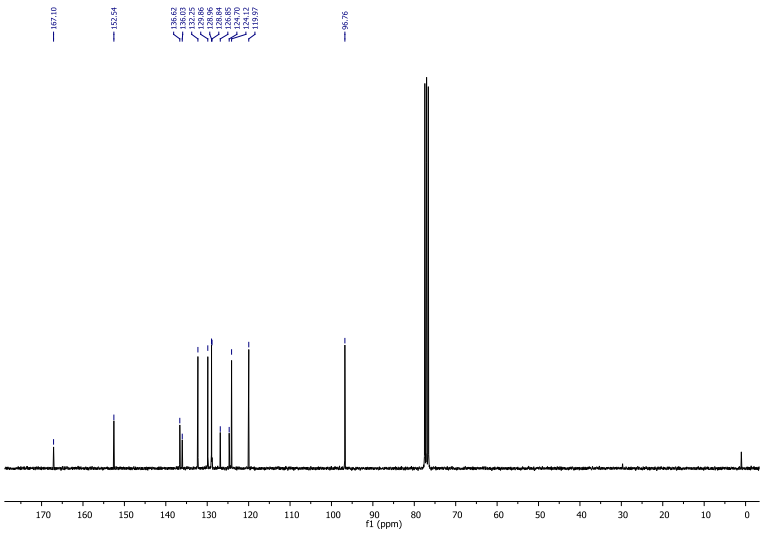
18h: 3-Methyleneisobenzofuran-1(3*H*)-one



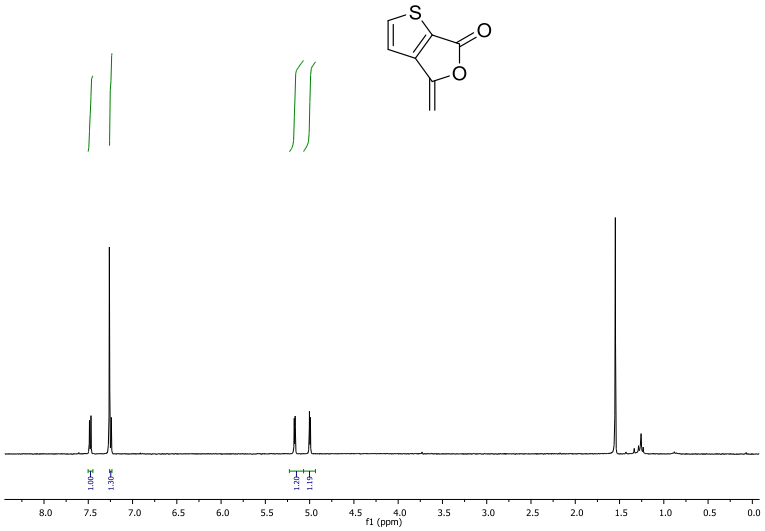


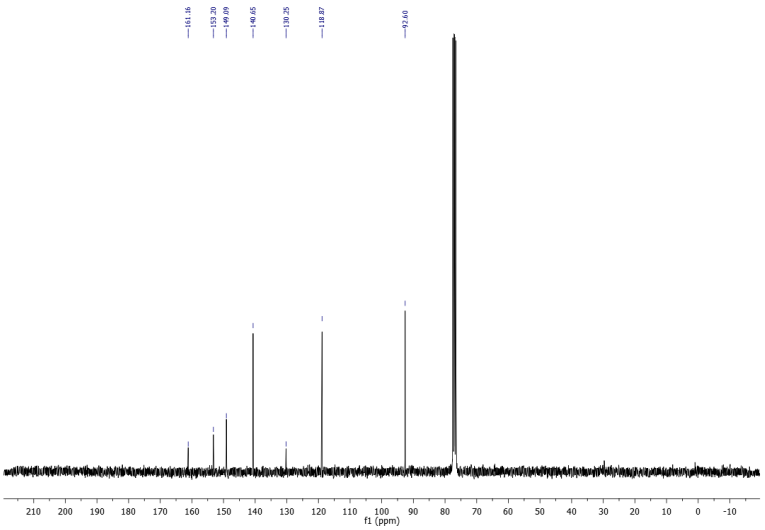
18i: 1-Methylenenaphtho[1,2-*c*]furan-3(1*H*)-one



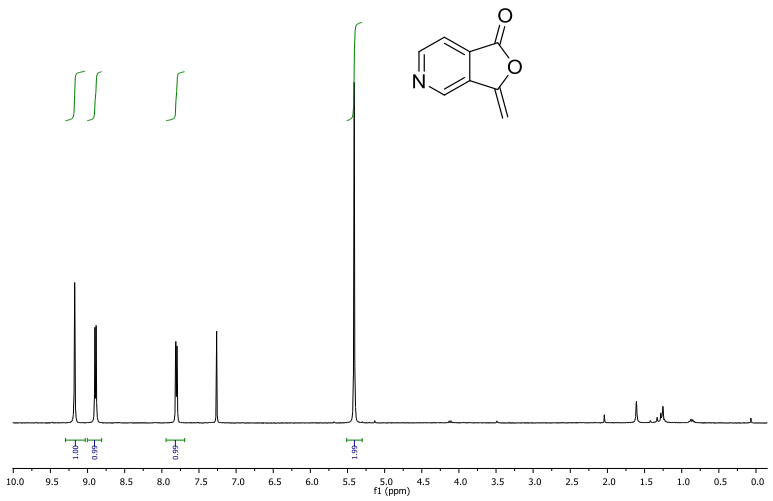


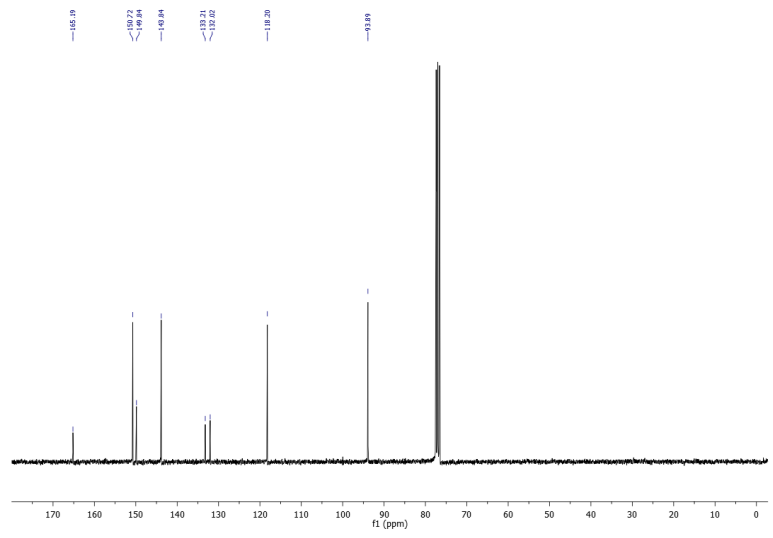
18j: 4-Methylenethieno[2,3-*c*]furan-6(4*H*)-one



