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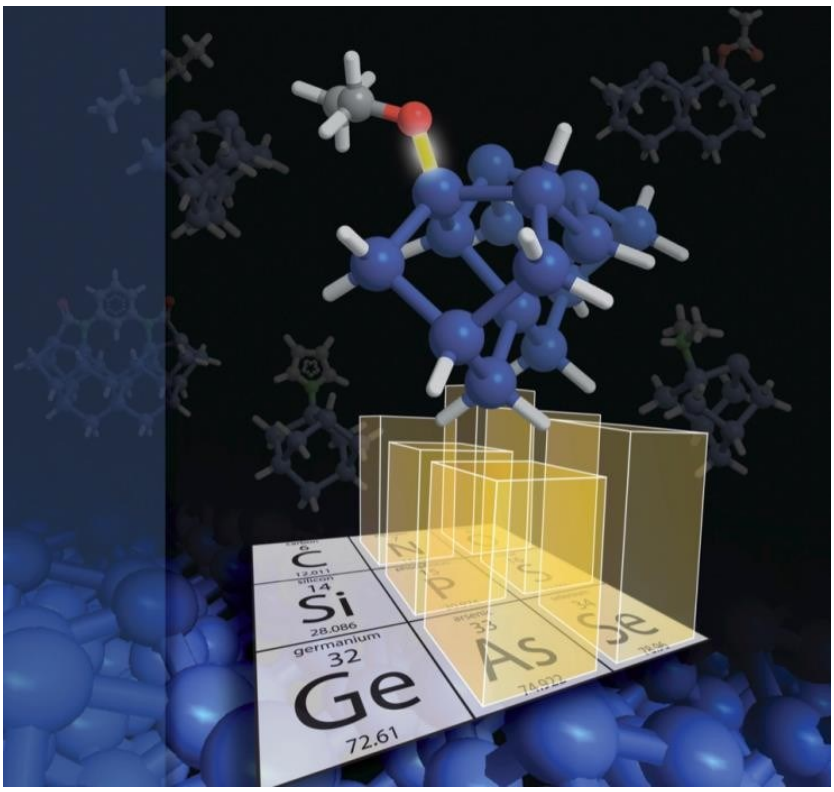
MÁSTER UNIVERSITARIO EN QUÍMICA ORGÁNICA

XIII Simposio del MQO
Facultad de Ciencias, UAM
17 y 18 de junio de 2021



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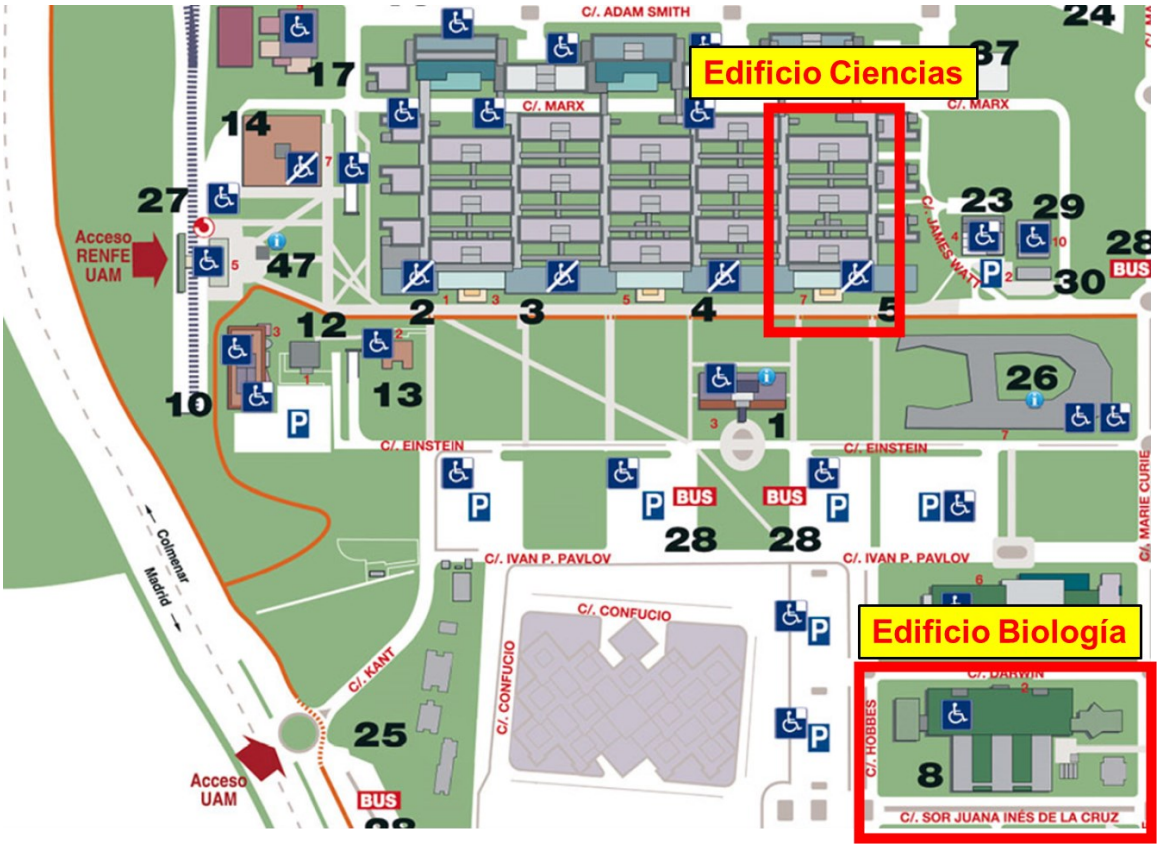
El XIII Simposio del Máster en Química Orgánica se celebrará en la Facultad de Ciencias (Edificios de Ciencias y Biología) de la Universidad Autónoma de Madrid, Campus de Cantoblanco, 28049, Madrid.



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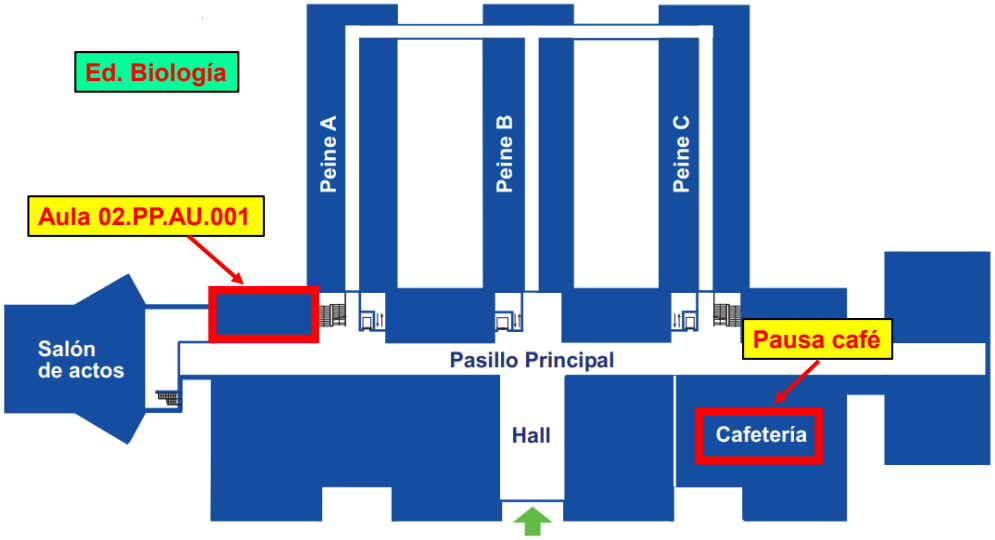
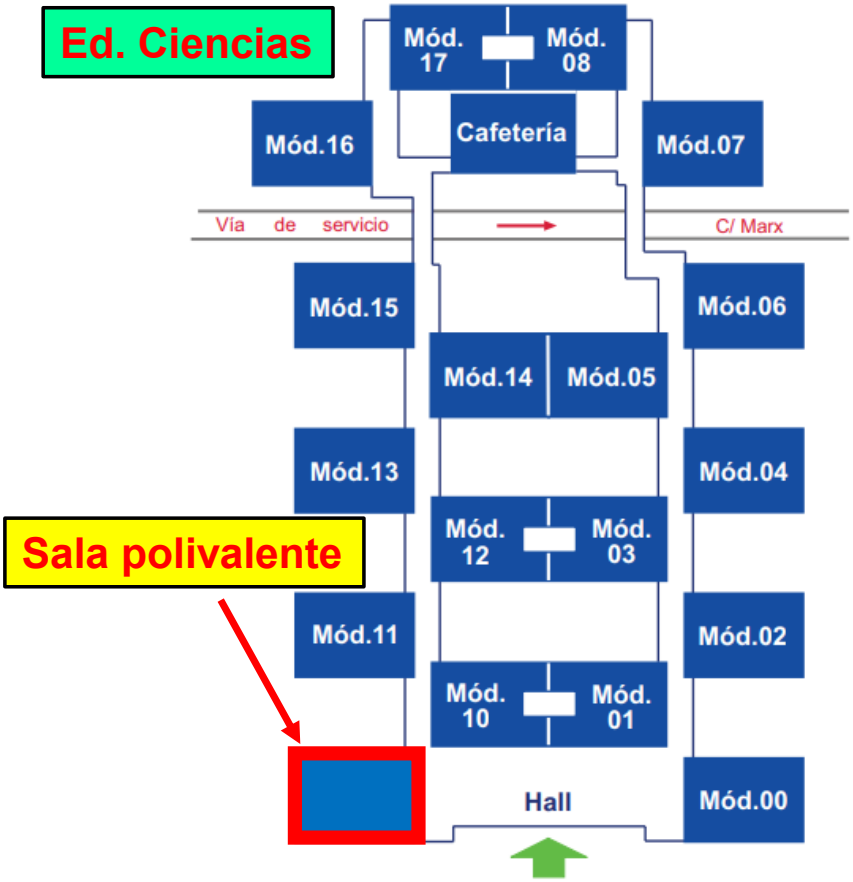
Las conferencias se impartirán en el **AULA 02.PP.AU.001** del **Edificio de Biología**.



Las sesiones de pósteres se realizarán en la **Sala Polivalente** de la **Facultad de Ciencias**.



PROGRAMA

Jueves 17 de junio

9:30-9:45 Apertura (*Aula 02.PP.AU.001, Ed. Biología*)

9:45-11:00 Sesión de Pósteres I (*Sala Polivalente de Ciencias, Ed. Ciencias*)

11:00-11:30 Pausa café (*Cafetería, Ed. Biología*)

11:30-12:30 Conferencia Dr. Daniel López Serrano (CNB) (*Aula 02.PP.AU.001, Ed. Biología*)

12:30-13:45 Sesión de Pósteres II (*Sala Polivalente de Ciencias, Ed. Ciencias*) / Mesa redonda con el conferenciante (*Aula 02.PP.AU.001, Ed. Biología*)

Viernes 18 de junio

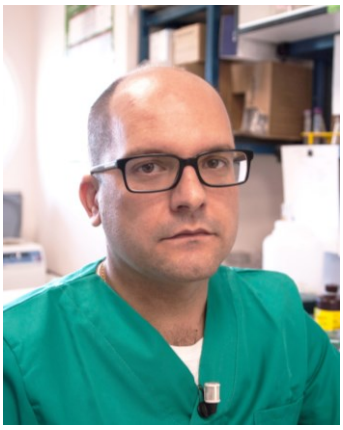
9:30-10:45 Sesión de Pósteres III (*Sala Polivalente de Ciencias, Ed. Ciencias*)

10:45-12:00 Pausa café (*Cafetería, Ed. Biología*)

12:00-13:00 Conferencia Dr. Javier García Martinez (U. Alicante) (*Aula 02.PP.AU.001, Ed. Biología*)

13:00-13:30 Mesa redonda con el conferenciante (*Aula 02.PP.AU.001, Ed. Biología*)

13:30-14:30 Encuesta, premios y clausura (*Aula 02.PP.AU.001, Ed. Biología*)



Dr. Daniel López Serrano
Centro Nacional de Biotecnología (CSIC)
"Organización de las membranas bacterianas y sus posibilidades como diana para combatir infecciones resistentes"
Jueves, 17 de junio, 11:30h
Aula: 02.PP.AU.001 (Ed. Biología)*

Dr. Javier García Martinez
Universidad de Alicante
"Química más allá de la capa de valencia"
Viernes, 18 de junio, 12:00h
Aula: 02.PP.AU.001 (Ed. Biología)*

* Asistencia de forma presencial exclusivamente para los estudiantes UAM y UCM del Máster QO.

Las dos conferencias se retrasmitirán a través de la plataforma MS Teams para las demás personas que quieran asistir.

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Tiemblo Martín, Marta	UCM	P51
Valdivia Pinaque, José	USC	P73
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Villar Castro, Daniel	USC	P74

ABSTRACTS PÓSTERES

SYNTHESIS AND AUTOCATALYSIS OF HYBRID COMPOUNDS FROM AMINO ACIDS AND NITROGEN BASES

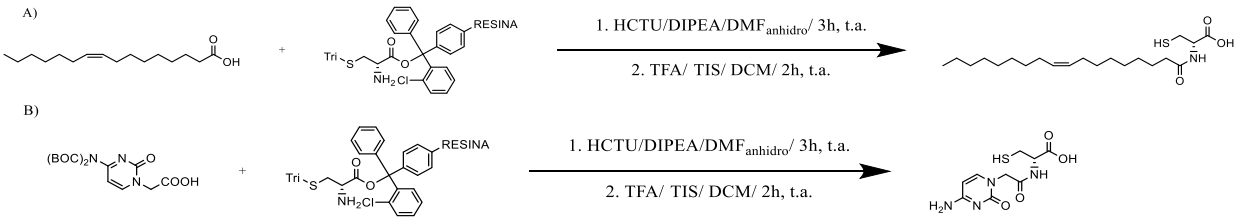
M. Aleksiev Pakovski[a], S. Vela-Gallego[a], A. de la Escosura[a]
Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid
e-mail: martin.aleksiev@estudiante.uam.es

***Keywords**:, Self-assembly, autocatalysis, System Chemistry*

Systems chemistry aims to understand the behavior of different biological systems through the study of simpler molecules. This area of chemistry is oriented towards the study of reactions outside thermodynamic equilibrium, and its main objective is to provide answers to questions such as how life could emerge from inert matter[1]. To this end, it focuses on studying molecular systems that are able to carry out self-assembly processes, which can produce emergent properties in the system[2], or autocatalytic properties in certain reactions, which is a fundamental concept for the origin of life[3].

The aim of this Master project is the synthesis and study of a dynamic library of compounds capable of carrying out autocatalysis-mediated replication. The achievement of these compounds is described in Scheme 1. It consists in a solid-phase synthesis, in which an amide bond is formed between the amino group of the amino acid L-Cysteine, which is bound on a solid support material, and a carboxylic acid group, previously activated with HCTU, which could come from Oleic acid (Compound 1O) or a carboxymethylated derivative of Cytosine (Compound 1C).

Once synthesized, the kinetics of formation of the corresponding disulfides is evaluated, in order to determine whether autocatalysis processes occur as a result of the self-assembly of supramolecular structures.



Scheme 1: A) Synthetic pathway for the preparation of compounds 1O. B) Synthetic pathway for the preparation of compounds 1C.

References:

[1] Morales-Reina, S.; Giri, C.; Leclercq, M.; Vela-Gallego, S.; de la Torre, I.; Caston, J.; Surin, M; de la Escosura, A.; Programmed Recognition between Complementary Dinucleolipids To Control the Self-Assembly of Lipidic Amphiphiles. *Chem. Eur. J.* **2020,** *26*,1082-1090.

[2] Ashkenasy, G.; Hermans, T.; Otto, S.; Taylor, A. Systems chemistry. *Chem. Soc. Rev*., **2017**,*46*,2543-2554.

[3] Ruiz-Mirazo, K.; Briones, C.; de la Escosura A. Prebiotic Systems Chemistry: New Perspectives for the Origins of Life. *Chem. Rev*. **2014**, *114*, 285-366.

Enantioselective synthesis of Ivabradine

C. Alonso, J. Teresa, A. Parra, M. Tortosa*

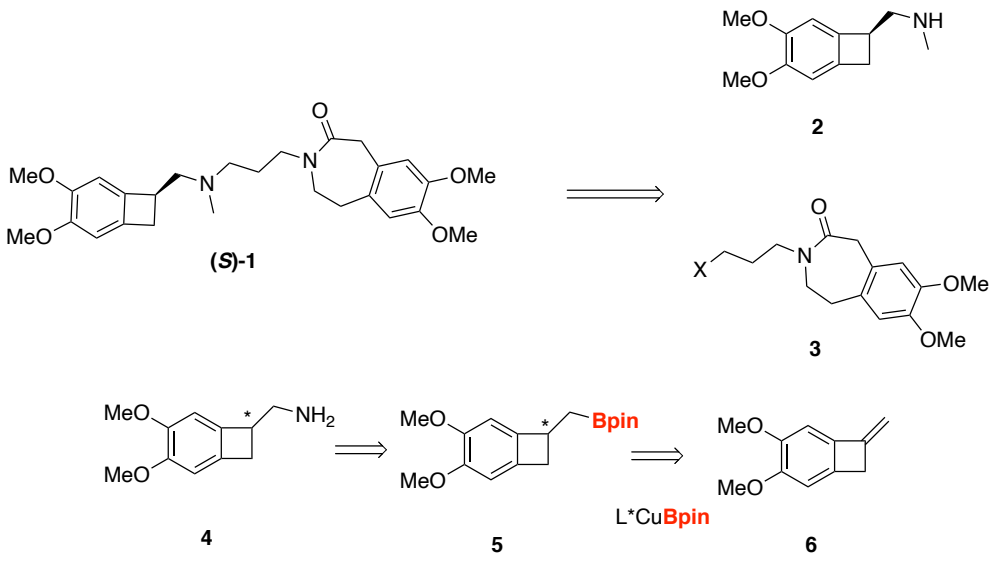
Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid

claudia.alonsol@estudiante.uam.es

***Keywords**: (ivabradine, enantioselective, borylation)*

Ivabradine is a commercialized drug used for the symptomatic relief of stable heart-related chest pain and heart failure. This molecule has one stereogenic center, and only the enantiomer **(*S*)-1** has biologic activity. The current route of synthesis involves a kinetic resolution as one of the steps to prepare the enantiomerically pure amine **2**, wasting half of the material to prepare this intermediate.[1] Therefore, the development of a more efficient and sustainable route is an attractive challenge.