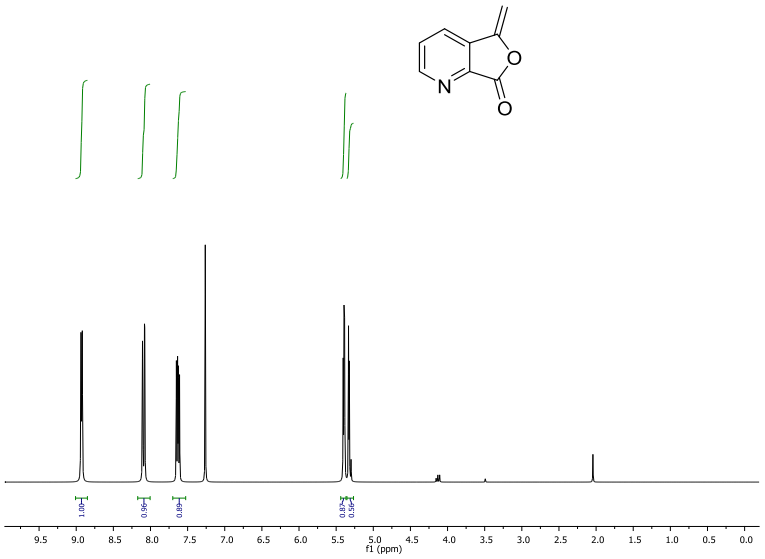


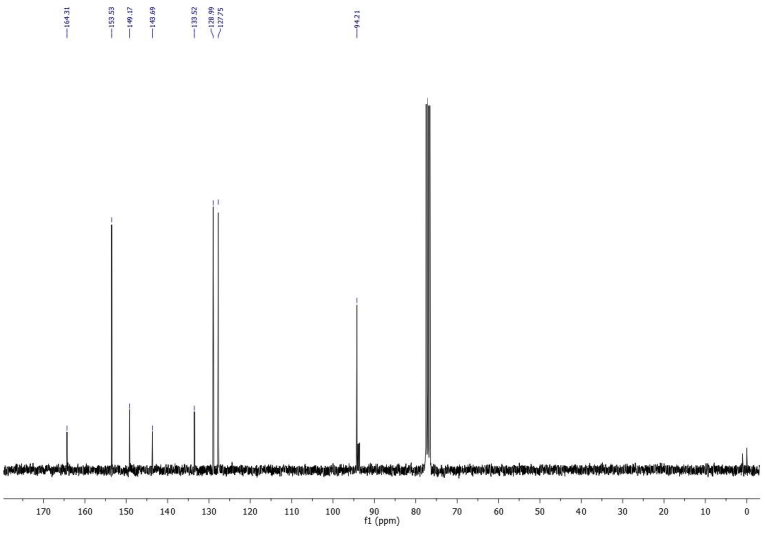
18k: 3-Methylenefuro[3,4-*c*]pyridin-1(3*H*)-one



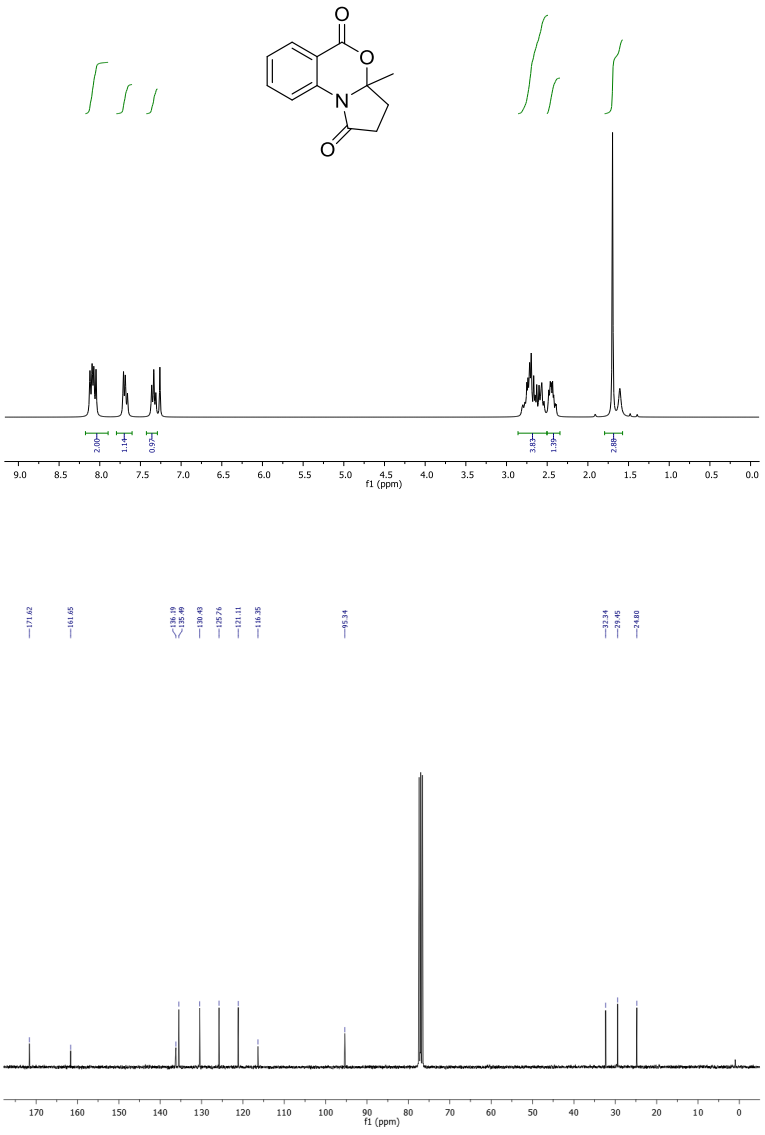


18l: 5-Methylenefuro[3,4-*b*]pyridin-7(5*H*)-one

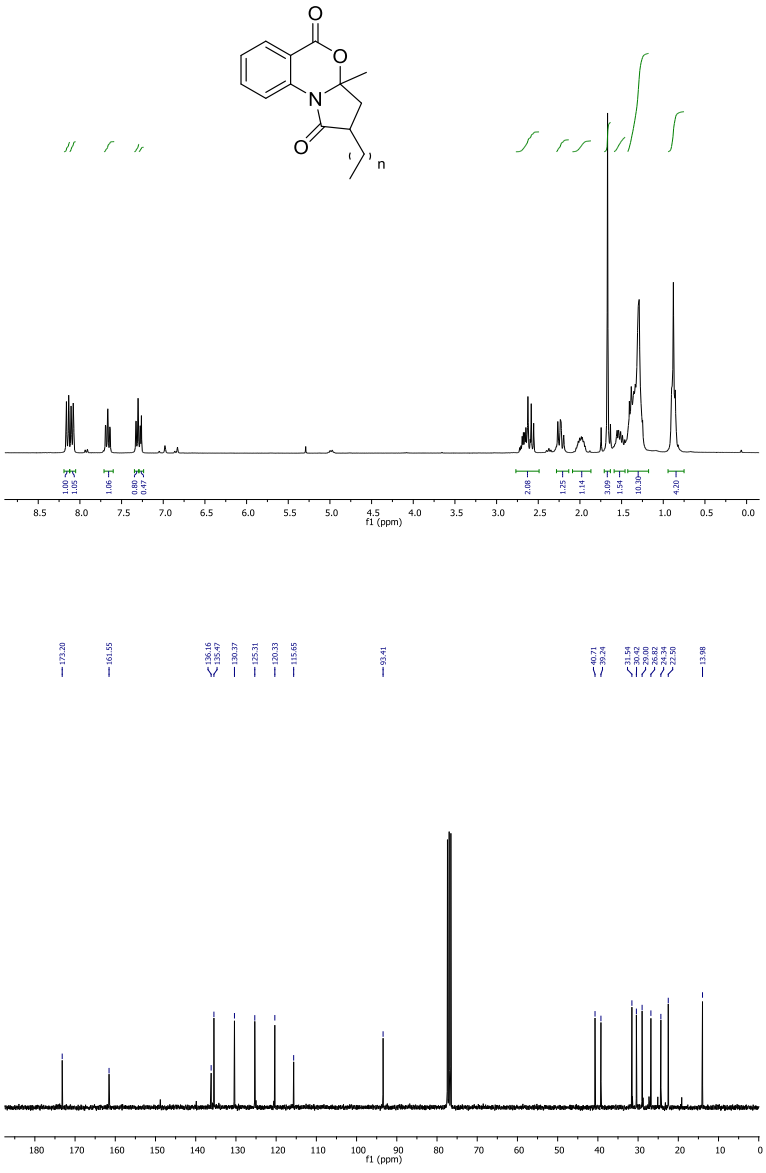




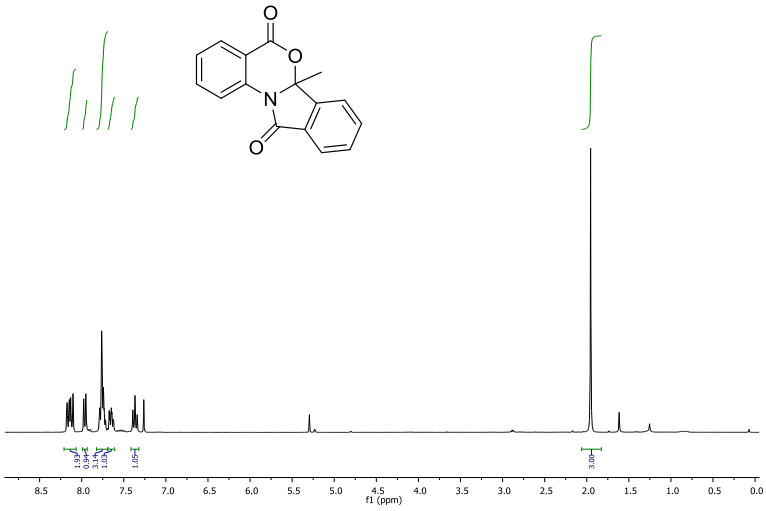
20a: 3a-methyl-3,3*a*-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione

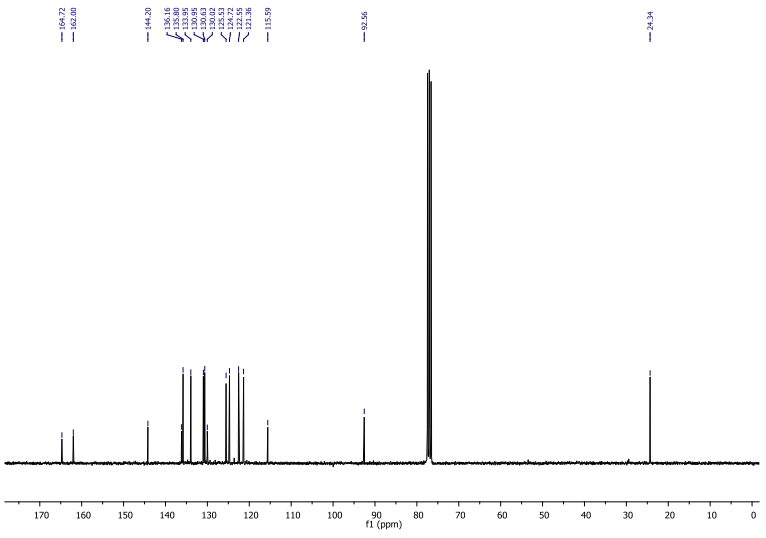


20b: 2-hexyl-3a-methyl-3,3a-dihydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione

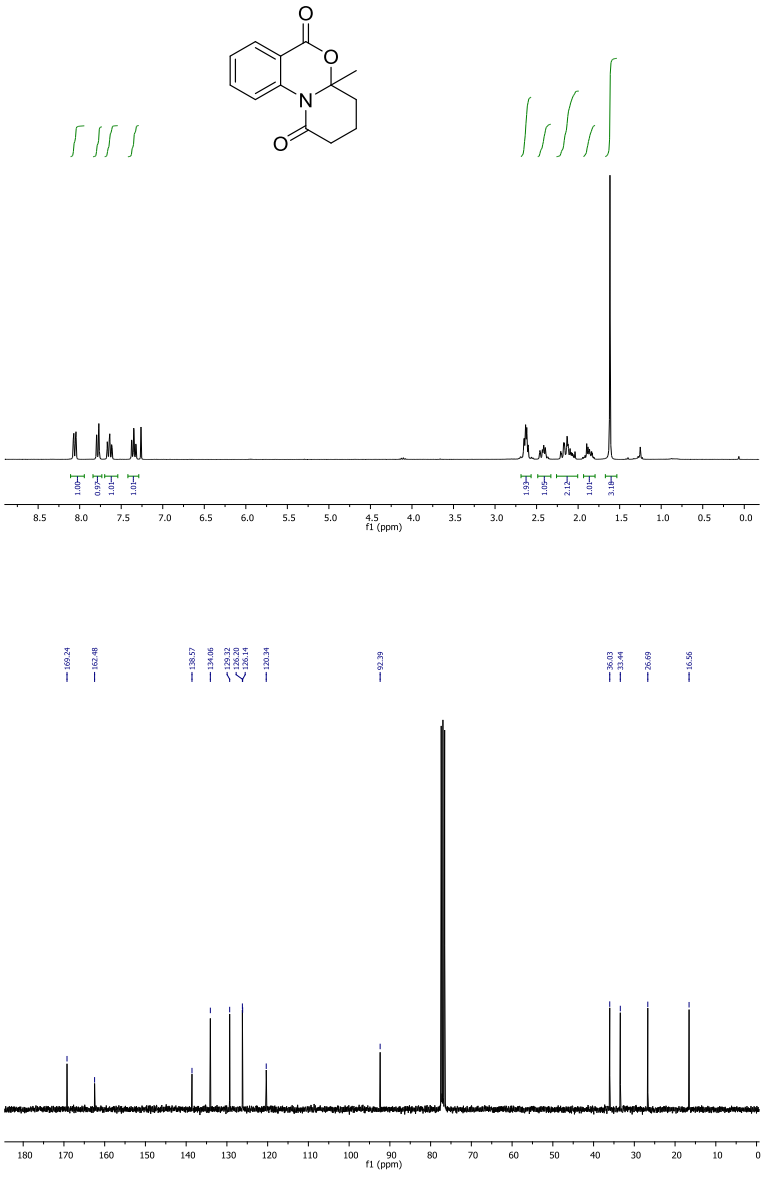


20c: 6a-methyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-dione

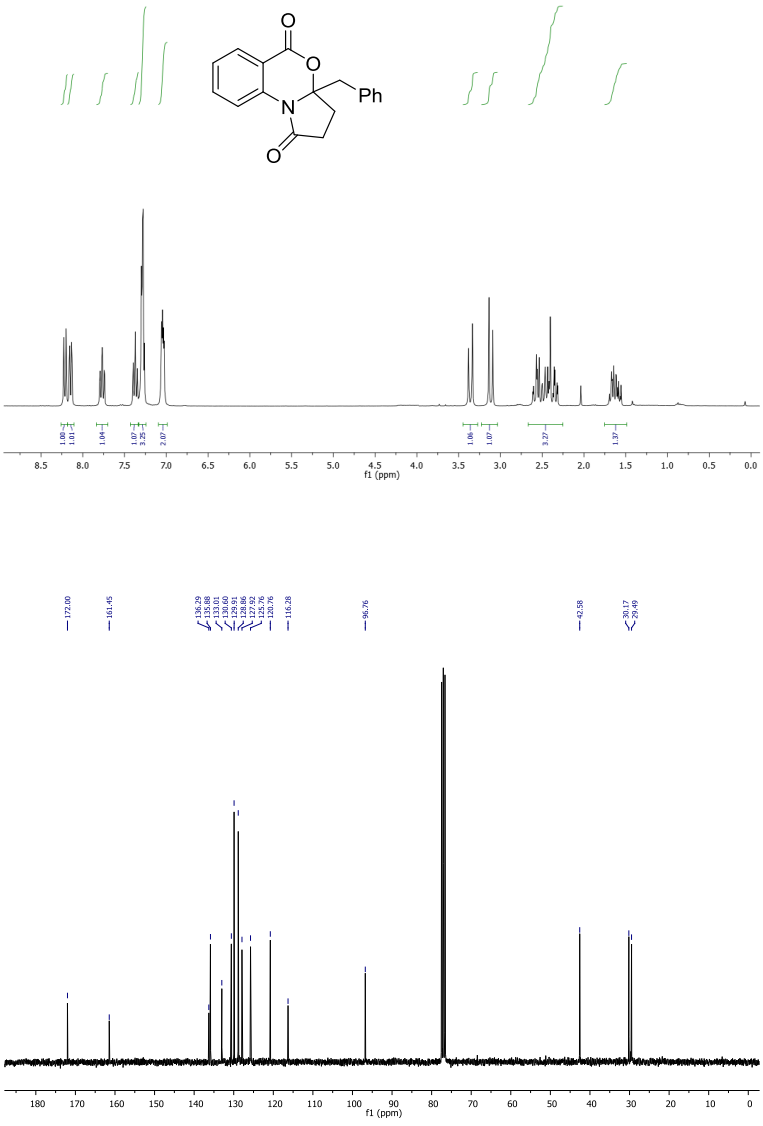




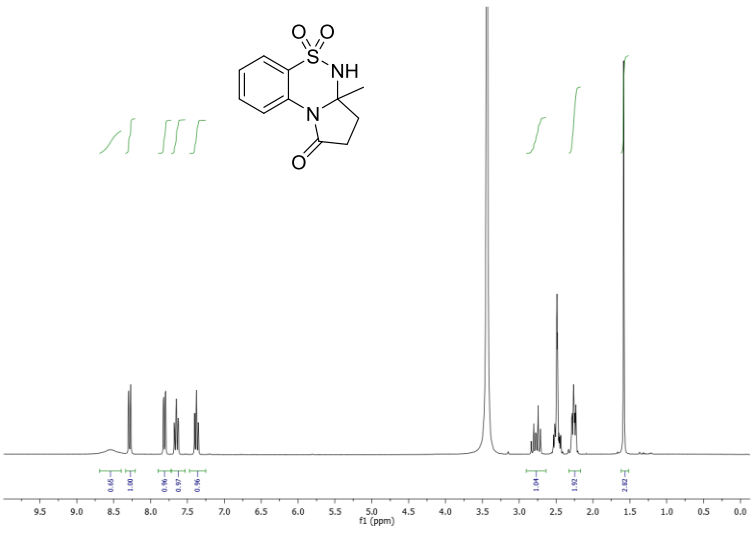
20d: 4a-methyl-2,3,4,4a-tetrahydro-1*H*,6*H*-benzo[d]pyrido[2,1-*b*][1,3]oxazine-1,6-dione

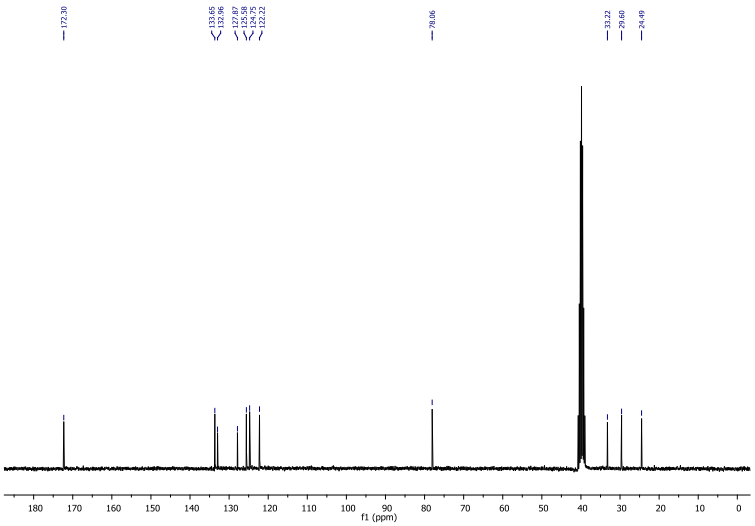


20e: 3a-benzyl-3,3a-dihydro-5*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine-1,5(2*H*)-dione