This project seeks to design a novel enantioselective approach to prepare Ivabradine. The key step in this process is a copper-catalyzed enantioselective borylation reaction of an exo-cyclobutene to prepare boronic ester **5**.[2] We have validated the synthetic route using non-chiral ligands, showing that the borylation step takes place in good yield and perfect regiocontrol. We have also demonstrated that it is possible to transform the boronic ester **5** into amine **4**, one of the key intermediates in the synthesis of Ivabradine.



Scheme 1

References:

[1] Pedragosa-Moreau, S.; Lefoulon, F. Process for the Enzymatic synthesis of (7*S*)- 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid and Application in the synthesis of Ivabradine and salts thereof. US 9 476 071, oct 25, 2016.

[2] Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed.* **2016**, *55,* 6969.

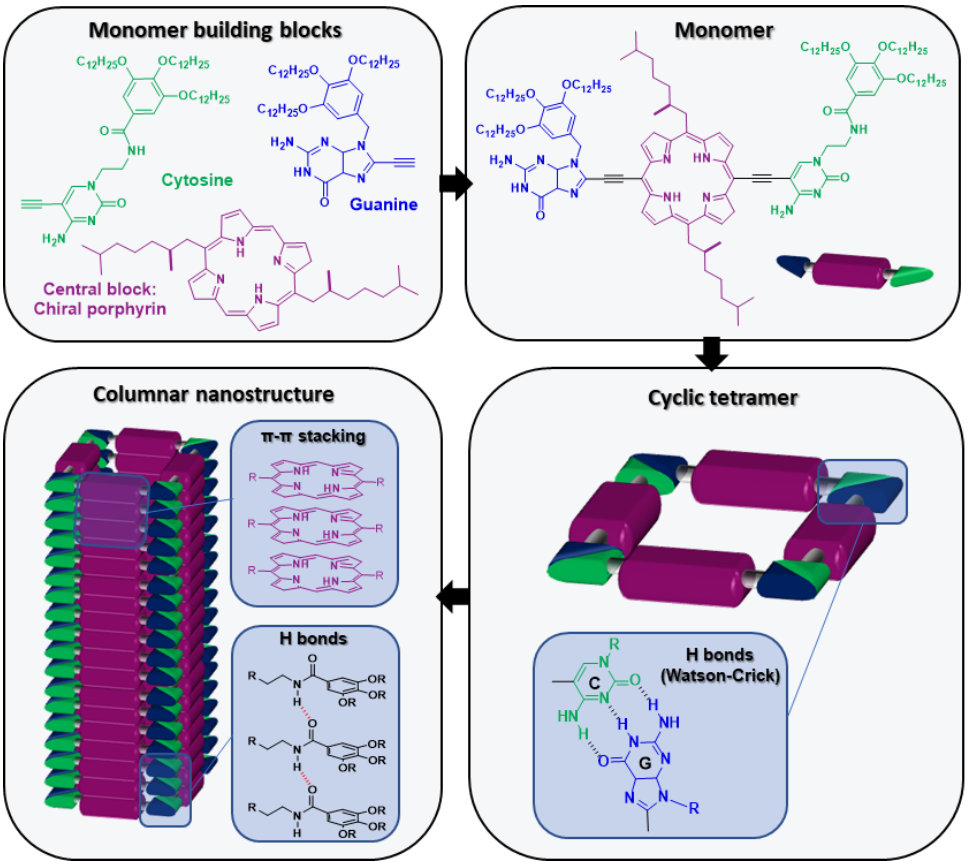
Self-organized π-conjugated systems for organic solar cells

G. Barquero Carmona, A. de Juan Garrudo, D. González Rodríguez

Departament of Organic Chemistry, Faculty of science, Universidad Autónoma de Madrid (UAM)
e-mail: gorkbark@gmail.com

***Keywords**: self-assembly, tetrameric macrocycles, columnar nanostructure.*

This project focuses on understanding the role of molecular organization in the efficiency of organic solar cells. The aim is to organize these molecules at the nanometric scale in an appropriate manner in order to optimize the parameters that have an effect on the photovoltaic efficiency. For this purpose, the synthesis of a monomer featuring a π-conjugated central porphyrin building block endowed with supramolecular information will be carried out. This monomer, synthesized through Shonogashira cross-coupling reactions with complementary guanine and cytosine nucleobases, will form tetrameric macrocycles [1] by self-assembly process due to the Watson-Crick hydrogen bonding. Upon cyclic tetramer formation, a columnar nanostructure [2] will be accomplished by combination of both π-π stacking between porphyrin units and secondary hydrogen bond interactions. These supramolecular processes will be studied by spectroscopic techniques (NMR, UV-vis, CD, fluorescence emission), and the final nanostructures will be analyzed by force and electron microscopy (AFM, TEM).



[1] Montoro-García, C.; Camacho-García, J.; López-Pérez, A. M.; Bilbao, N.; Romero-Pérez, S.; Mayoral, M. J.; González-Rodríguez, D. *Angew. Chem.* **2015**, *127*, 6884.
[2] Vázquez-González, V.; Mayoral, M. J.; Chamorro, R.; Hendrix, M. M. R. M.; Voets, I. K.; Gonzalez-Rodriguez, D. *J. Am. Chem. Soc.* **2019**, *41*, 16432.

Enantioselective Intramolecular Cycloaddition of Azomethine Ylides with Fluorinated Dipolarophiles

[b]Christian Cristóbal, [a,*]Carlos del Pozo, [a]Daniel Gaviña, [b,c,*] Javier Adrio

[a] Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain.
[b] Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049 Madrid, Spain
[c] Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain

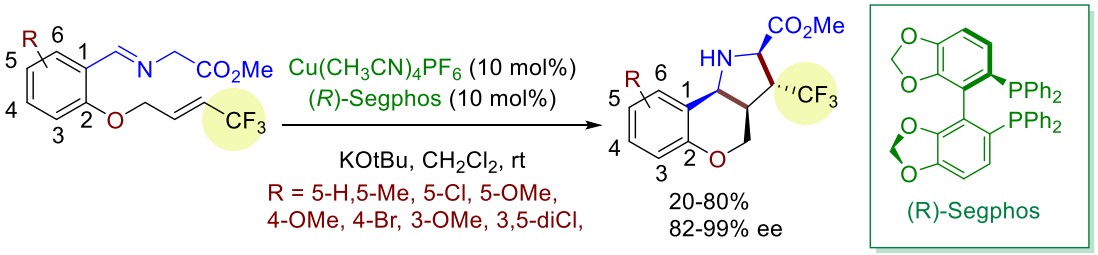
christian.cristobal@estudiante.uam.es

Keywords: *Enantioselective ● Cycloaddition ● Fluorinated*

The catalytic asymmetric 1,3-dipolar reaction of azomethine ylides with activated olefins is a powerful tool for the enantioselective preparation of pirrolidines[1]. This heterocycle has great importance in Organic and Medicinal Chemistry due to its presence in a wide variety of natural products and biologically active compounds.

The intramolecular version of this cycloadition provides a straightforward procedure for the preparation of azabiciclyc or azatriciclyc compounds. This reaction has been widely studied in its racemic version, however, there are only a few examples of catalytic asymetric cycloadditions, and are limited to the employment of strongly deactivated dipolarophiles, derived from α, β-unsaturated carboxilyc acids. [2]

Herein we report the first example of an enantioselective intramolecular azomethine ylide cycloaddition, using a trifluoromethylated dipolarophile. In the presence of Cu(I)/(R)-Segphos as the catalytic system, the process takes place with total conversion and excellent levels of diastereo- and enantioselectivity.



Scheme 1. General procedure for the preparation of the optically enantioenriched compounds.

References:

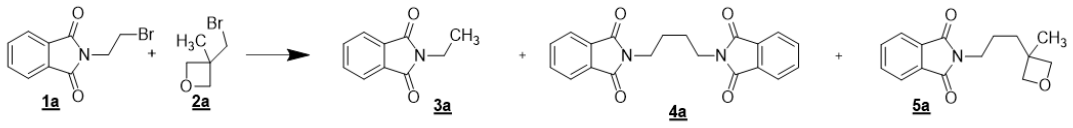
[1] For a recent review, see: Adrio, J.; Carretero, J. C. *Chem. Commun.* **2019**, *55*, 11979.
[2] (a) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431. (b) Li, N.; Song, J.; Tu, X.-F.; Liu, B.; Chen, X.-H.; Gong, L.-Z. *Org. Biomol. Chem.* **2010**, *8*, 2016. (c) Vidadala, S. R.; Golz, C.; Strohmann, C.; Daniliuc, G.-C.; Waldmann, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 651

Metallaphotoredox-Catalyzed cross-electrophile Csp^3-Csp^3 coupling: bridging the gap from batch reaction screening to flow.

Paula Cuerva Sotomayor, Pablo Garcia-Losada[1].

[1] *Eli Lilly and Company*: Centro de Investigación Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

Photochemical organic chemistry is at the center of the most current breakthroughs in synthetic chemistry. The huge interest and possibilities is due to its ability to perform and/or simplify challenging transformations that otherwise would be impossible or would take more steps. However one of the limitations is the inconsistencies observing while transferring the reaction conditions described in the literature and their application as efficient processes for drug discovery efforts. This is because there is still much to learn in the effects of increasing scales and light sources.
Aside from exploring how to circumvent these issues, currently the exploring of a transformation requires the screening of different wavelenghts, intensitiy and other reaction parameters to replicate previously described methods.



Scheme-1: Metallaphotoredox-Catalyzed cross-electrophile Csp^3-Csp^3 coupling

In this poster, in order to simplify this currently more-or-less manually process, we reported the use a flow chemistry reactor prototype that allows to use LED arrays of different wavelengths with intensity, to be used for parallel batch reaction optimization. The system has the potential to perform rapid screening and hits identification (see model reaction in Scheme-1), and quick transfer for scale up delivery just moving from the batch set up to a plug flow reactor setup.

The investigation demonstrates the reproducibility of this approach, which was extended to supply on demand different substrates for milligram scale preparation.

Marzo, L., Pagire, S. K., Reiser, O.* and Kçnig, B*. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem. Int.* **2018,** *57,* 10034 – 10072.

Smith R. T., Zhang X., Rincón, J.A., Agejas, J., Mateos, C., Barberis, M., García-Cerrada, S., de Frutos, O. and MacMillan, D. W. C. Metallaphotoredox-Catalyzed Cross-Electrophile Csp 3 −Csp 3 Coupling of Aliphatic Bromides. *J. Am. Chem. Soc.* **2018**, *140,* 17433−17438.

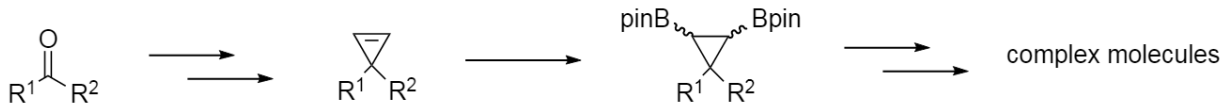
Synthesis and diboration of cyclopropenes

G. Delgado Caballero,[a] A. Viso,[a] M. Tortosa[b]

[a]*Instituto de Química Orgánica General IQOG–CSIC, Juan de la Cierva 3, 28006 Madrid, Spain.*
[b]*Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain.*
gonzalo.delgadoc@estudiante.uam.es

***Keywords**: Cyclopropenes, Cyclopropanes, Diboration.*

Cyclopropanes are 3-carbon rings frequently present in pharmaceuticals and other molecular structures biologically active.[1] In order to prepare functionalized cyclopropanes, cyclopropylboronates have gained increasing attention recently.[2] The broad range of transformations the C-B bond can perform into other functional groups with high stereoselectivity convert cyclopropylboronates into useful building blocks for the synthesis of larger and chiral functionalized cyclopropanes.[2] Starting from commercial available ketones, in this work we synthesized several cyclopropenes that after some optimization were submitted to transition-metal-free diboration reactions.[3] These resulting bis-borocyclopropanes open the door to the testing of chemo- and stereospecific transformations on the new two C-B bonds, which could make these compounds suitable building blocks for the development of more complex and biologically active molecules.[4]



References:

[1] (a) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J. A. *Chem. Soc. Rev*. **2012**, *41*, 4631-4642. (b) Dian, L.; Marek, I. *Chem. Rev.* **2018**, *118*, 8415–8434.

[2] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833–15836.

[3] (a) Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed*. **2011**, *50*, 7158-7161. (b) Das, K. K.; Paul, S.; Panda, S. *Org. Biomol. Chem.* **2020**, *18*, 8939-8974.

[4] Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494.

Synthesis and Antimalarial Activity of 2-carboxymethylpyrrole Derivatives

H. Fernández Piedra,[a] J. López de Echazarreta Leciñana,[a] M. Remuiñan,[b] and J. Adrio[a,c]

[a] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain,* [b] *GlaxoSmithKline, Tres Cantos, España,* [c] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid (Spain)*

helenafernandezpiedra@gmail.com

Keywords: *1,3-dipolar cycloaddition, pyrroles, Malaria*

Malaria is a life-threatening disease caused by parasites of the Plasmodium genus. Only in 2018, it was the cause of more than 400,000 deaths, being the African Region the hardest hit. To make the situation even worse, resistance is being generated to existing drugs. Consequently, there is an urgent need for the development of new effective drugs.

In this context, our research group has found a new drug candidate with antimalarial activity based on the structure of 2-carboxymethylpyrrole. The aim of this work is to prepare a broad spectrum of pirrole derivatives by 1,3-dipolar cycloaddition of azomethine ylides with sulfonyl dipolarophiles and subsequent aromatization.[1] The biological activity of these pyrroles against malaria will be evaluated in other to carry out a study of activity structure relationship.

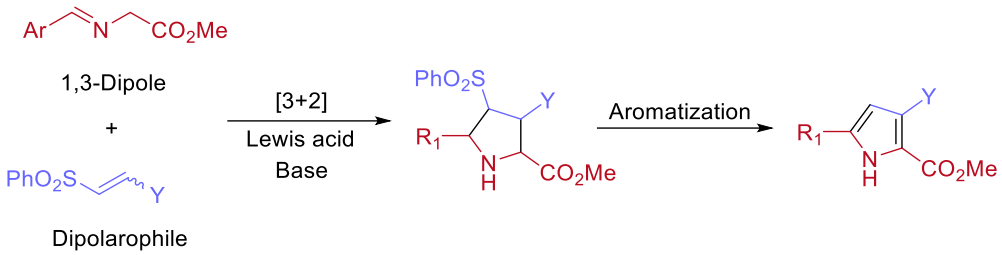


Figure 1. General procedure for the preparation of 2-carboxymethylpyrroles

References:

[1] Robles-Machín, R.; López-Pérez, A.; González-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 9864–9873.

Nitrone reduction and imine coupling using pyridine-boryl complexes. Preliminary heterogeneous approach.

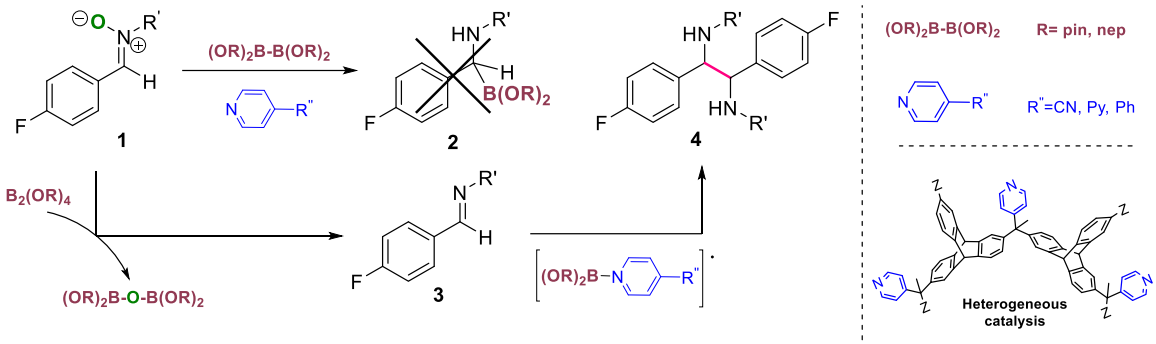
V. A. Francés Pérez,[a] E. L. Vargas,[a] M. Franco,[a] M. B. Cid[a]

[a]*Department of Organic Chemistry, Universidad Autónoma de Madrid Cantoblanco, 28049 Madrid, Spain.*
e-mail: victoria.frances@estudiante.uam.es

***Keywords**: (nitrones, imines, diamines)*

Nitrones are compounds with interesting biological activities and highly useful in organic synthesis. They allow a wide variety of transformations like cycloadditions and reactions with nucleophiles or radicals, which provide key intermediates in the preparation of biologically important nitrogen-containing compounds.[1]

Previous preliminary studies performed in our laboratory addressed to the borylation of nitrones using diboron sources in the presence of pyridine catalysts[2] revealed that instead of the desired borylated product **2**, the reaction evolved through deoxygenation of the nitrones to form the corresponding imine **3** and diamines **4** (Scheme 1).[3]



Scheme 1. Syntheses of diamines using diboron compounds and pyridine catalyst.