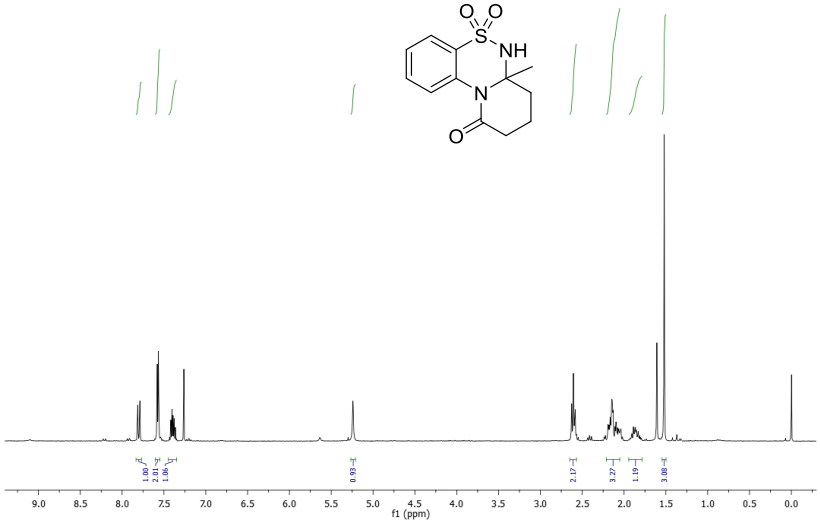


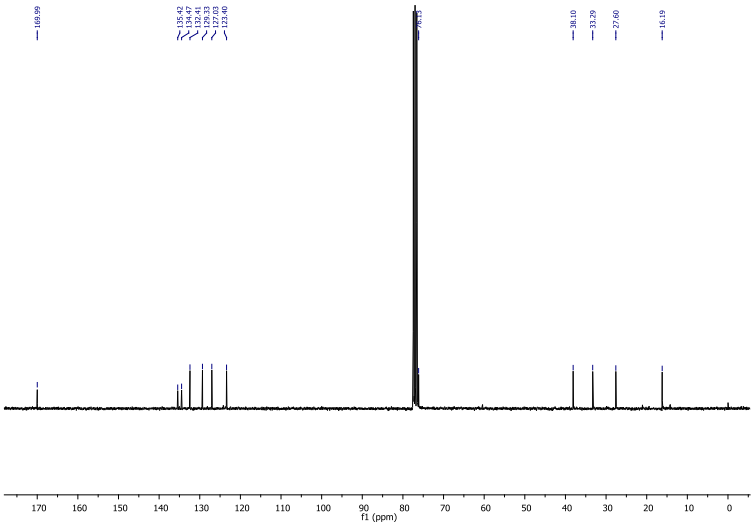
20f: 3a-methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*e*]pyrrolo[2,1-*c*][1,2,4]thiadiazin-1-one 5,5-dioxide



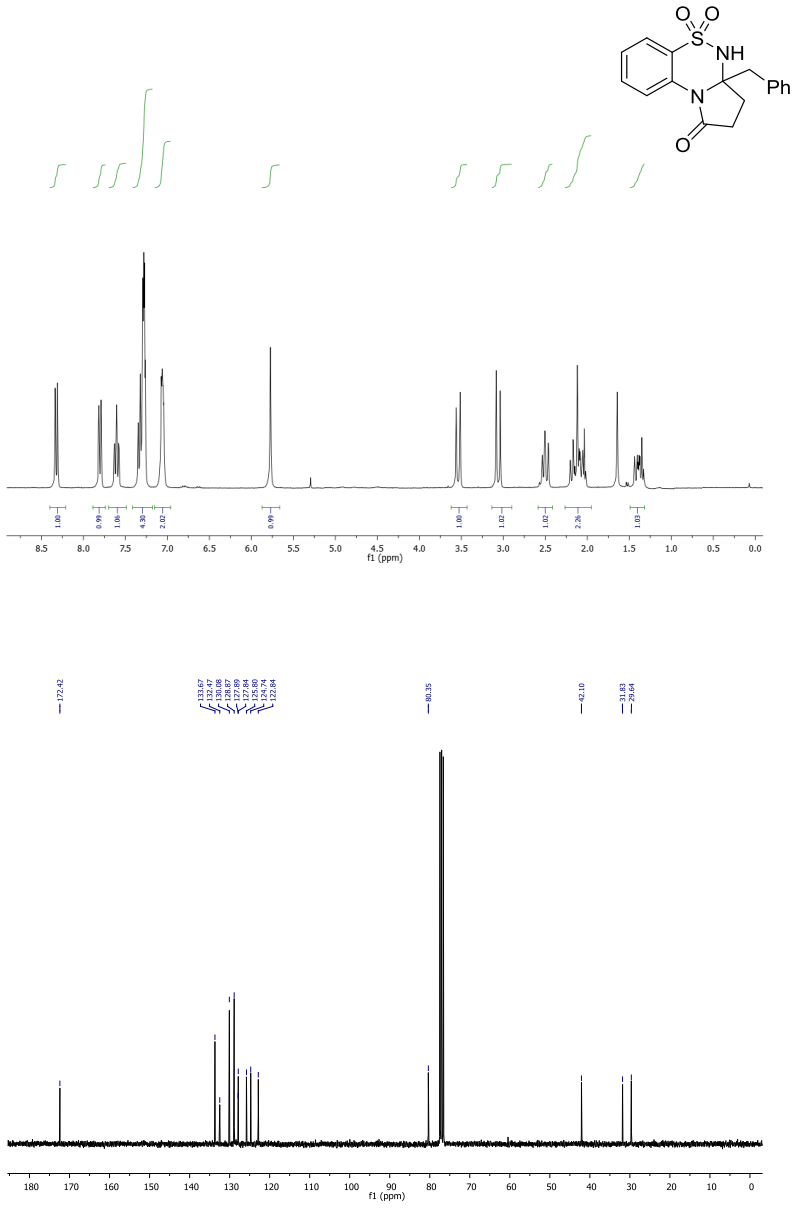


20g: 6a-methyl-6a,7,8,9-tetrahydrobenzo[*e*]pyrido[2,1-*c*][1,2,4]thiadiazin-10(6*H*)-one 5,5-dioxide

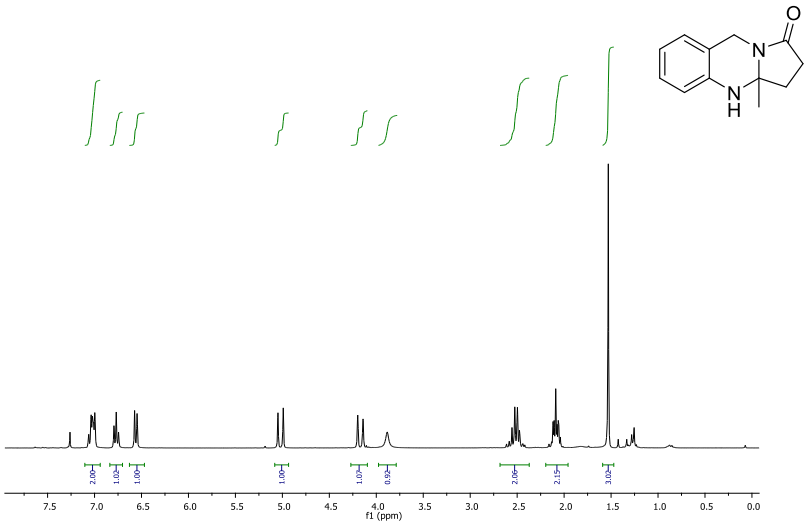


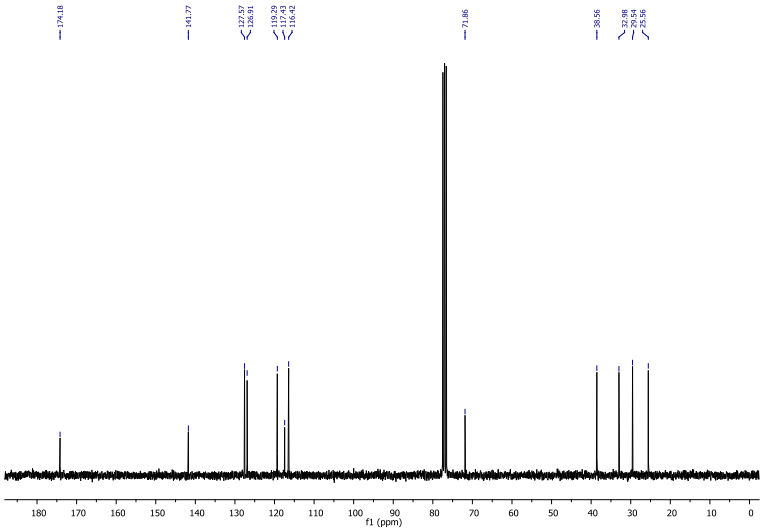


20h: 3a-benzyl-2,3,3a,4-tetrahydro-1*H*-benzo[*e*]pyrrolo[2,1-*c*][1,2,4]thiadiazin-1-one 5,5-dioxide