This work has been focussed on the optimization of these reactions, exploring different boron sources, pyridine derivatives and reaction conditions to provide selective and useful processes. Using NMR techniques and control experiments, we have partially unravelled the mechanism of both transformations. In order to make the method more sustainable, we are performing some preliminary attempts using a heterogeneous pyridine-based catalyst (see above).[4]

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Pd-Catalysed ε-C(sp^2)–H intramolecular alkenylation of peptides

Enrique Gallent,[a] Nuria Rodríguez,[a,b] Ramón Gómez Arrayás [a,b]

[a] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid (UAM), Cantoblanco, 28049 Madrid, Spain*

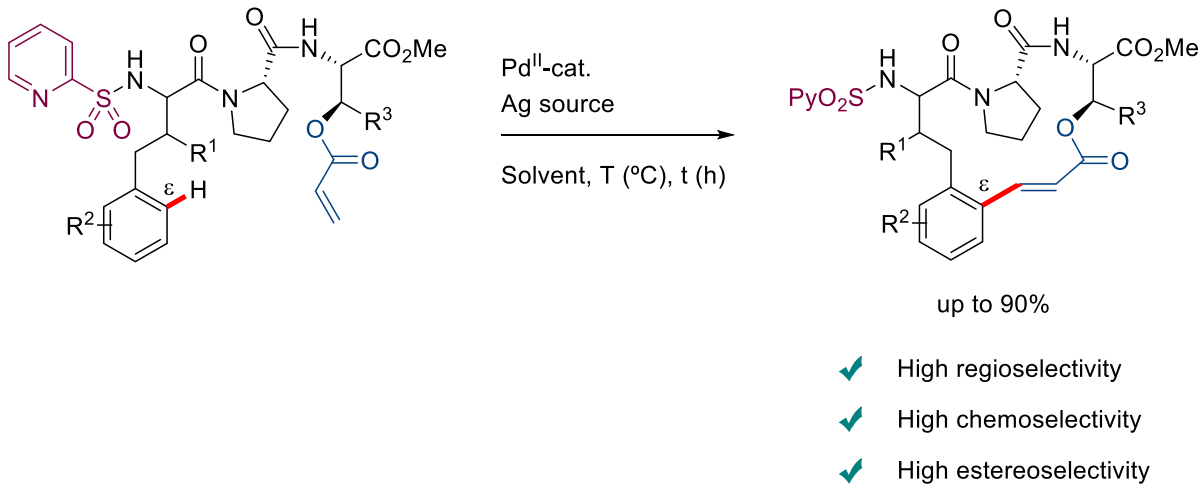
[b] *Institute for Advanced Research in Chemical Sciences (IAdChem), UAM, Cantoblanco, 28049 Madrid, Spain*

e-mail: enrique.gallent@estudiante.uam.es

Keywords: *C–H activation, macrocyclization, palladium catalysis*

Peptides and peptidomimetics are important pharmaceutically active molecules in drug discovery due to their high target specificity and low toxicity.[1] Within the great existing variety, cyclic peptides stand out, since their well-defined conformation gives them a series of drug-like properties: enhanced cell permeability, thermostability and resistance to proteolytic degradation.[2,3] Conventionally, the synthesis of these cyclic peptides has been achieved with methods that require the presence of a specific functional group, such as lactamization, ring-closing metathesis, cycloaddition azide/alkyne and internal disulfide formation.[4] As an attractive alternative, C–H functionalization permits the synthesis of macrocyclic peptides with a wide structural and positional diversity.[5]

Herein, we present a protocol to achieve the cyclization of linear peptides through the *N*–SO_2Py-assisted Pd-catalyzed C(sp^2)–H intramolecular alkenylation at the remote ε-position of γ-aryl peptides at the *N*-terminus position. This process occurs through a Fujiwara-Moritani type-coupling reaction with excellent yields and complete control of the chemo-, regio- and diastereoselectivity. The macrocycle that forms contains in its structure an endocyclic double bond with *E*-stereochemistry.



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Pd-Catalyzed γ-C(sp^3)–H/N–H electrophilic amination of amino acid derivatives

Andrea García [a], Nuria Rodríguez [a,b], Inés Alonso [a,b]

[a] *Dpto. de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid (UAM), Cantoblanco, 28049 Madrid, Spain.*

[b] *Institute for Advanced Research in Chemical Sciences (IAdChem), UAM, Spain.*

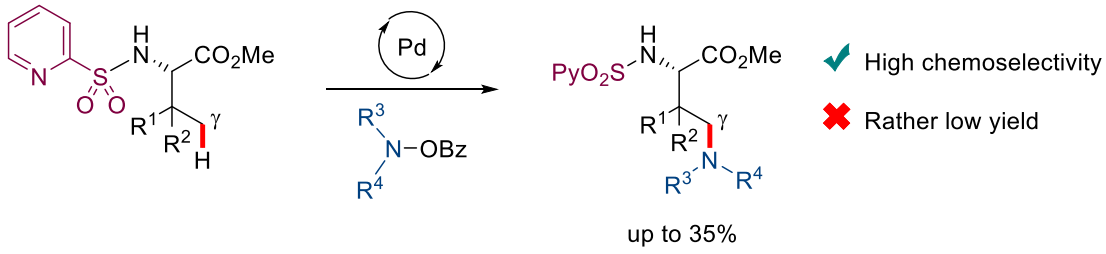
e-mail: andrea.garciafernandez@estudiante.uam.es

Keywords: *C–H activation, electrophilic amination, α-amino acids*

Methods for the synthesis and transformation of α-amino acids (α-AAs) have enormous potential for advances in drug discovery, agro chemistry and pharmaceutical industries. Complementary to conventional strategies, the emerging repertoire of C−H activation methodologies has undoubtedly unlocked attractive synthetic routes.[1]

Within this line, our research group has demonstrated the potential of the *N*-(2-pyridyl)sulfonyl (*N*-SO_2Py) auxiliary group to mediate the functionalization of distal C−H bonds at the side chains of α-AAs, broadening the synthetic utility of Pd-catalyzed directed C−H functionalization reactions.[2] Herein, we present the initial results obtained in the development of a methodology for the Pd-catalyzed γ-C(sp^3)–H/N–H electrophilic amination of AAs derivatives. Electrophilic aminations involve an umpolung of a nitrogen atom.[3] In this work, we have employed *O*-benzoylhydroxylamine derivatives as reagents for the nitrogen umpolung because their properties can be easily tuned through structural modification. However, their use implies to find the conditions for controlling the chemoselectivity of the process favoring the amination product over the C–O bond formation.

Preliminary experimental and theoretical studies have confirmed the viability of the desired C–N bond formation with high selectivity albeit with rather low yield. The low conversion is due to the inhibition of the catalytic activity of the palladium by chelation of the amination product. Diverse strategies are being evaluated to circumvent this issue.



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Nickel-catalyzed reductive cross-electrophile coupling of benzyl sulfonium salts with alkyl bromides

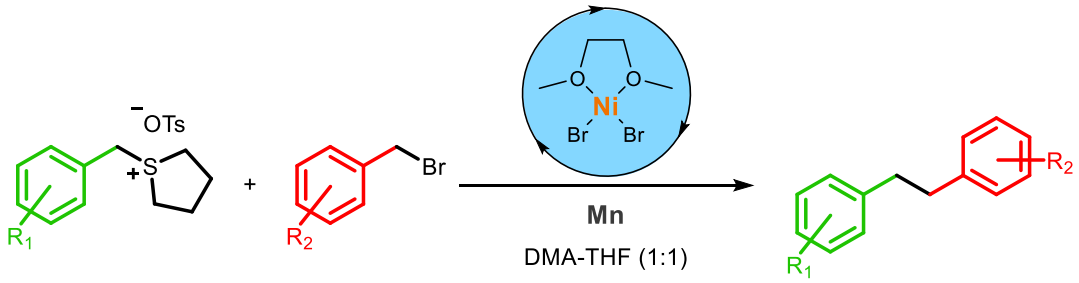
D. García Matesanz, R. del Rio Rodríguez,[a] J. A. Fernández,[a] A. Collado[b]

[a]Departamento de Química Orgánica y [b]Departamento de Química Inorgánica,
Universidad Autónoma de Madrid, 28049, Madrid (España)
e-mail: diego.garciamatesanz@estudiante.uam.es

Keywords: *reductive cross-coupling, nickel catalysis, sulfonium salt*

Nickel-catalyzed reductive cross-coupling (RCC) reactions have emerged in the last decades as powerful synthetic methods to couple two electrophiles.[1] This strategy appeared as an alternative to classical cross-coupling reactions, as the latter requires the synthesis of the carbon nucleophile component, which are rarely commercially available. Although the cross-coupling of two electrophiles arose as a rational solution, this technology also presents its own limitations and drawbacks specially related to selectivity issues that need to be overcome.[2] The reagents used for RCC are mainly limited to halogen for the coupling of C(sp^2)-C(sp^3) electrophiles as the different reactivity of the coupling partners allows selective cross-couplings, while C(sp^3)-C(sp^3) couplings have been less developed.[1 2]

Sulfonium salts have been used as good leaving groups in organic synthesis, due to its easy synthesis from organic halides.[3] Nevertheless, they have not been used in reductive cross electrophile coupling reactions. Herein, we have explored the coupling of sulfonium salts with different benzyl bromides using nickel catalysis for the synthesis of interesting bibenzyl derivatives in a single step. Bibenzyl moieties are the central core of many natural products with pharmacological activities, like antitubulin or antioxidant.[4]



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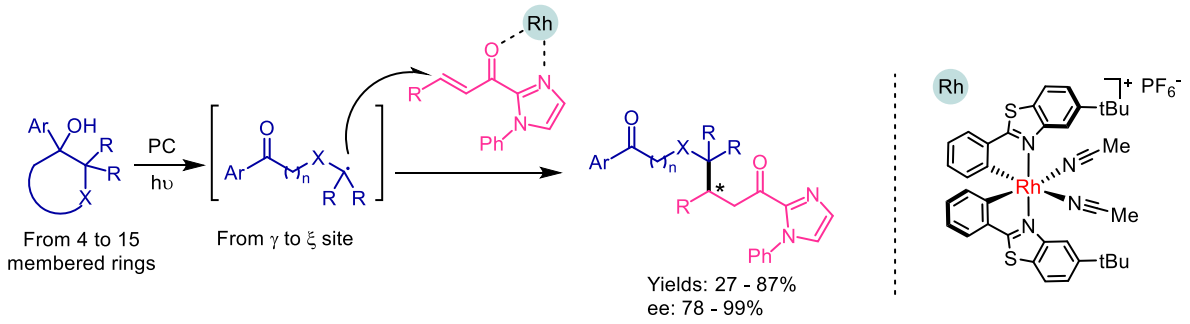
Enantioselective addition of remote alkyl radicals, generated *via* photocatalytic oxidation and C-C bond cleavage of cycloalkanols, to electron deficient alkenes

A. Heredero Sánchez,[a] N. Salaverri,[a] L. Marzo[a]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, Ciudad Universitaria de Cantoblanco, 28049-Madrid (España)*
e-mail: alejandro.herederos@estudiante.uam.es

***Keywords**: (radical addition, enantioselective, photocatalysis)*

Free radical addition to double bonds is a very powerful reaction that allows the formation of new carbon-carbon bonds. However, the development of new asymmetric catalytic transformations entails a challenge due to the high reactivity of the involved radicals, which leads to racemic background reactions. In this sense, Meggers developed the direct formation and addition of alkyl radicals to electron deficient double bonds in an enantioselective fashion with a chiral rhodium complex. [1] This method was then applied to distal radicals generated by a 1,5-hydrogen atom transfer process and their addition to electrophilic alkenes. [2] Nevertheless, this reaction is restricted to the formation of alkyl radicals in the δ-position due to the favored six-membered transition state. The work herein presented shows the formation of alkyl radicals in remote positions of ketones through photocatalyzed oxidation of cyclic alcohols followed by C-C bond cleavage, [3] and its enantioselective addition to electron deficient alkenes. This method allows the asymmetric functionalization of aryl ketones from the γ to the ξ position, depending only on the ring size of the starting alcohol. Moreover, this reaction shows a broad scope concerning both alcohols and electrophiles; among these, aromatic and aliphatic enones are included. Besides, a mechanistic hypothesis is proposed based on experimental measurements.



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Lithiation in flow chemistry

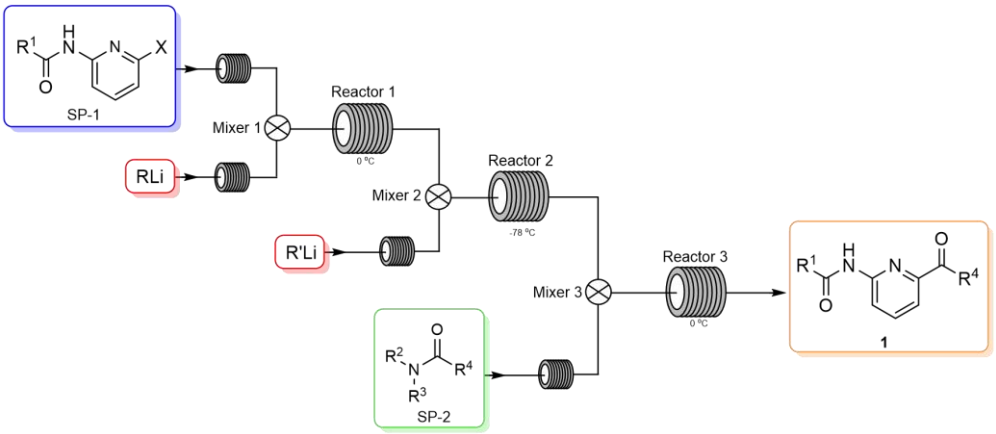
A. Herranz de la Cruz,[a]

[a]*Synthelia Organics*
e-mail: ana.herranzd@estudiante.uam.es

***Keywords**: flow chemistry, lithiation reaction, heterocycle.*

Flow chemistry[1] is an innovative technique that has been upgraded over the last decades. Recently, smaller versions have become available to organic synthesis. This technology presents numerous advantages such as controlled heat-transfer, controlled mixing, controlled used of toxic materials or increased capacity to run serial reactions, among others. Almost all these advantages are due to the small size of the reactors.[2] However, flow chemistry also presents some challenges like handling of solids or the integration of new features.[3,4] It is important to highlight that flow chemistry does not change the chemistry or the kinetics of a reaction. It is a tool to eliminate or reduce concentration gradients that may be detrimental to extremely fast reactions.[1]

The reaction studied in this project is shown in Scheme 1. This reaction presents two key factors, long reaction times and low temperatures. These long times are needed to afford the corresponding dianion while keeping control of the exothermicity of the reaction. The low temperatures not only are difficult to maintain due to the high exothermicity of the lithiation process but also are needed to control heat and mass transfer. The formed anion is a very reactive intermediate, hence absence of the corresponding electrophile (SP-2) leads to several side reactions or even the decomposition of the intermediate.



Scheme 1. Lithiation of the halo-compound SP-1 and addition on SP-2 to yield the final product **1**.

These challenges can be solved using flow chemistry because this technique increases heat and mass transfer in addition to the diminishing of the reaction times. This decrease of the reaction time results in a better control of the reactive intermediate, lowering the formation of by-products. In order to achieve these objectives, different reactors, flow rates, liquid pumps and temperatures were studied until the most suitable conditions were found.