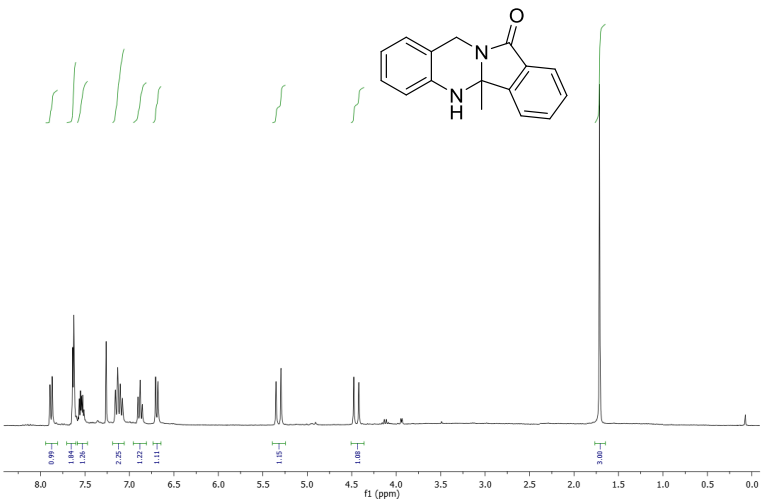


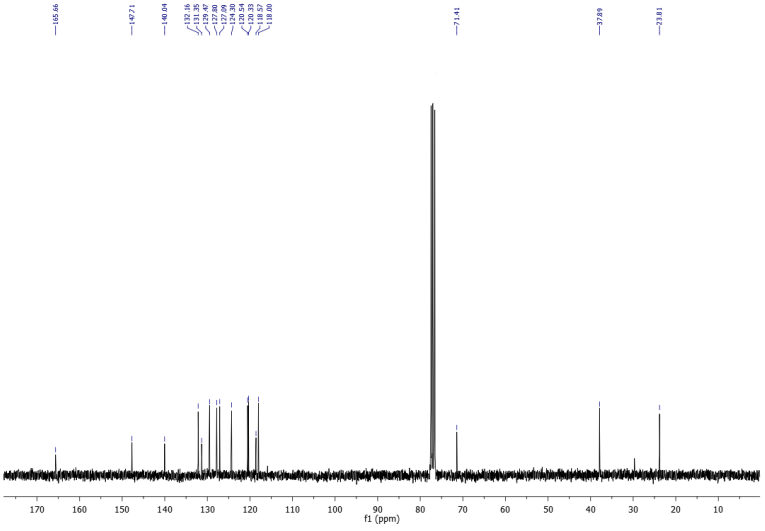
20i: 3a-methyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one



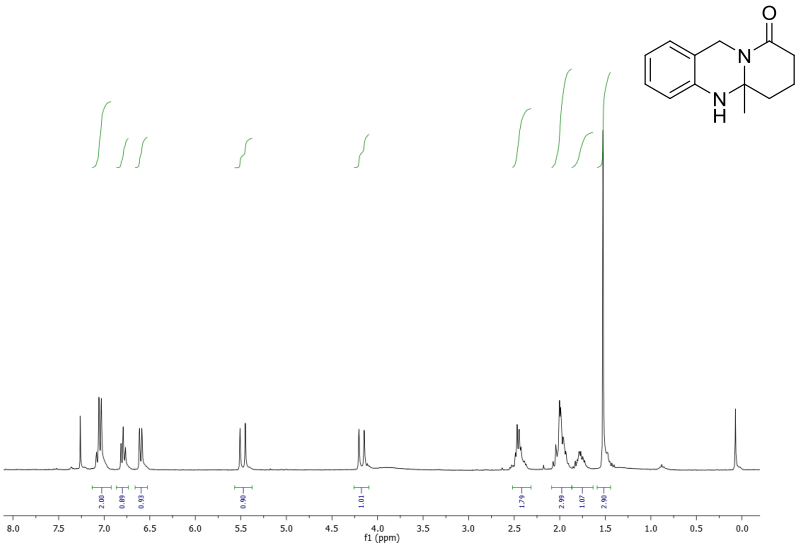


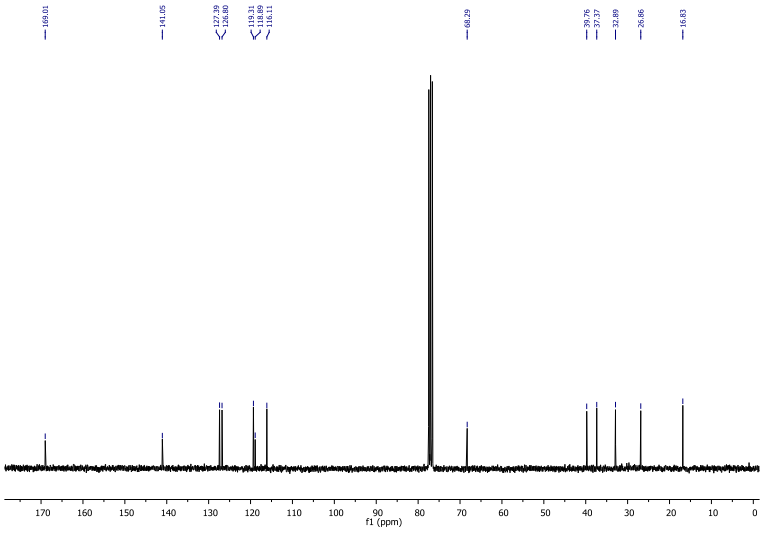
20j: 4b-methyl-5,10-dihydroisoindolo[1,2-*b*]quinazolin-12(4b*H*)-one



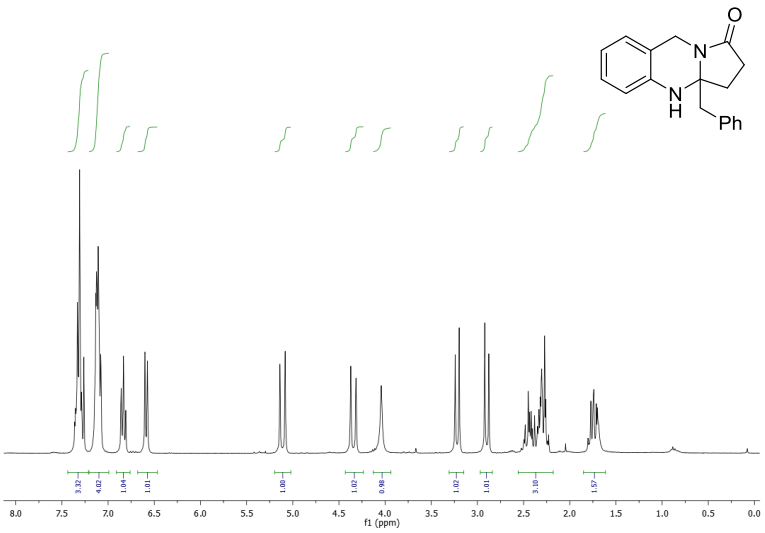


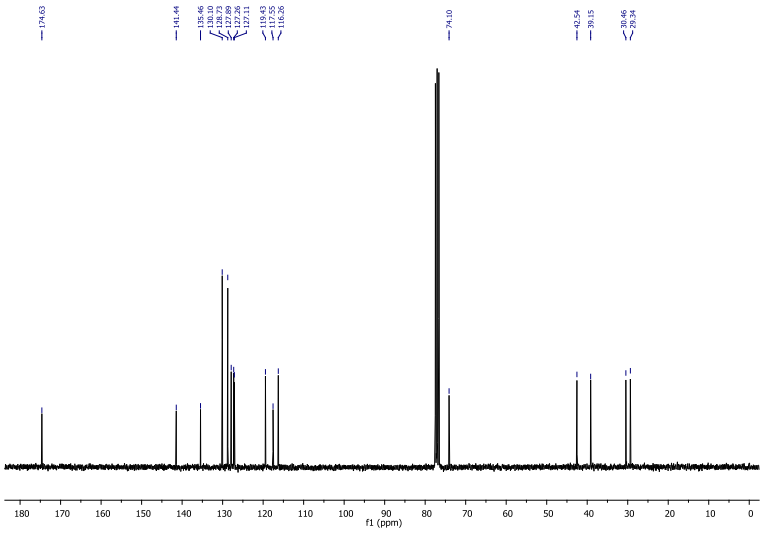
20k: 5a-methyl-5,5a,6,7,8,11-hexahydro-9*H*-pyrido[2,1-*b*]quinazolin-9-one



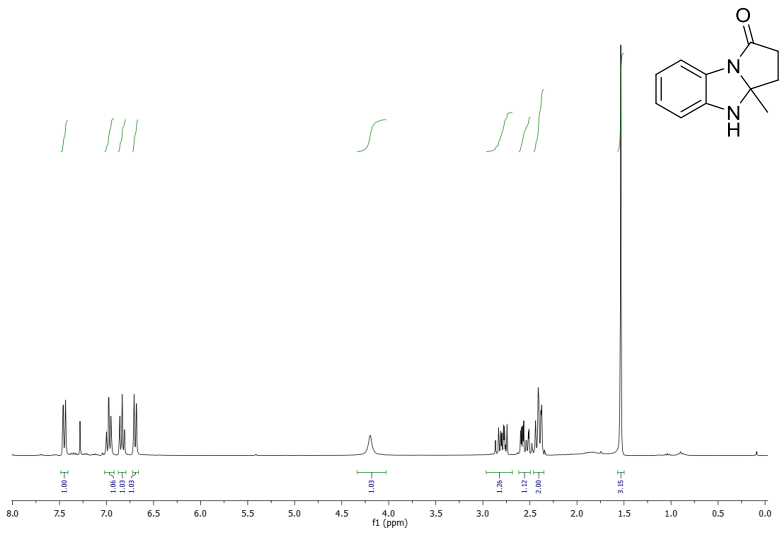


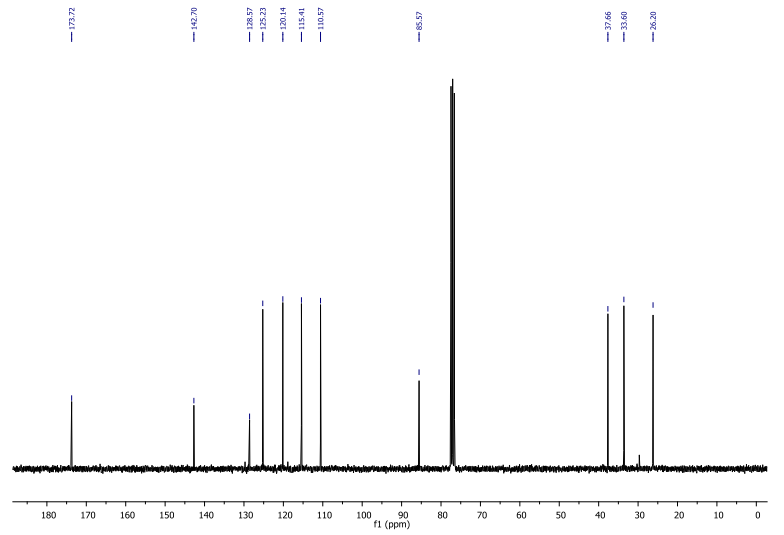
20l: 3a-benzyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one