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Exploring Self-Assembly Fatty Acylated Biomolecules

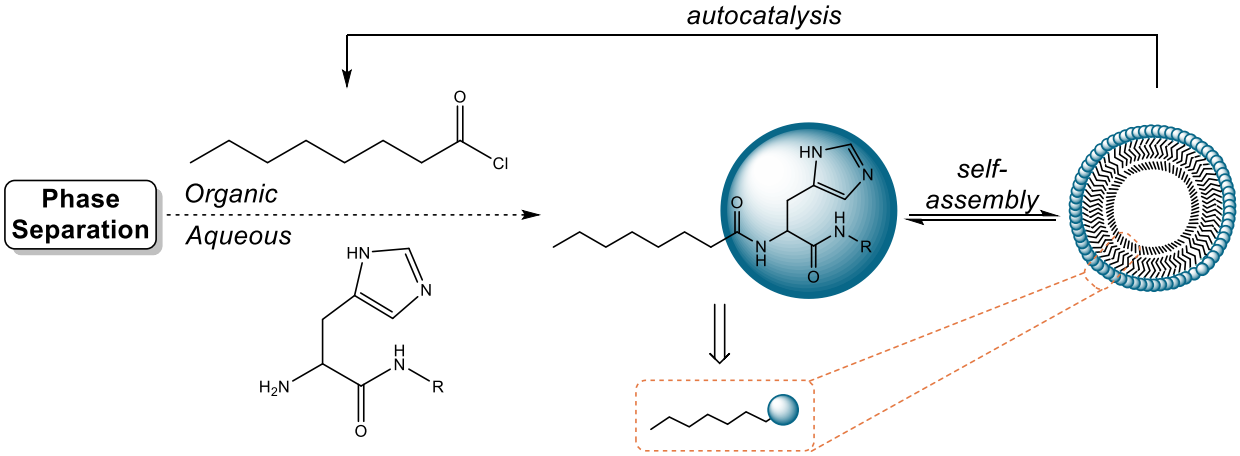
D. Khosraviani,[a] I. Colomer [a]

[a] *Department of Organic Chemistry. Universidad Autónoma de Madrid. Francisco Tomás y Valiente, 7, 28049, Madrid, Spain.*
e-mail: dario.khosraviani@estudiante.uam.es

***Keywords**: Self-assembly, Autocatalysis, Systems Chemistry*

There are many different hypotheses regarding how life might have originated, and what precursor of existing biomolecules played a key role in the evolution (RNA, peptides, amyloids). However, there must have been some symbiotic interactions between the different prebiotic molecules that led to emergent functional properties allowing to take the leap from chemical to biological systems.[1] Within these fundamental functions are: 1) the ability to separate themselves from the environment (compartmentalization), 2) the capability of creating copies of themselves (replication) and 3) the appearance of a basic metabolism.[2]

In this work we have followed an interesting approach that consists in studying self-replicating molecules that autocatalyze their formation while generating amphiphilic supramolecular structures, similar to those of protocell models, affording compartmentalization.[3] In particular, we have used simple biochemical monomers, such as dipeptides containing histidine and polar or apolar aminoacids (serine, cysteine, aspartic acid, valine or phenylalanine). Alternatively, in order to increase the complexity and explore extra non-covalent interactions, we have used peptide nucleic acids (PNAs) by coupling histidine with different nucleobases (cytosine and guanine). Under phase separation conditions, we have studied the autocatalytic fatty-acylation of these small biomolecules, where amphiphilic products are obtained. Kinetics experiments point towards an autocatalytic behavior via the formation of supramolecular compartmentalized structures across the interphase, that is modified, facilitating the reaction between phase-separated reactants.



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Synthetic Applications of Unsaturated Sulfoxides

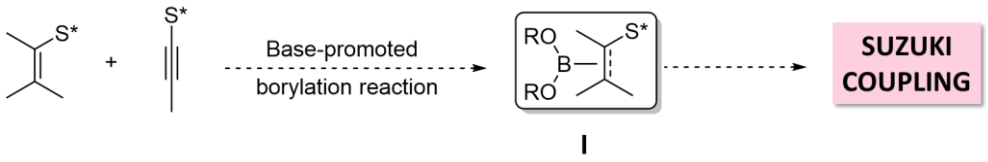
P. López Jiménez,[a] R. Fernández de la Pradilla, [b] A. Viso[b]

[a] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049-Madrid,*
[b]*Instituto de Química Orgánica General (IQOG), CSIC, Juan de la Cierva 3, 28006-Madrid*
paula.lopezj@estudiante.uam.es

***Keywords**: sulfinyl derivatives, Suzuki-Miyaura coupling, sigmatropic rearrangement.*

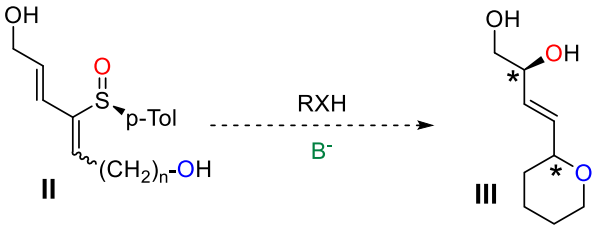
The search of new synthetic strategies and methodologies to obtain enantiopure compounds is one of the objectives in pharmaceutical industry. Compounds with chiral sulfur[1] functionalities such us, sulfoxides, sulfoximines, sulfinamides and other derivates play an important role in asymmetric synthesis as versatile auxiliaries, ligands and catalysts.

On the one hand, this project is aimed to look for new chiral sulfur derivatives type **I** by base-promoted boration reaction of unsaturated sulfoxides. This new boron derivatives could be used in asymmetric Suzuki-Miyaura[2] reactions as starting materials (Scheme 1).



Scheme 1 Base-promoted borylation reaction of chiral sulfur derivatives type **I**.

On the other hand, we are pursuing to extend a cascade process, previously studied in our laboratory, that involves a base triggered intramolecular nucleophilic addition of an alkoxide followed by [2,3]-sigmatropic rearrangement[3,4] (Scheme 2). Initially, we have carried out a 6 step-sequence for the synthesis of a 2-sulfinyl dien-diol derivate (**II**, n=4) that will eventually render to a tetrahydropyran derivative (**III**) with two new chiral centers in a 1,4 relative position. Currently, we have good results in a small-scale preliminary experiments although we still need to confirm the diastereoselectivity of the process, by means of the conversion to methoxy phenyl acetate derivatives.



Scheme 2 Tandem intramolecular addition/sigmatropic rearrangement onto 2-sulfinyl dienes.

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Synthesis and characterization of columnar supramolecular polymers based on hexa-substituted subphthalocyanine aromatics

E. López-Serrano,[a] J. Labella,[a] T. Torres,[abc]

[a]*Department of Organic Chemistry, Universidad Autónoma de Madrid, 28049 Madrid, Spain.*, [b]*Institute of Advanced Research in Chemical Sciences, Universidad Autónoma de Madrid. Campus de Cantoblanco, 28049, Madrid, Spain.*, [c]*IMDEA- Nanociencia, C/ Faraday 9, Campus de Cantoblanco, 28049, Madrid, Spain.*
e-mail: elisa.lopezs@estudiante.uam.es

Keywords: *Subphthalocyanines, liquid crystals, columnar aggregates.*

Subphthalocyanines (SubPcs) are aromatic macrocycles composed of three diiminoisoindole units assembled around a tetrahedral boron atom which, in turn, holds the so-called axial substituent.[1] As a result of this particular chemical structure, SubPcs exhibit a conical π surface which renders them with excellent properties for photovoltaic and optoelectronic applications, such as strong absorption and emission, rich redox behaviors or excellent charge transport capabilities. Importantly, they have an intrinsic dipole moment along the axial axis. This, together with a suitable peripheral functionalization, enables the formation of columnar-based molecular materials that nowadays have a great potential in variety of applications. [2-3]

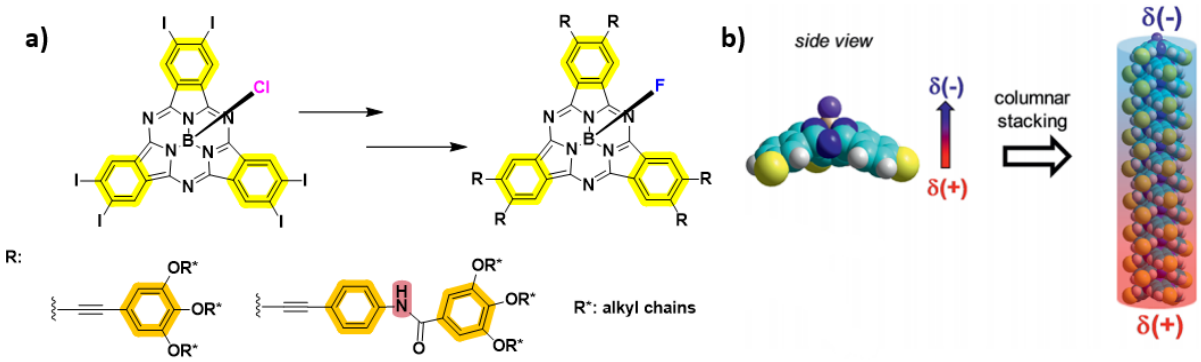

Figure 1. a) Chemical structure of the **R_6-SubPcs-F** and b) molecular model of SubPc-based columnar stacks.

Up to this work, these columnar stacks have been prepared using SubPcs with just three peripheral substituents. However, one could think that the use of hexa-substituted SubPcs could led to more stable aggregates since the number of intermolecular interactions is increased. Therefore, the present work is focused on the synthesis, characterization, and study of supramolecular aggregation of novel hexa-substituted SubPcs (Figure 1a) that are able to form columnar stacks both in solution and in the mesophase (Figure 1b). The general strategy to prepare these derivatives involves a Sonogashira reaction to couple different alkynes on the I_6-SubPc-Cl followed by the fluorination of the axial position.

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Ni-Catalyzed Borylative Cyclizations and Cycloisomerizations of Enallenes

I. Mac Lean Gariboldi,[a] J. C. Nieto Carmona,[a] A. M. Martín Castro[a]

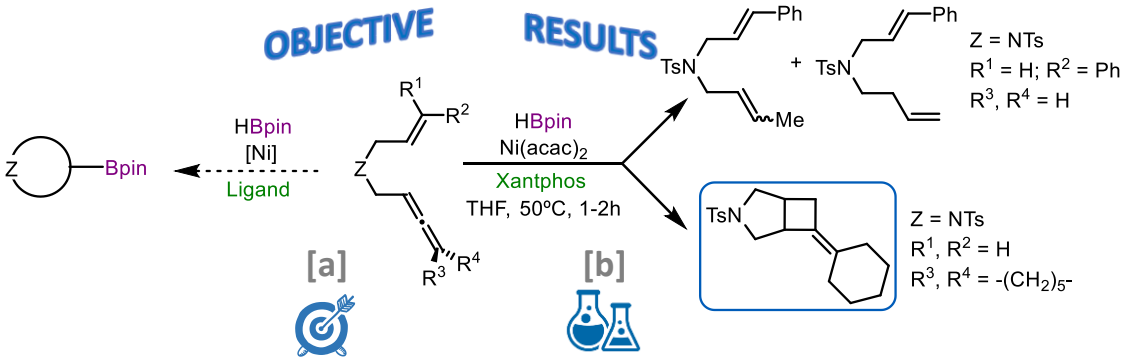
[a]*Departamento de Química Orgánica, Universidad Autónoma de Madrid (UAM), Cantoblanco, 28049-Madrid*
ian.maclean@estudiante.uam.es

***Keywords**: Ni-Catalyzed, Borylative Cyclizations, Cycloisomerizations*

Transition metal-catalyzed cyclization reactions of polyunsaturated species have special interest in Organic Chemistry because they allow to obtain more complex molecules in a single step. In particular, enallenes have a high versatility because of the presence of an allene moiety in their structure, which opens the door to different reactivities and products.

Additionally, borylative cyclizations allow to generate carbo- and heterocycles with C–B bonds. The boron derivates are easily transformed into a variety of functional groups and C–C bonds, being important substrates in Suzuki cross-coupling reactions and processes mediated by transition metal catalysts, which permit to obtain a wide range of compounds.[1] Furthermore, boron derivates exhibit low toxicity, which makes them very practical and easy to handle.

Our group is pioneering in the development of transition metal-catalyzed hydroborylative cyclizations.[2] Particularly, the group has developed the Ni-catalyzed hydroborylative cyclization with enynes[3] and, more recently, with allenynes (unpublished results). Based on previous works, this project looks for Ni-catalyzed hydroborylative cyclization of enallenes (Scheme 1 [a]).



Scheme 1: General reaction for Ni-catalized hydroborylative cyclizations of enallenes. [a] Objectives for the Master's project. [b] Achieved results

A methodological survey has revealed that the results are highly dependent on the substitution pattern of the starting enallenes (Scheme 1 [b]). As a result, starting form a substrate bearing a trisubstituted allene, we have reached a cycloisomerization product with high efficiency, through a catalytic cycle with an oxidative cycloisomerization and reductive elimination, where boron hydride used (HBpin) initiates the process with a Ni^{II}-Ni^{0} reduction.

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DESIGN AND SYNTHESIS OF SUBPORPHYRINOIDS FOR PHOTODYNAMIC THERAPY (PDT).

A. Malfaz Vázquez,[a] M.S. Rodríguez-Morgade[a,c] y T. Torres [a,b,c]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco 28049, Madrid (Spain).*
[b] IMDEA-Nanociencia, C/ Faraday 9, *Cantoblanco 28049, Madrid (Spain).*
[c] Institute for Advanced Research in Chemical Science (IAdChem), *Cantoblanco 28049, Madrid (Spain).*
e-mail: andreamalvaz@gmail.com

***Keywords**: photodynamic therapy, subphthalocyanine, subphenanthrenocyanine.*

Photodynamic therapy (PDT) combines light, molecular oxygen and a photosensitizer (PS) to produce reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$), which lead to the selective, non-invasive and localized destruction of tumor cells.[1,2] Porphyrins (Ps) and phthalocyanines (Pcs) constitute efficient singlet-oxygen photosensitizers. Subporphyrazines (SubPzs, Fig. 1) and subphthalocyanines (SubPcs, Fig. 1) belong to the family of tripyrrole subporphyrinoids, macrocycles characterized by a nonplanar, cone-shaped structure, with a 14 π-electron aromatic core.[3] Their smaller aromatic circuit related to that of Pcs (18 π-electrons) gives rise to blue shifted absorption bands, out of the phototherapeutic window (λ= 630-850 nm).

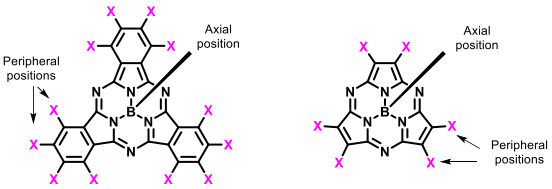


Figure 1. Structures of SubPc (left) and SubPz (right).

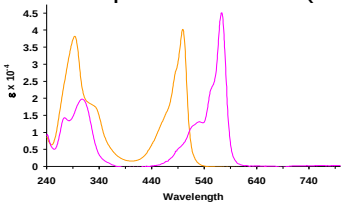
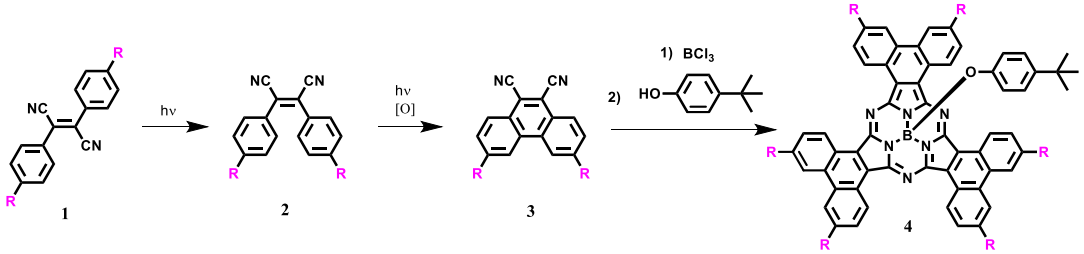


Figure 2.UV/Vis spectra of a SubPz (orange) and a SubPc (pink).

We have synthesized a new family of subporphyrinoids that we have called subphenanthrenocyanines (**4**, Sch. 1), through a boron-assisted cyclotrimerization reaction of the corresponding phenanthrene-9,10-dicarbonitriles (such as **3** in Sch. 1). The latter were prepared by photoisomerization reaction of diarylfumaronitriles (**1**, Sch. 1),[4] followed by electrocyclic ring closure and oxidation. The extension of the conjugation through six additional benzene rings related to the SubPc skeleton provides macrocycles with strong, red shifted absorptions, at the limit of the phototherapeutic window. We have donated the dyes with fluorinated groups at their periphery, in order to obtain redox-stable photosensitizers with high singlet oxygen quantum yields. The photochemical properties of the new dyes have been studied.