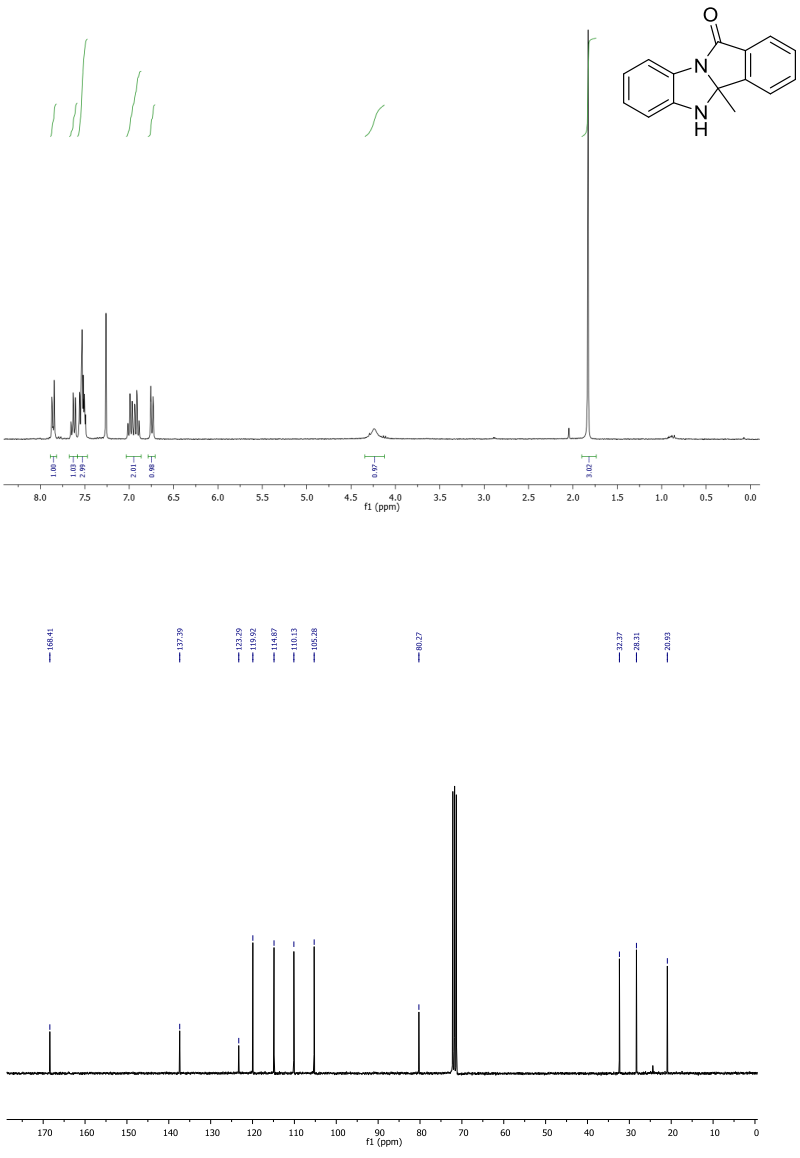


20m: 3a-methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one**3a-methyl-2,3,3a,4-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazol-1-one**

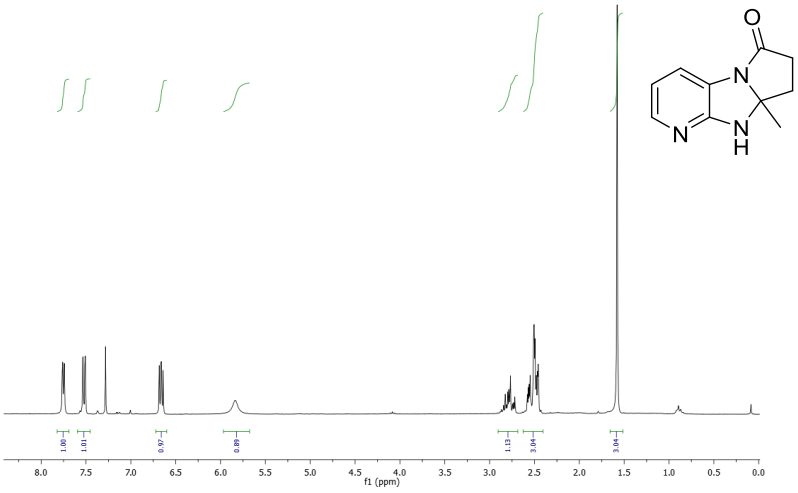


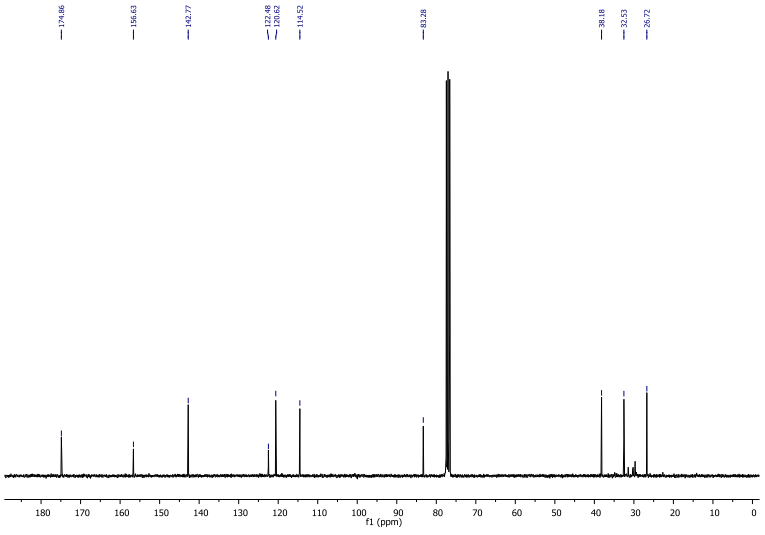


20n: 4b-methyl-4b,5-dihydro-11*H*-benzo[4,5]imidazo[2,1-*a*]isoindol-11-one

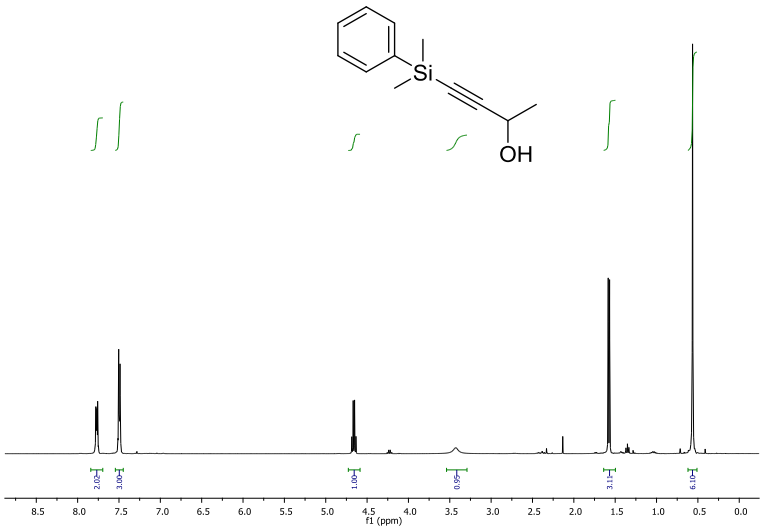


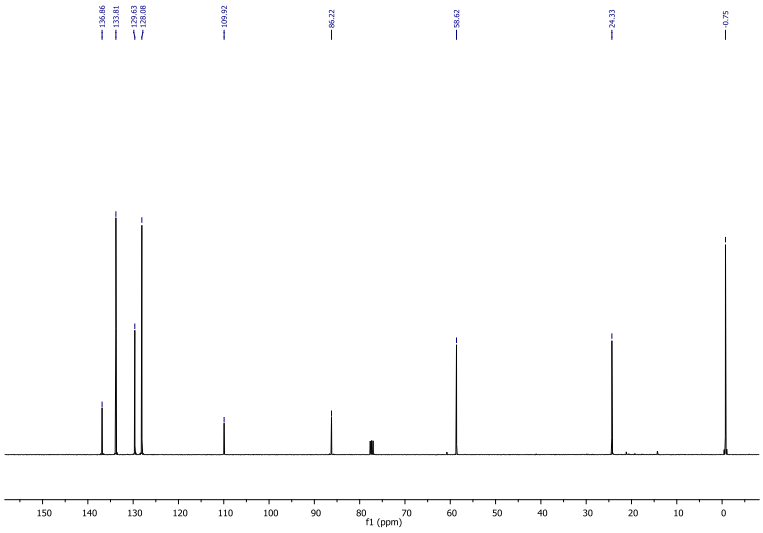
20o: 8a-methyl-7,8,8a,9-tetrahydro-6*H*-pyrrolo[1',2':1,2]imidazo[4,5-*b*]pyridin-6-one





37: 4-(dimethylphenylsilyl)-but-3-yn-2-ol





36: (*E*)-4-(dimethylphenylsilyl)-but-3-en-2-ol