*Scheme 1. Synthesis of subphenantrenocyanines (**4**).*

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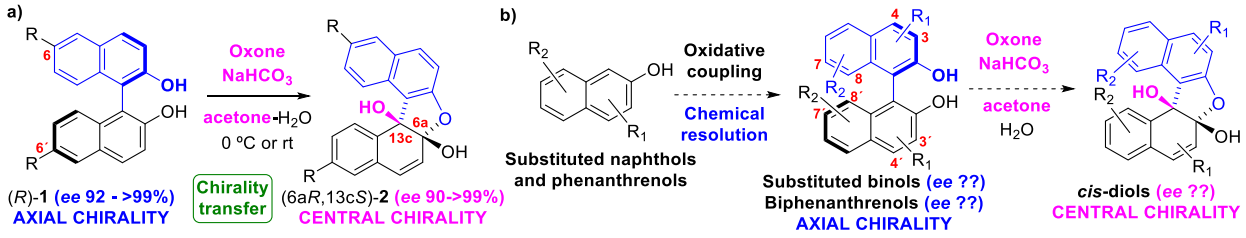
Study of the chirality transfer from the oxidative dearomatization of enantiopure substituted binols and phenanthrenols with the system Oxone/$NaHCO_3$/acetone

María Martín Martín,[a] Sara Vallejo Lázaro,[a] Antonio Urbano*[a,b]

[a]*Departamento de Química Orgánica, Universidad Autónoma de Madrid (UAM), Cantoblanco, 28049-Madrid.*
[b]*Institute for Advanced Research in Chemical Sciences (IAdChem), UAM.*
e-mail: maria.martinm01@estudiante.uam.es

***Keywords**: Oxidative dearomatization · Oxone · Axial-to-central chirality transfer*

In recent years, our research group have studied the oxidative dearomatization of differently substituted *para*-alkyl phenols with the system Oxone/$NaHCO_3$/CH_3CN, as the source of singlet oxygen ($^1O_2$),[1] giving the corresponding *para*-peroxyquinols or *para*-quinols, after a subsequent reduction step.[2] More recently, we have developed a quite general highly site-selective oxidative dearomatization of substituted phenols and naphthols into the corresponding *ortho*-quinols or epoxy-*ortho*-quinols using, as the final oxidant, dimethyldioxirane (DMDO)[3] generated *in situ* with the system Oxone/$NaHCO_3$/acetone.[4] Furthermore, when this oxidative dearomatization was performed with commercially available axially chiral unsubstituted binol (*R*)-**1** (>99% *ee*), the pentacyclic hemiacetalic *cis*-diol (6a*R*, 13c*S*)-**2** (R = H, 98% *ee*), bearing two new stereogenic centers, was obtained, suggesting an efficient axial-to-central chirality transfer (***Scheme 1a***).[5] Later, we expanded the scope of this process to differently 6,6'-disubstituted (*R*)-binols (*ee* 92 – >99%), easily obtained from unsubstituted (*R*)-binol, giving rise to differently substituted pentacyclic *cis*-diols **2** with *ee* ranging from 90 to >99%.[5]



Scheme 1

The aim of this project is to study the oxidative dearomatization process of enantiopure binols and biphenanthrenols substituted at other positions of the aromatic rings (***Scheme 1b***). Firstly, we have synthesized the starting materials from the corresponding naphthols and phenanthrenols after two processes comprising oxidative coupling followed by chemical resolution of the racemic derivatives and have evaluated their optical purities using chiral HPLC. Next, we have performed the oxidative dearomatization of such enantiopure derivatives with the system Oxone/$NaHCO_3$/acetone to evaluate the enantiomeric purities of the resulting *cis*-diols and to establish the efficiency of the axial-to-central chirality transfer process.

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Development of novel methods for the selective cleavage of C-N bonds

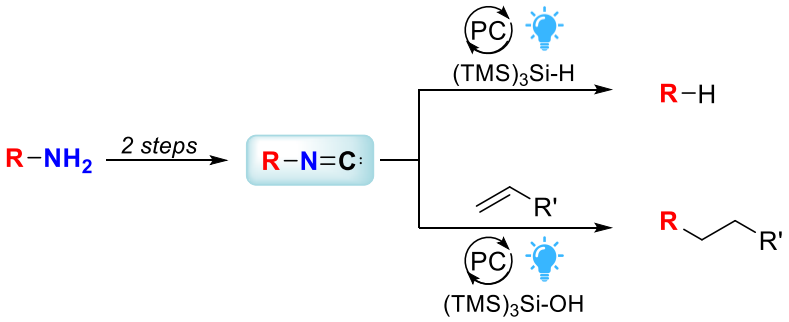
L. Muñoz Gloder,[a] L. Nóvoa,[a] I. Colomer,[a] M. Tortosa[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid*
laura.munnozgloder@estudiante.uam.es

Amines are ubiquitous molecules, widely and easily accessible as well as commercially available, which makes them a really attractive feedstock for the preparation of functionalized molecules through C-N bond activation. However, their potential as building blocks is still underexploited and remains a challenge, mainly due to the high bond dissociation energy of the C-N bonds.

The aim of this project is to develop a deaminative strategy to harness primary amines as building blocks via C-N bond activation. In order to achieve this goal, we want to use of visible-light photoredox catalysis to cleave a C-N bond and generate alkyl radicals under mild conditions, that can later participate in a variety of bond forming reactions.

In this Master's Thesis, the C-N homolytic cleavage was approached through the transformation of amines into isonitriles.[1,2] Using an iridium complex as the photocatalyst and silicon derivatives as radical initiators, we have observed the homolytic cleavage of the C-N bond. We proposed the in situ formation of an imidoyl radical that undergoes β-fragmentation to form a carbon centered radical.[3] This alkyl radical can either be trapped by a Michael acceptor or undergo a hydrogen atom transfer that will lead to the deamination product.



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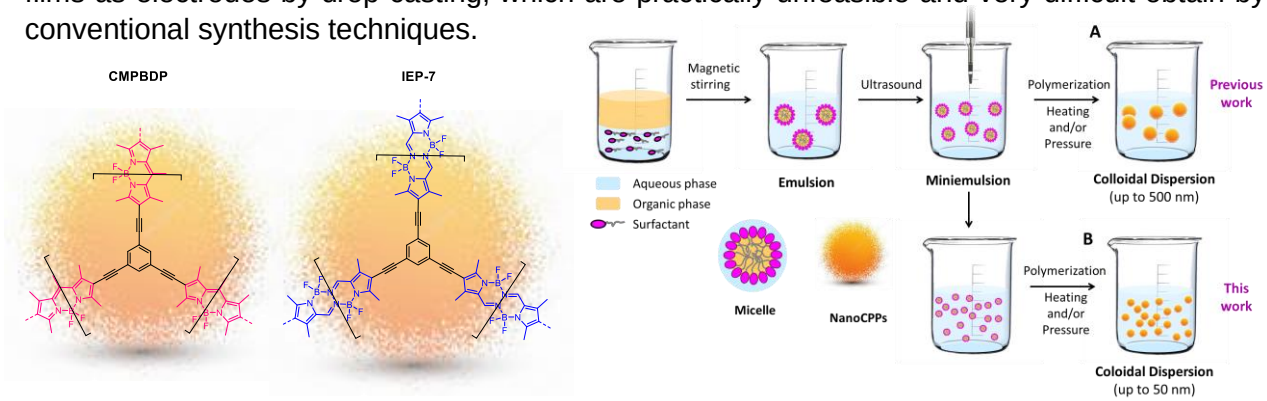
Nanostructured Porous Conjugated Polymers for Photoelectrochemical Applications

S. Palenzuela Rebella,[a] T. Naranjo,[a] M. Liras[a]

[a]*Photoactivated Processes Unit, IMDEA Energía*
sandra.palenzuela@estudiante.uam.es

***Keywords**: NanoCPPs, dyes, hydrogen production*

The development of new strategies to produce solar fuels remains as an ongoing objective in the current society since fossil fuel reserves are limited and energy demand is increasing. In previous studies, conjugated porous polymers (CPPs), 3D amorphous polymeric networks that comprise π-conjugated systems, have demonstrated improved light harvesting properties, thermal and photobleaching resistance, and optoelectronic properties when compared with the linear conjugated polymers as well as improved stability regarding their crystalline counterparts covalent organic frameworks (COFs).[1] Taking advantage of its exceptional behaviour, CPPs, which are based on boron dipyrromethene nucleus (BODIPYs[2] and BOPHYs[3]), have been synthesized during this project. These compounds can be used, as previously demonstrated by our research group, as photocatalysts for hydrogen production,[3] reaching good results due to their stability under physiological conditions, strong UV absorption and the emission of relatively sharp fluorescence peaks with high quantum yields.[4] In this regard, the novel of this project relies on the use of new techniques,[5] allowing polymerization to occur through a Sonogashira type reaction, giving rise to polymeric nanoparticles (NanoCPPs) of CMPBDP (from BODIPY moiety) and IEP-7 (from BOPHY moiety) to improve their processability, by means of lessening the particle size and enhancing its dispersed size. Also, it has been prepared the same polymers by means of conventional miniemulsion techniques in order to compare control size and dispersity. The use of novel techniques allows to present a greater photocatalytic surface for the hydrogen production through water splitting using methanol as a sacrificial agent, obtaining some outstanding preliminary results compared with the previously reported studies.[6] Furthermore, its effectiveness in the photoelectrochemistry hydrogen have been tested, forming thin and uniform films as electrodes by drop casting, which are practically unfeasible and very difficult obtain by conventional synthesis techniques.



Scheme 1. Polymerization by means of novel techniques: A) previous work and B) this work.

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Pt(II)-BODIPY supramolecular coordination complexes for phototherapeutic applications

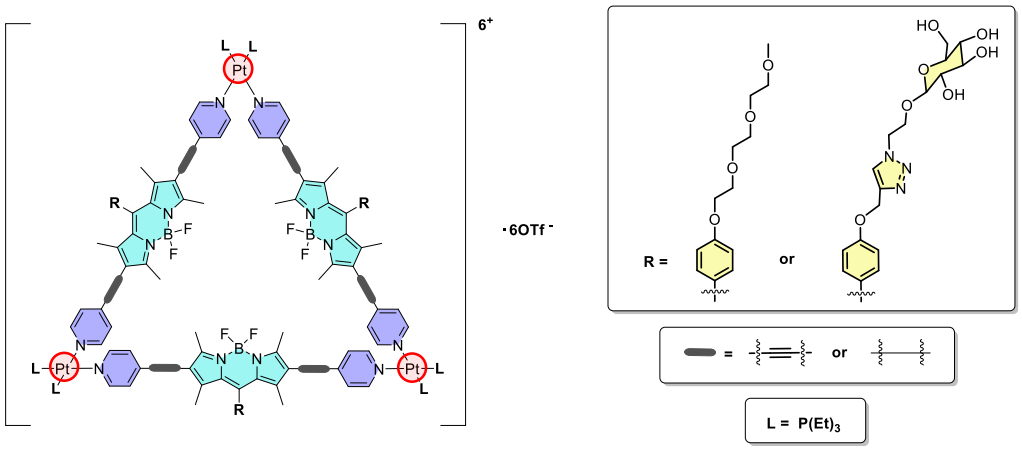
C. Paramio Pérez,[a] M. Moreno Simoni,[a] G. Durán Sampedro,[a] G. de la Torre,[a,b]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco 28049, Madrid (Spain)*
[b] *Institute for Advanced Research in Chemical Science (IAdChem), Cantoblanco 28049, Madrid (Spain)*
e-mail: celia.paramio@estudiante.uam.es

***Keywords**: BODIPY, Supramolecular coordination complex, Photodynamic therapy*

Photodynamic therapy (PDT) is a form of phototherapy that utilizes harmless light to activate non-toxic photosensitive chemicals called photosensitizers (PS) to generate cytotoxic species for malignant cell eradication. A relevant advance in the development of more effective treatments for cancer phototherapy is the application of theranostic agents that possess simultaneous monitoring (i.e. fluorescence) and therapeutic competencies. In this regard, BODIPY derivatives are well-recognized by their excellent fluorescence properties, and some derivatives have been also applied as PS in PDT.[1] Last, multimodal therapies, which utilize a combination of two or more therapeutic modalities (chemo-photodynamic) is an ongoing avenue of research.

Here, we report the coordination driven self-assembly of Pt(II)-based supramolecular coordination complexes containing pyridyl-functionalized BODIPY-based bridging ligands, where the platinum acceptors behave as chemotherapy drugs and the BODIPY donors are imaging probes and PS.[2] With the aim of finding application as phototheranostic, multimodal agents, the initial objective of this study is the synthesis of water-soluble metallo-macrocycles. For this purpose, BODIPYs functionalized with hydrophilic groups in the *meso* position were designed. The substituents chosen were a polyethylene glycol (PEG) chain and a β-D-glucose unit, providing the molecule water solubility and biocompatibility, together with improved uptake features by the tumor tissues. In addition, the influence of the bridge between the BODIPY and the metal coordinating pyridine has also been studied, and how this spacer can modify the size and shape of the metallo-supramolecular structure. Preliminary photophysical experiments have been performed to determine their potential as PS and imaging probes.



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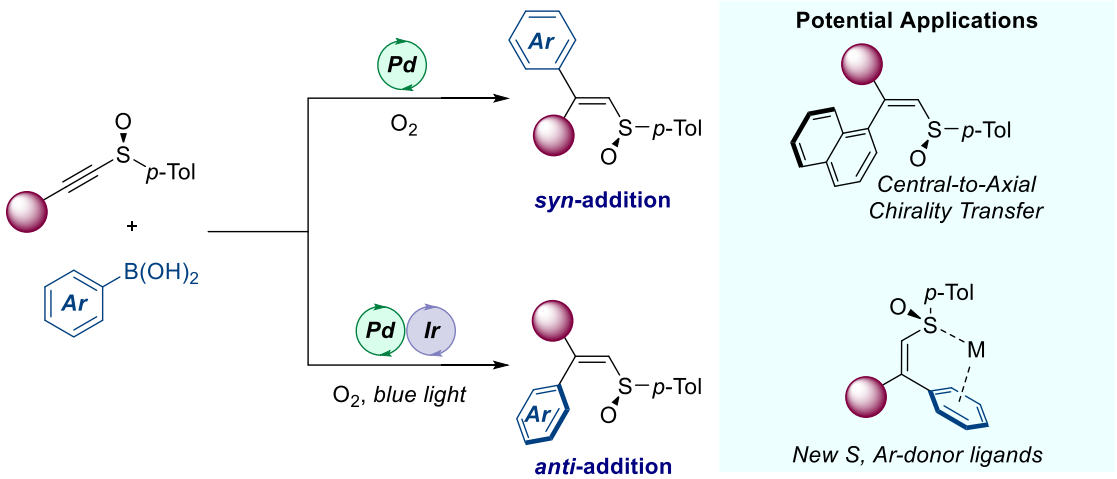
Stereodivergent Hydroarylation of Alkynyl Sulfoxides: Atroposelective Synthesis of Styrenes and Applications as Ligands in Catalysis

Carmen Pérez-Alonso,[a] Javier Corpas,[a] Pablo Mauleón,[a] Ramón G. Arrayás,[a] and Juan C. Carretero.

[a]*Department of Organic Chemistry,* Faculty *of Sciences, Universidad Autónoma de Madrid (UAM)*
carmen.perezalonso@estudiante.uam.es

Keywords*: Stereodivergent hydroarylation, photocatalytic alkene isomerization, Central and Axial Chirality*

The sulfinyl group is a privileged functionality as an element of stereocontrol in Organic Synthesis.[1] However, the stereodivergent synthesis of trisubstituted alkenyl sulfoxides still remains a challenge. In this work, we present a regioselective and stereodivergent catalytic hydroarylation of alkynyl sulfoxides with arylboronic acids, which allows access to the two both *Z* and *E* stereoisomers of the corresponding trisubstituted alkenyl sulfoxides.[2] The *E* selectivity is achieved through a *syn*-carbopalladation process in which the sulfinyl group enables complete control of the regioselectivity. The complementary diastereoisomer is reached as a result of a second Ir-photocatalyzed E→Z photoisomerization.[3] In addition, an evaluation of the sulfinyl group as stereocontroller in the atroposelective synthesis of chiral styrenes, as well as the potential behavior of the corresponding *Z*-isomers as new *S, Ar*-donor ligands is presented.



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A Dual Ligand Approach Towards Copper^{I}-Catalyzed *anti*-Hydroboration of Internal Alkynes

Jonathan Ramírez-Cárdenas,[a] Javier Corpas,[a] Pablo Mauleón,[a,b] Ramón Gómez,[a,b] and Juan C. Carretero[a,b]

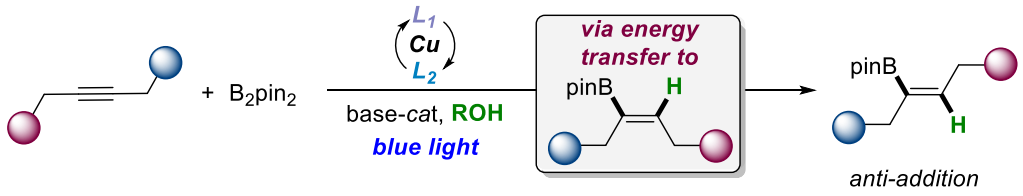
[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain.*
[b]*Institute for Advanced Research in Chemical Sciences (IAdChem), UAM. Cantoblanco, 28049 Madrid, Spain.*

e-mail: jonathan.ramirez@estudiante.uam.es

Keywords: *Photoisomerization, hydroborylation, dual ligand catalysis.*

Alkenylboronates are versatile synthetic intermediates in organic synthesis for the construction of C-C and C-X bonds.[1] A direct approach for the synthesis of this structural platform consists in the transition-metal-catalyzed hydroboration of alkynes. However, because of the intrinsic nature of the *syn*-addition of the catalytically active species across the C—C triple bond, the design of *anti*-hydroboration processes still remains a challenge.[2]

Herein we present a solution towards the formal *anti*-hydroboration of internal alkynes employing diboron reagents under copper catalysis. This strategy exploits a one metal/dual ligand strategy (ML_1L_2) in which a first CuL_1 complex participates in the *syn*-hydroboration of the triple bond.[3] Further ligand exchange *in situ* enables the formation of a photoactive CuL_2 complex which is prone to photosensibilization of the resulting *syn*-isomer to deliver the desired *anti*-addition product. Kinetic and Stern-Volmer analysis have revealed that both processes operate under a tandem catalytic scenario through an energy transfer mechanism.[4]



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Synthesis of new nanosensors based on azo compounds

L. Rodríguez Fernández,[a] A. Pascual Escudero,[a] M. Ribagorda Lobera[a,b*]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049, Madrid, Spain.*[b]*Institute for Advance Research in Chemical Science (IAdChem), Universidad Autónoma de Madrid, Spain*

e-mail: laura.rodriguezf03@estudiante.uam.es

***Keywords**: hypoxia, azo compound, BODIPY*

Hypoxia is a condition associated with the reduction of molecular oxygen in tissues or cells, seen characteristically in cardiovascular or inflammatory diseases. In this way, detection of hypoxia is a key factor for the identification of malignant solid tumors. The reduction of oxygen partial pressure causes changes in genetic expression, such as overexpression of reductase enzymes. Design of new sensors dependent on these reductase-type enzymes is an interesting tool for the detection of hypoxic level.

The aim of this project is the synthesis and design of a family of azo compounds as fluorescence inhibitors[1] for their future linkage to upconverting nanoparticles (UCNP). The synthesis of these compounds generates interest for the *in vivo* detection of hypoxia, thanks to their application as fluorescent probes in bio-imaging techniques.[2] The main structure of these azo compounds is composed by a BODIPY (Boron Dipyrromethene) acting as a fluorophore[3] linked to an azo group through an organic linker.

Azo compounds can be employed as fluorescence inhibitors when are located close to fluorophores due to the photoisomerization process of the N=N double bond. This feature in combination with the ability to recover the fluorescence in a reducing medium due to the cleavage of the N=N bond, make azo compounds excellent candidates in bio-imaging.

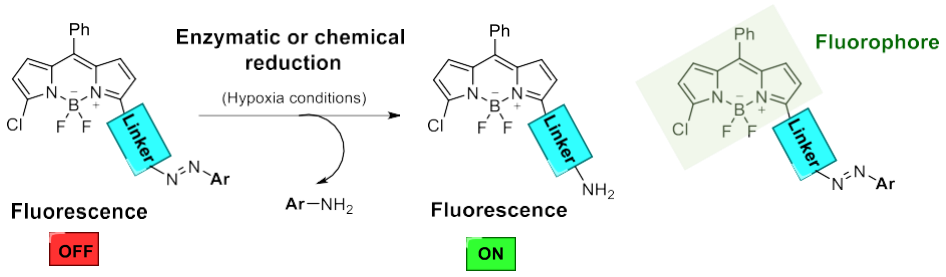

Figure 1: Reductive cleavage of N=N double bond under reducing conditions

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Self-Healing Polymeric Materials based on Cooperative Supramolecular Interactions

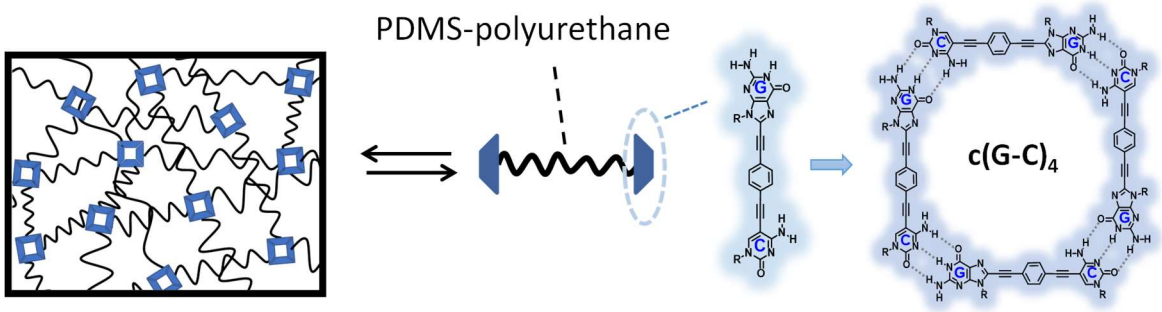
Miguel Sánchez-Rubio Abenia, David González-Rodríguez, Anselmo Del Prado Abellán

Departament of Organic Chemistry, Faculty of science, Universidad Autónoma de Madrid (UAM)
e-mail: miguel.sanchez-rubio@estudiante.uam.es

***Keywords**: Self-repairing, polymers, supramolecular chemistry.*

The development of stimuli-responsive self-healing polymers along the last two decades have experienced different phases and diverse approaches have been intensely investigated.[1] One of the most promising directions considers the use of **supramolecular polymers**,[2] in which polymer chains are endowed with chemical functions that can associate selectively by means of reversible and dynamic noncovalent interactions. However, the main problem resides in the balance between self-healing ability and mechanical properties of the material at working conditions.

Our main objective is to tackle this problem by introducing cooperative ***all-or-nothing* interactions** in supramolecular polymers. Hence, our strategy will be the synthesis of a polymer that combines supramolecular motifs able to strongly bind through multiple and cooperative noncovalent interactions by tetramer species formation,[3] with polymer chains that are flexible enough to facilitate recombination after damage. Here we describe the preparation of a telechelic polyurethane functionalized at both edges with a synthetic dinucleoside motif carrying guanosine and cytosine functions. This supramolecular motif generates a dynamic network through cooperative hydrogen bonding (Watson and Crick interactions) that allows self-healing ability and reprocessing. The functionalized polyurethane and the self-assembling process will be studied by H-RMN, fluorescence spectroscopy, circular dichroism, and rheology techniques.



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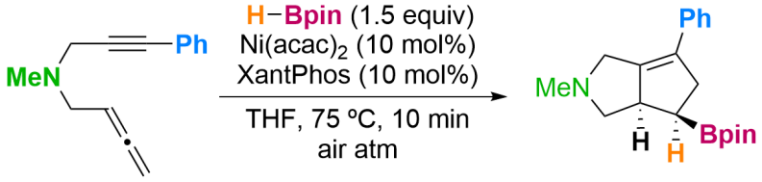
Mechanism of the Ni-catalyzed hydroborylative cyclization reaction of allenynes

E. Velasco Juárez, D. J. Cárdenas Morales [a]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049, Madrid, Spain.*
e-mail: elena.velascoj@estudiante.uam.es

This work shows a computational mechanistic study of the hydroborylative cyclization reaction of stereoselective 1,5-allenynes catalyzed by Ni in which pinacolborane (HBpin) is used as a borylating agent. This allows the formation of synthetically useful bicyclic alkylboronates that are prepared under smooth conditions, constituting a fully atom-economic eco-friendly method. As shown in scheme 1, two C-C and one C-B bond are formed in a single operation. Although the experimentally observed product contains two contiguous stereogenic carbons, the reaction proceeds in a diastereoselective manner, generating the derivatives with the H of the afore-mentioned carbons in cis arrangement. The computational study was carried out to try to determine the mechanism of the reaction, knowing that the active catalytic species of the cycle is NiL (0) (L = xantphos) as it was determined through previous experimental studies. Our results suggest that the reaction proceeds by an initial oxidative cyclometalation step of the polyunsaturated organic chain to the NiL species to give a nickelacyclopentene. This species then evolves through σ-metathesis in which the borylating agent enters the structure forming a single regioisomer containing a nickel hydride. Next, a 1,2-insertion step of the C-C double bond of the alkenylboronate into the Ni-H bond takes place, and this step determines the stereoselectivity of the final compound. Finally, the reductive elimination stage leads to the experimentally observed product together with the recovery of the initial active catalytic species.



Scheme-1: Hydroborylative cyclization reaction of stereoselective 1,5-allenynes catalyzed by Ni.

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Design and "bottom-up" synthesis of molecular nanographenes

Jaime T. Alcolea Cerdán,[a] Jesús M. Fernández-García,[a] Nazario Martín[a,b]

[a]*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain,* [b]*IMDEA-Nanociencia, Campus de la Universidad Autónoma de Madrid, 28049 Madrid, Spain*
e-mail: jaimetal@ucm.es

***Keywords**: molecular nanographenes, bottom-up synthesis, chirality*

Despite the outstanding properties of graphene, its applications in organic electronics are limited because its zero-energy band-gap.[1] However, molecular nanographenes (nanosized pieces of graphene) can confine electrons in a reduced space opening this band-gap. The structure and therefore the properties of molecular nanographenes can be controlled by stepwise organic synthesis, the so-called bottom-up synthesis.[2] This methodology allows the introduction of defects such as helicity[3] and curvature[4] which provide chirality to those systems.

On this work, we have carried out the selective synthesis of molecular nanographenes with helicity **1** or negative Gaussian curvature **2**. This selectivity has been controlled depending on the oxidant agent used in the graphitization (Scholl reaction) of the poliphenylene **3**.[4] The main challenge of this project is to achieve the selective closure of the C–C bond between the naphtyl moieties (green bond, **Figure 1**), because it can avoid the formation of regioisomers in the Scholl reaction. For the synthesis of **3,** we proposed three different pathways: a) [4+2] Diels-Adler cycloadittion between the tetraarylcyclopentadienone **4** and dinaphtyleacetylene **5**; (b) [4+2] Diels-Alder cycloaddition between the diarylpicenecyclopentadienone **7** and di-(4-*tert*-butylphenyl)acetylene **6**; (c) [4+2] Diels-Alder cycloaddition between the diarylcyclopentadienone triflated **8** and di-(4-*tert*-butylphenyl)acetylene **6** and a Suzuki coupling to close the green bond.

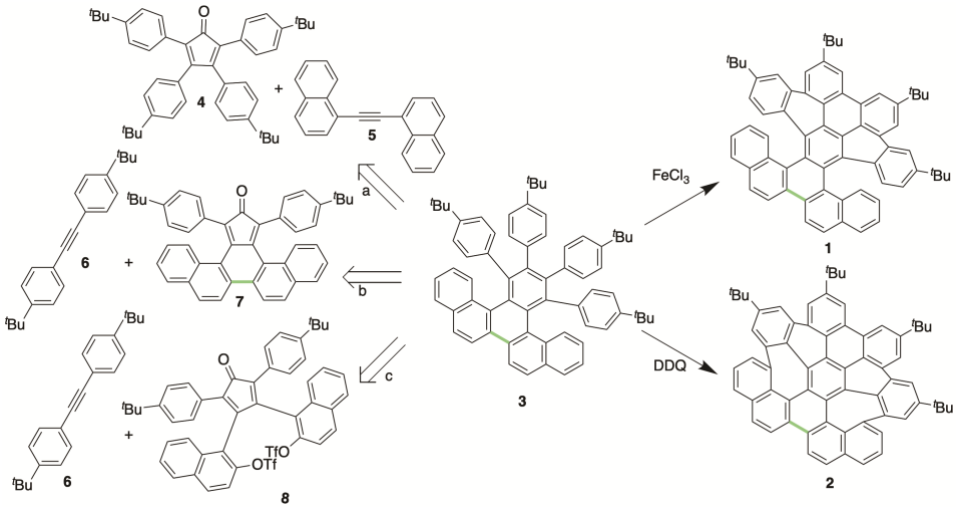

Figure 1. Scheme of the different routes tested and the further Scholl reaction.

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Synthesis and functionalization of di-iodinated carbazoles

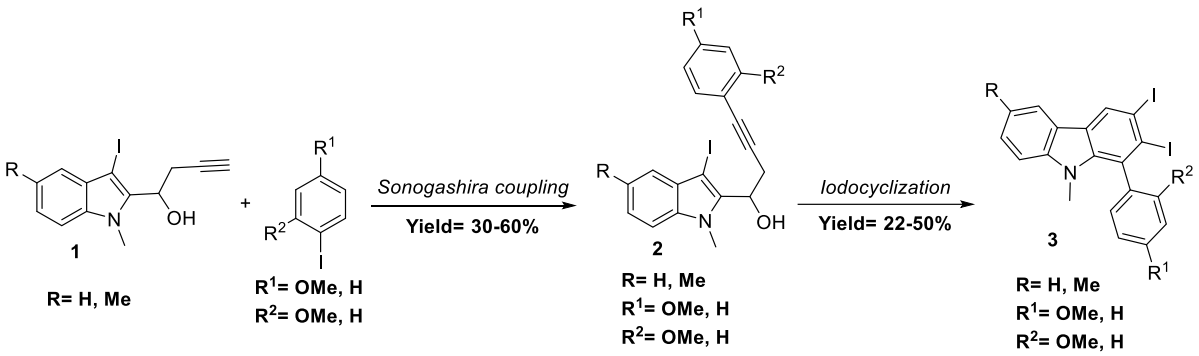
S. Arasil Torroella, P. Almendros, C. Aragoncillo

Departamento de Química Orgánica I, Facultad de C.C Químicas, Universidad Complutense de Madrid, 28040, Madrid.

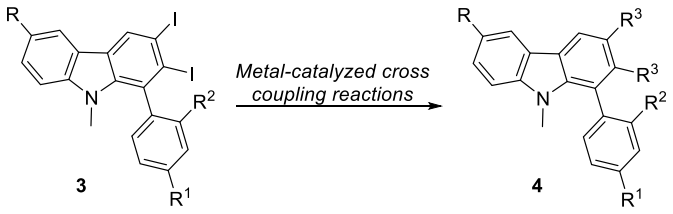
sarasil@ucm.es

Keywords: *carbazole, indole*

Carbazole and its derivatives have shown a wide range of properties, standing out the biological and medical fields acting as anti-cancer, anti-inflammatory, antibacterial, antifungal and sedative agent.[1] Furthermore, they present interesting electrochemical and optoelectronic properties which can be used in electrophotography or to produce electro photovoltaic devices.[2] Recently in our research group, we are studying the synthesis of di-iodinated carbazoles from alkynyl indoles **1.** The synthetic route begins with a Sonogashira coupling of alkynyl indoles. The next step is the use of a reagent which involves iodocyclization, migration and aromatization to give di-iodinated carbazoles **3** (Scheme 1).[3] Compounds **4** have been functionalized using metal-catalyzed cross coupling reactions as it is shown in Scheme 2.[4]



Scheme 1: Synthesis of di-iodinated carbazoles



Scheme 2: Functionalization of di-iodinated carbazoles

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Design and synthesis of surfactants for the development of new nucleic acids vectors. Applications in gene therapy against cancer.

I. Del Barrio Gómez,[a] J.Osío Barcina,[a] A. Guerrero Martínez[b]

[a]*Department of Organic Chemistry, Faculty of Chemistry, Universidad Complutense de Madrid, 28040, Madrid, Spain.* [b]*Department of Fisical Chemistry, Faculty of Chemistry, Universidad Complutense de Madrid, 28040 Madrid, Spain.*

e-mail: isdelbar@ucm.es

Keywords: *cationic lipids (CL), lipoplex.*

Cationic lipids (CL) are commonly used vectors to improve the efficiency in the distribution of nucleic acids as a consequence of their structural similarity with cell membranes. However, their use is limited due to cytotoxicity. For this reason, new lipids such as cationic gemini lipids (GCL) have been investigated. In their structure we can differentiate three parts: the polar head group (two positive charges), the hydrophobic chain, which can suffer changes in length and in the number of unsaturations, and the linker between them. They are cationic lipids with improved properties. They are also amphiphilic and the linker between the polar and non-polar parts is really useful because it can determine certain properties depending on the length and nature. [1] The polar head group confers the possibility of benefiting from the multivalence effect because CL are preferentially formed with excess positive charge. (***Figure 1***):

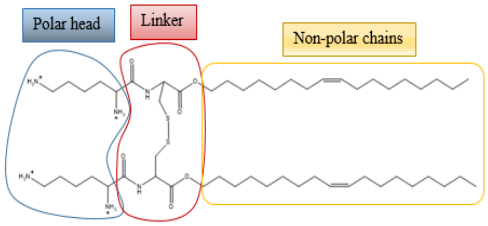

Figure 1. *Example of GCL with the different parts of the molecule.*

To deal with cancer and other diseases is really useful to know how the CL can interact with nucleic acids and how the corresponding complexes between them (lipoplexes) are formed. This kind of complexes are efficiently prepared by simply mixing preformed cationic liposomes and DNA in an aqueous solution. The steps that must be followed to overcome gene delivery with non-viral vectors are (***Figure 2***): 1) Complexation and condensation of the polynucleic acid by the cationic lipid into a lipoplex. 2) Electrostatic attraction to the cell surface. 3) Uptake by endocytosis. 4) Degradation in a lysosome. 5) Escape from the endosome. 6) Entry into the nucleus. 7) Expression as a protein. 8) Therapeutic effect. [2]

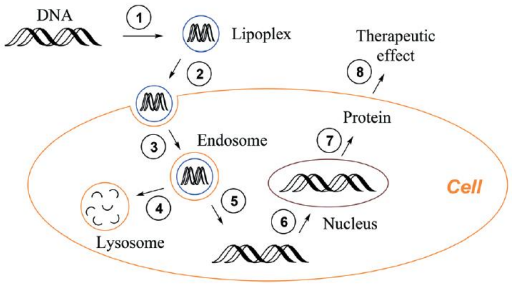

Figure 2. *Steps and barriers to overcome in gene delivery with non-viral vectors.*

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Bioconjugates based on cannabinoid ligands with therapeutic applications

Beatriz del Campo Herrero,[a] Mar Martín-Fontecha,[a] María L. López-Rodríguez[a]

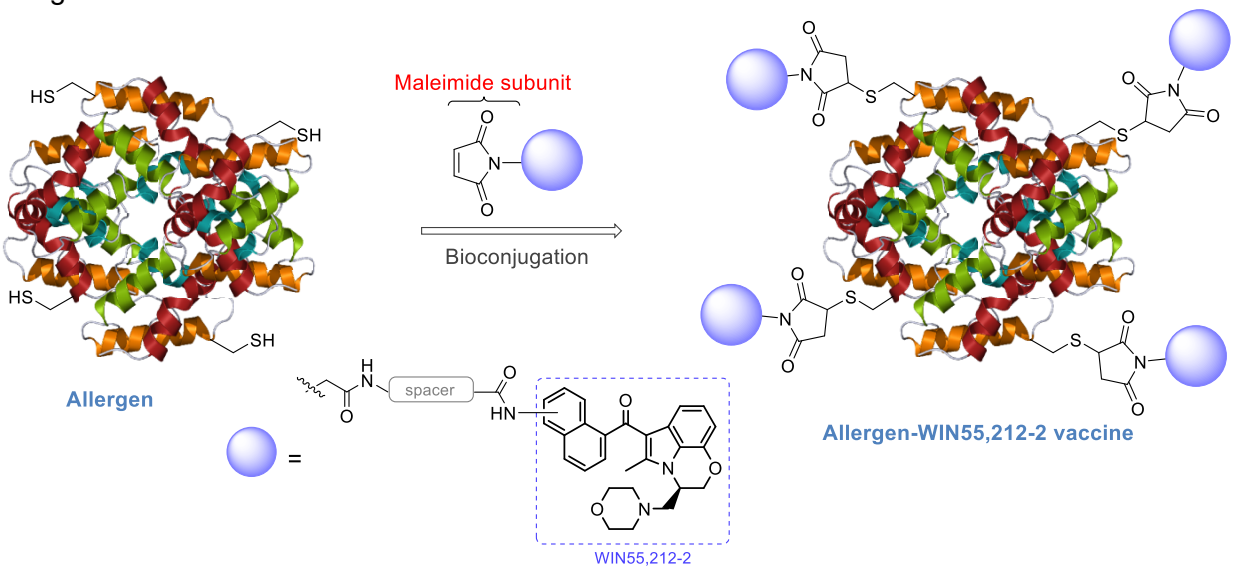
[a]*Dpto. de Química Orgánica, Fac. Ciencias Químicas, Universidad Complutense de Madrid, E-28040 Madrid, Spain*

e-mail: beadelca@ucm.es

Keywords: *Allergy, cannabinoid-based vaccines, WIN 55,212-2*

Allergic diseases constitute a public health problem with a high socio-economic impact, whose only curative treatment to date is the allergen-specific immunotherapy (AIT).[1] However, it still faces several drawbacks regarding the long treatment duration, patient compliance, side effects or low efficacy for some patients. Therefore, novel vaccines for more efficient, safer and shorter AIT treatments are highly demanded and represent an unmet need in the field of allergy.

Several studies showed that cannabinoid ligands might regulate immune responses in the context of allergy. Cannabinoid receptor 1 (CB_1R) is upregulated in allergic patients at the mRNA level and is highly expressed in different immune system cells at the protein level,[2] suggesting that this receptor may be a potential target in allergy. In fact, preliminary studies in a peanut-allergy mouse model showed that WIN55,212-2, a non-selective CB_1 and CB_2R agonist, might regulate peanut-induced anaphylaxis.[3] In light of these results, the main objective of this project is the development of cannabinoid-based vaccines that may represent novel strategies for the prevention and treatment of food allergy. As a proof of concept, WIN55,212-2 will be functionalized with a maleimide subunit through different spacers and conjugated to peanut allergens via thiol-Michael addition.



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Synthesis of PNAs as biosensor recognition systems for the detection of resistance to antiretroviral drugs (anti-HIV)

A. Campo, S. de Castro, M.J. Camarasa

Instituto de Química Médica (IQM, CSIC) Juan de la Cierva, 3, 28006, Madrid
e-mail: angcampo@ucm.es

***Keywords**: HIV, PNA, biosensor*

Drug resistance tests have become an essential tool to choose the optimal combination of drugs for the treatment of HIV-infected patients. The use of biosensors may allow to the development of new diagnostic tests that are faster, cheaper, and more accessible than those currently available.[1] A Biosensor is mainly formed by a specific biological receptor and a transducer capable of transform the interaction into a quantifiable signal (Figure 1). Peptide nucleic acids (PNAs) have proven to be good recognition systems for DNA mutations in biosensors.[2]

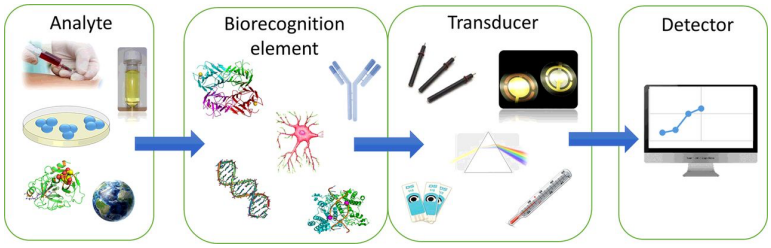

Figure 1: General structure of a biosensor

In a previous work in our group of research, we demonstrated that the 9 mer PNA (TATG**C**AC CT) shows a high selectivity to detect a single nucleotide mutation (M184V), in the HIV-1 DNA, but with low affinity. This mutation is related to resistance to the antiretroviral drugs Emtricitabine and Lamivudine. In order to achieve higher affinity and selectivity we describe herein the design, synthesis and hybridization studies by NMR and circular dichroism of a series of 11, 13 and 15 mer PNAs (Table 1). On the other hand, the influence of a solid support in the affinity and selectivity PNA/DNA will be studied by surface plasmon resonance (SPR) experiments using biotin-spacer-9 mer PNAs anchored to a streptavidin chip.

Table 1. DNA and PNA sequences related with M184V mutation

M184V	**Wild type**			T CAA TAC ATG GAT GAT
	Mutant			T CAA TAC **G**TG GAT GAT
	PNA[a]	**9 mer**		T ATG **C**AC CT
		11 mer		TT ATG **C**AC CTA
		13 mer		GTT ATG **C**AC CTA C
		15 mer		A GTT ATG **C**AC CTA C
		Biotin - (aeea)$_n$- 9 mer	**n=0**	Biotin - T ATG **C**AC CT
			n=1	Biotin - (aeea) - T ATG **C**AC CT
			n=2	Biotin - (aeea)$_2$ - T ATG **C**AC CT

[a]The location of the mutation is indicated in bold

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Kynurenine analogues for the treatment of cerebrovascular diseases

A. Del Castillo, A. Lago, A. Castro

Instituto de Química Médica, CSIC
alejandro.delcastillo@iqm.csic.es

***Keywords**: spirocompounds, indolamine-2,3-dioxygenase, kynurenine pathway*

The kynurenine pathway (KP) is primarily responsible for tryptophan metabolism. This pathway generates a range of metabolites, collectively known as kynurenines, involved in inflammation, immune response, and excitatory neurotransmission.[1] The solid evidence that KP is implicated in a variety of disease states, offers the possibility to employ pharmacological strategies and to develop drug discovery programs. In particular, we have focused our attention to one of the rate-limiting enzymes of tryptophan metabolism, indoleamine-2,3-dioxygenase (IDO1), a relevant target whose modulation plays an important role in certain neurodegenerative diseases.[2] Therefore, we have started a project aimed at the identification of new IDO1 inhibitors. In order to find new chemical prototypes, we considered some previous unpublished results, in which spirocompounds, depicted in ***Figure 1***, have shown some preliminary good inhibitory activity against IDO1.

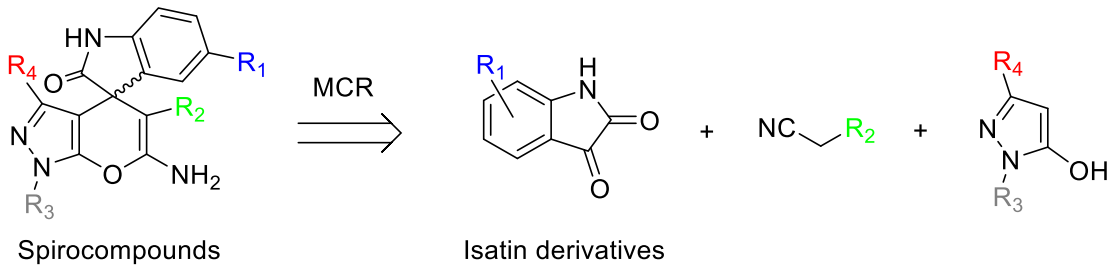

***Figure 1.** General formula and retrosynthesis of spirocompounds.*

On this basis, a series of new compounds were designed and synthesized using multicomponent reaction (MCR) as synthetic strategy. The spiro-oxindole scaffold of the initial prototypes could be synthesized through a multicomponent cascade reaction using isatin as starting material. Isatins and their C3 functionalized derivatives occupy a prominent place in organic and medicinal chemistry.[3] This reactivity could constitute an opportunity for the construction of privileged scaffolds, especially spirofused cyclic frameworks. Then, a small library of spirocompounds was evaluated as potential enzymatic inhibitors of IDO1. The initial structure-activity relationships analysis (SAR) showed the importance of placing an aromatic ring directly attached to the nitrogen of the pyrazole fragment and the importance of CN group in the biological activity. With the aim of improving the activity, a hit to lead optimization process was carried out, in which derivatization of these molecules has been focused on making open derivatives.

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Development of new compounds for the treatment of progeria

D. Fernández Cabellos, J. Macicior Michelena, S. Ortega Gutierrez

Dpto. de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, E-28040 Madrid, Spain
e-mail: dafern12@ucm.es

***Keywords**: Progeria, Chemical Probes, Therapeutic Targets*

Hutchinson-Gilford progeria syndrome (HGPS) or progeria is a rare genetic disease that causes premature aging, leading to a drastic reduction in the life expectancy of patients. The disease is mainly caused by the intracellular accumulation of a mutant protein called progerin, generated from a mutation in the LMNA gene.[1] Currently, there are not very effective treatments for this disease, one of the reasons being the lack of effective tools for the direct visualization of progerin in cellular models of the disease, as the available antibodies are not suitable for some applications.

In this context, protein visualization can be performed using chemical probes, small molecules with affinity, specificity and selectivity against a protein.[2] Chemical probes have three parts: (i) the bioactive subunit, responsible for recognizing and efficiently binding to the target protein, (ii) the fluorophore responsible for the visualization of protein and (iii) a linker between the moieties. The objective of this work is the design, synthesis and validation of a chemical probe (Figure 1) based on (+)-decursinol, a progerin ligand, in progeroid cell models.

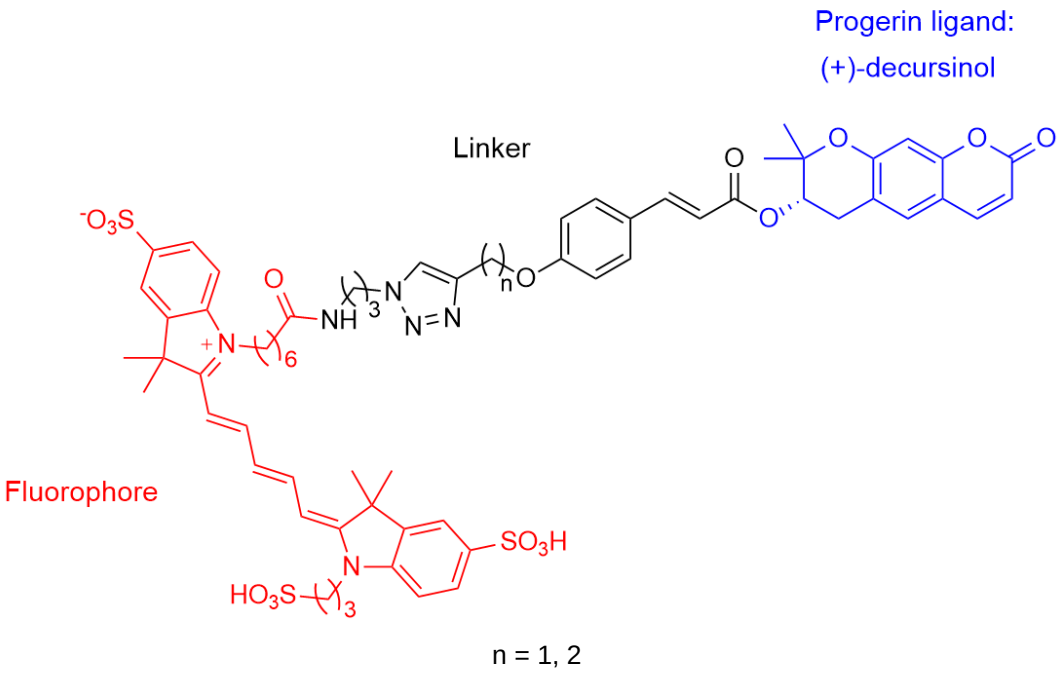

Figure 1. Structure of the chemical probe designed for the visualization of progerin.

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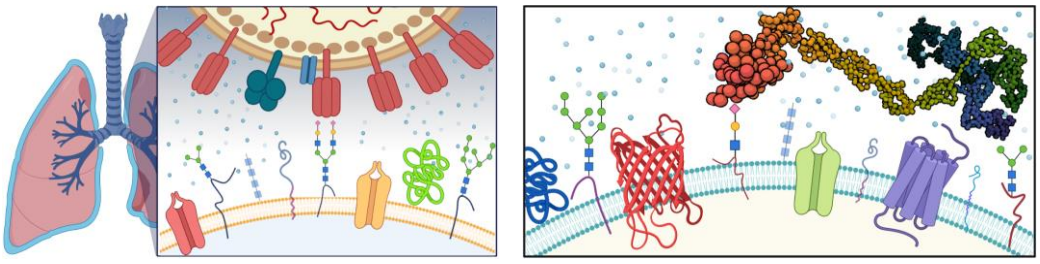
Protein-glycan interaction studies with nuclear magnetic resonance and computational simulations

B. Fernández del Río,[a,b] F. J. Cañada Vicinay,[b] M. A. Canales Mayordomo[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid,*
[b]*Departamento de Biología Estructural y Química, Centro de Investigaciones Biológicas Margarita Salas (CSIC)*
beatfe11@ucm.es

***Keywords**: NMR, interaction, simulation*

Molecular recognition takes part in almost all physiological processes, and it involves both receptors, usually biomacromolecules, such as proteins, and ligands (small molecules frequently), among which glycans stand out.[1] Nuclear Magnetic Resonance (NMR) is very useful for the study of ligand-receptor interaction, allowing analysis at the atomic level and in solution.[2] The objective of this project is to use different NMR methodologies to deepen the acknowledge about the process of Influenza virus infection on one side and about self/non-self cellular discrimination in the immunological system by human Factor H of complement on the other side. In addition, these studies are complemented by modelling the most stable conformations of glycans involved in these processes. This work has been focused on the study of interactions between hemagglutinin (from Influenza virus) or Factor H and different glycans, containing sialic acid at the non-reducing end of glycans, present on the surface of several human cells (2,3- and 2,6-Sialyllactose and Biantennary TriLacNAc). Methodologically, approaches from the perspective of the ligand and of the protein have been apply. From the ligand perspective, applying Saturation Transfer Difference experiments, two hemagglutinin strains (mutant California 2009 and mutant Taiwan 2013) have been tested. The results support that 4 mutations in California 2009 strain can change the specificity of the binding site, recognizing preferentially terminal 2,6- over 2,3-Sialylated glycans. In the case of Taiwan 2013 strain with a single mutation the recognition of long, branched 2,6-Sialic glycans is observe, without losing the interaction with small and lineal glycans. From the receptor perspective, applying Chemical Shift Perturbation method, the last two domains of the C-terminal end of human Factor H have been studied. The results indicate that the presence of ligand produces both specific and non-specific variations on the protein NMR signals. In this context, the work is ongoing and further studies are needed to define the specific interactions. Finally, Molecular Dynamics simulations of the 2,3 and 2,6-Sialillactose have been performed in order to identify their most stables conformations in solution compatible with the NMR data.



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Folate receptor-mediated drug targeting of DNA minor groove binders to leishmania parasites

M. Gil, C. Dardonville

Instituto de Química Médica - CSIC
mgil13@ucm.es

***Keywords**: Dicationic compounds, folate-drug conjugates, T. brucei*

The mitochondrial DNA (kDNA) of kinetoplastid parasites (e.g., Trypanosoma brucei) is a target of the dicationic DNA minor groove binders (MBGs) discovered in our group in the last years [1] (Figure 1). To improve its cellular uptake (and therefore antiparasitic activity) a folate receptor-mediated drug [2] will be designed to deliver dicationic antileishmanial drugs to the intra-macrophage parasite using a self-immolative linker.

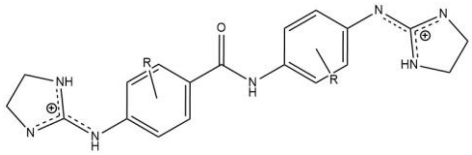
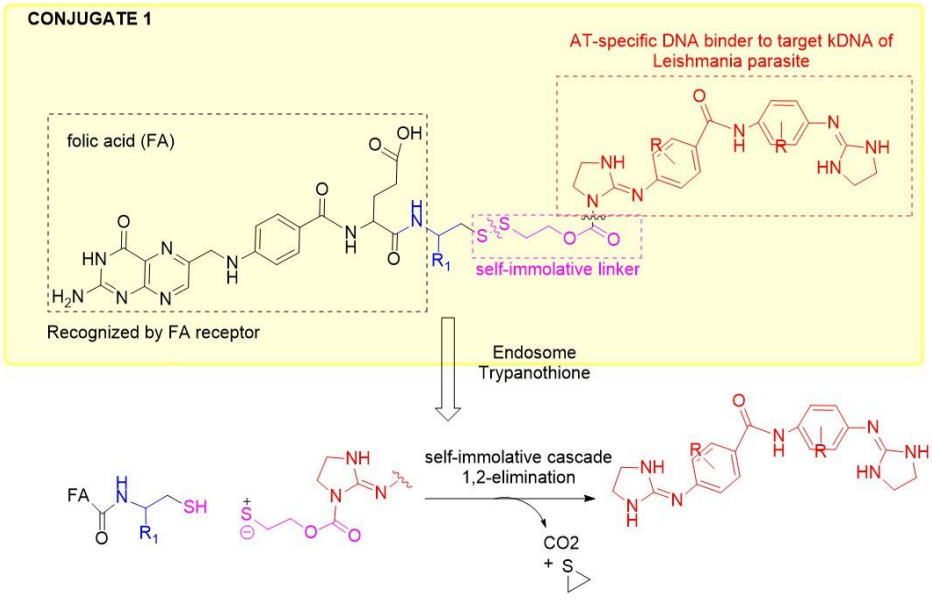


Figure 1. Example of kDNA MBGs developed in the group

Figure 2. Example of design of folate receptor-mediated drug targeting conjugate

In this project, the **CONJUGATE** (yellow) **1** of a bis(2-aminoimidazoline) DNA binder (red) with α-conjugated folic acid (black) with a spacer (blue) will be synthesised using a disulfide-based self-immolative linker (pink). The linker will be attached to the DNA binding drug via the heterocyclic nitrogen atoms and the self-immolative linker is based on a 1,2-elimination mechanism triggered by the reduction of disulfide bond by a reducing medium of the parasite interior (Figure 3)



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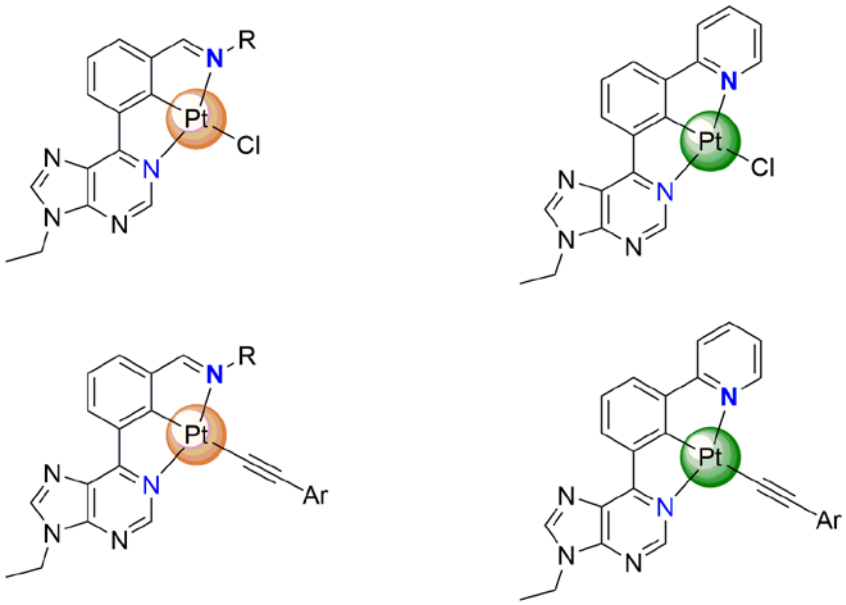
Nucleobase-derived Pt(II) (N^C^N) pincer complexes

J. Gómez Olivares, C. Lorenzo-Aparicio, M. G. Gallego, M. A. Sierra

Dpto. Q. Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense
Av. Complutense s/n, 28040, Madrid
e-mail: jorgom02@ucm.es

***Keywords**: Cyclometalated Pt(II) complexes*

The strong luminescent properties of cyclometalated Pt(II) complexes are well-known and have been employed in different fields, from phosphorescent devices to self-assembled materials,[1, 2] sensors[3] or as anticancer agents.[4] In this work we report the preparation of a new class of cyclometalated Pt(II) (N^C^N) (L) complexes derived from nucleobases (L = Cl, alkynyl). The photoluminescent properties of the Pt(II) (N^C^N) alkynyl pincer complexes made would be modulated by modifications on the structure of the cyclometalating ligand constructed on the purine-based skeleton. The alkynyl ligand linked to the metal would be also used as the anchoring point to incorporate organic fragments, from simple aryl groups to more complex nucleobases, nucleosides or nucleotides.



Scheme 1. Structures of some of the complexes studied in this work.

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Synthesis of ortho- functionalized benzenes by insertion of aryne to sigma bonds under photocatalytic conditions

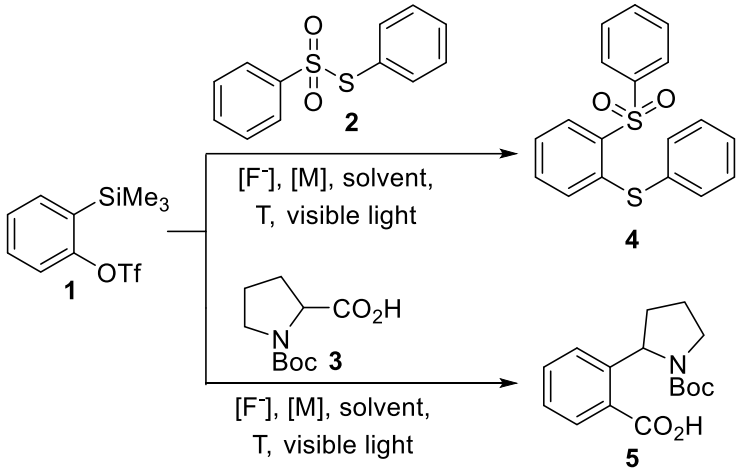
P. Jordán,[a] P. Almendros,[a] J.M. Alonso[a]

[a]*Grupo de Lactamas y Heterociclos Bioactivos, Unidad Asociada al CSIC, Departamento de Química Orgánica, Facultad de Química, Universidad Complutense de Madrid, 28040, Madrid*
pjorda01@ucm.es

***Keywords**: aryne, photocatalyzed insertion to sigma bonds*

In the present work, we have investigated the synthesis of *ortho*-functionalized benzenes through the photocatalyzed insertion of *in situ* generated arynes to sigma bonds. The Kobayashi precursor **1**[1] has been selected as aryne precursor, and benzothiosulfone **2**[3] and aminoacid **3**[3] as co-reactants in the presence of different photocatalysts and diverse reaction conditions (Scheme 1).

To the best of our knowledge, there is no precedent in the literature of aryne insertions to sigma bonds under photocatalytic conditions. This work would therefore constitute a promising alternative of greater efficiency and sustainability for the preparation of *ortho*-functionalized benzene rings.



Scheme 1

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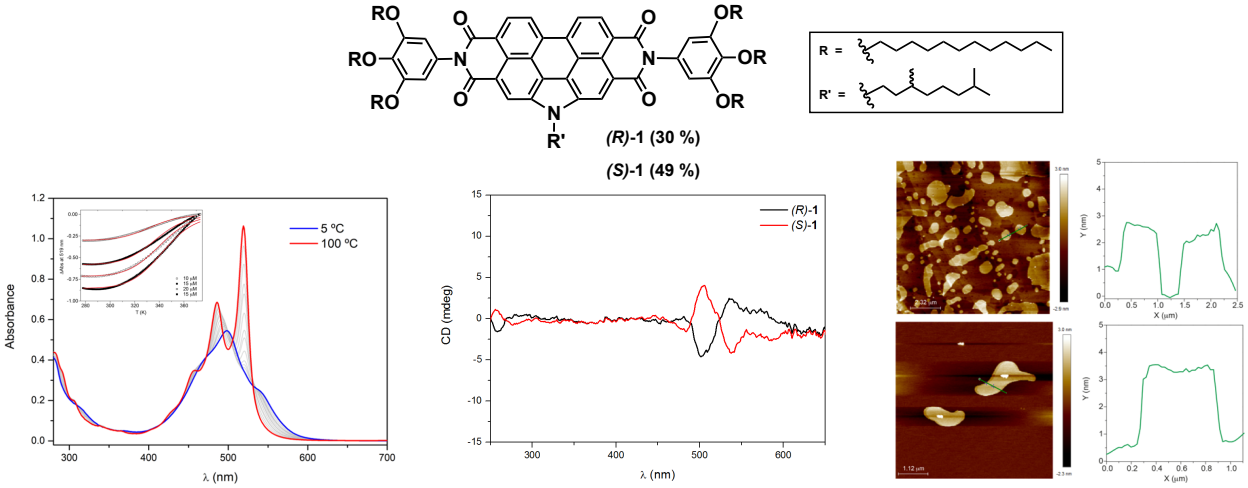
Synthesis and study of chiral supramolecular polymers

L. López Gandul, M. A. Martínez Orosa, L. Sánchez Martín

Grupo de Moléculas Anfifílicas y Polímeros Supramoleculares
Departamento de Química Orgánica. Facultad de CC. Químicas
lucial06@ucm.es

Keywords: *Perylene bisimides, Self-assembly, Supramolecular Polymers*

Supramolecular polymerization constitutes a very active line of research in which a large variety of self-assembling units have been investigated. Among these systems, perylene bisimide derivatives (PBIs) are one of the most outstanding ones, with important applications in the fields of organic electronics or biomedicine.[1] In the last few years, our group has focused on *N*-annulated PBIs, where side chains have proven to play a vital role in the self-assembly process.[2,3] In the present project, the multistep synthesis of two enantiomers of *N*-annulated PBIs and their self-assembling features are reported (Fig. 1a). The large aromatic surface of these molecules favors their aggregation into supramolecular polymers mainly by the π –stacking of the aromatic units. These supramolecular polymers exhibit a helical structure, the helicity of which is determined by the stereogenic centers present in the aliphatic chains linked to the *N*-annulated core. The formation of supramolecular aggregates was firstly confirmed by variable-concentration ^{1}H-NMR experiments. However, the supramolecular polymerization mechanism has been studied by means of (VT) UV-Vis spectroscopy experiments, using decaline (Dec) as solvent (Fig. 1b). Plotting the absorbance at λ = 519 nm versus temperature evidences a sigmoidal fashion, characteristic of an isodesmic mechanism. In addition, chiroptical experiments have demonstrated the formation of helical supramolecular species (Fig. 1c) with mirror-image circular dichroism (CD) signals. Finally, the morphology of the aggregates has been visualized by Atomic Force Microscopy (AFM) showing ~3 nm high layered nanosheets (Fig. 1d).



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Synthesis of triarylated tryptophan trimers and tetramers

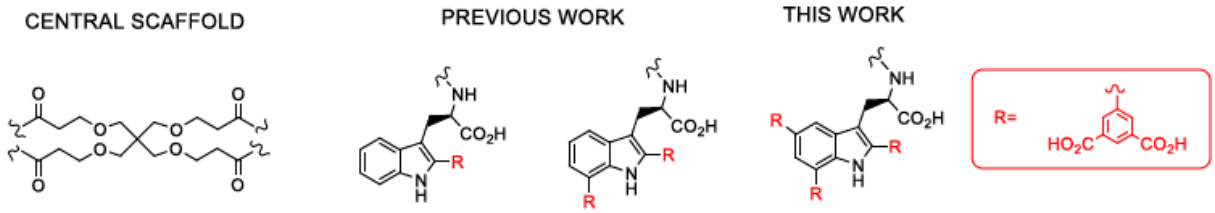
B. López, O. Martí-Marí, A. San-Félix

Instituto de Química Médica, CSIC
benatlop@ucm.es

***Keywords**: HIV, dendrimers, tryptophan*

The entry of HIV into host cells is a complex multi-stage process mediated by the viral envelope (Env) spike glycoproteins gp120 and gp41. Each of the entry steps is critical in the HIV life cycle and consequently represents an attractive target for the development of new antiviral agents. In fact, compounds that interfere with these early steps have several advantages over other existing therapeutic approaches that target intracellular viral enzymes such as reverse transcriptase or protease. Firstly, they may prevent healthy cells from being infected with HIV and thereupon block the spread of infection. Secondly, entry inhibitors have the advantage of acting before the virus is inside the cell, thus eliminating the need to cross the cell membrane. Finally, because of their distinct mechanism of action, entry/fusion inhibitors are likely to show remarkable efficacy against viruses resistant to other classes of antiretroviral drugs (e.g. reverse transcriptase, protease and integrase inhibitors).

We have recently described a novel generation of potent HIV and EV71 replication inhibitors that block viral entry. The prototypes contain in their tripodal or tetrapodal structures three or four tryptophan (Trp) residues bearing an isophthaloyl moiety at the C2 position of each side-chain indole ring. This earlier work is further extended by both shifting the position of the isophthaloyl moiety to C7 and synthesizing doubly arylated C2/C7 derivatives. One tetrapodal doubly arylated compound, **33 (AL-518)**[1], displays single-digit nanomolar potency against HIV-1 and is also the most potent inhibitor of EV71 replication. The fact that **33 (AL-518)** is 10-fold more potent against HIV-1 than the previous C2 prototype (**AL-471**)[2] is in consonance with its higher affinity for gp120 of the HIV envelope. Results from competition binding experiments with several monoclonal antibodies and molecular modeling studies strongly suggest that **33 (AL-518**) interacts with the tip and base of the gp120 V3 loop. Taken together, these findings further support the interest of this new generation of multivalent Trp-decorated derivatives as useful prototypes for anti-HIV/EV71 drug development. In this work, the synthesis of the triply arylated Trp derivatives with carboxy phenyl rings directly attached at C2 + C7 +C5 positions of the indole ring have been described.



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Synthesis and phenotypic study of molecules inspired on microbiota metabolites

M. Marqués Martínez, I. Arribas Álvarez, H. Vázquez Villa, B. Benhamú Salama

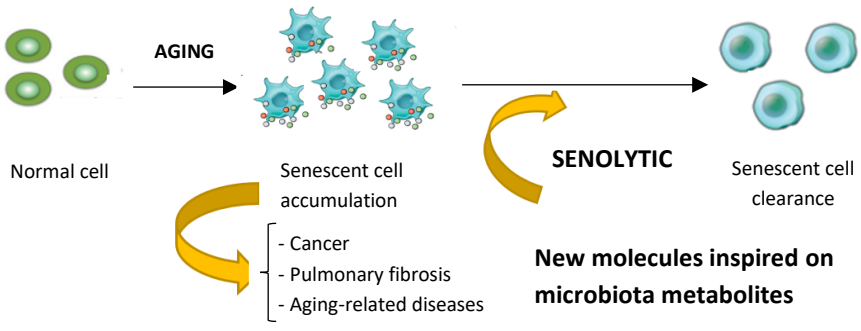
Department of Organic Chemistry, Faculty of Chemistry, Universidad Complutense de Madrid, 28040, Madrid, Spain.

e-mail: mamarq11@ucm.es

***Keywords**: Microbiota, phenotype, senolytics*

During aging, a number of biological processes are those that globally induce dysfunction of the whole organism, a fundamental mechanism that underlies many diseases in old age. Senescence —a process in which damaged cells, rather than dying, persist and become toxic to cells around them— is considered a cellular basis of human aging as senescent cells accumulate in human tissues, playing a key role in pathologies such as cancer or idiopathic pulmonary fibrosis.[1-3] There are two types of anti-senescence agents that emerge as promising drugs to delay, prevent, alleviate, or reverse aging-related diseases. Senomorphics can restore the appropriate cellular function, preserve viability, and prolong the lifespan, while senolytics induce apoptosis in senescent cells allowing the remaining non-senescent population to preserve or restore tissue function.[2,3]

Human microbiota and health develop and age hand-in-hand, and recent studies suggest the linkage between microbiota dysbiosis and aging-related diseases.[4] In this context, the research group is involved in a project focused on the development of new small molecules inspired on microbiota metabolites that could lead to the identification of novel drug candidates for the treatment of aging-related pathologies. Following a phenotypic screening of a focused library of synthetic compounds, UCM-13211 was identified as a senolytic hit that has entered a medicinal chemistry program for optimization in terms of activity and pharmacokinetic properties. The present Master Thesis, as a part of this program, aims at the synthesis of new related compounds using multicomponent stereoselective organocatalytic reactions. Synthesized compounds are currently under evaluation as potential senolytics in a β-galactosidase assay as a well-established model of cellular senescence, which could offer a novel approach for the treatment of aging-related diseases.



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Síntesis de redes orgánicas covalentes (covalent organic frameworks, COFs)

C. Merino Grande,[a] M. Martínez Fernández,[a] S. Royuela,[a] R. Gavara,[b] F. Zamora,[b] J. L. Segura[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040,*
[b]*Departamento de Química Inorgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049*
carlomer@ucm.es

***Keywords**: COFs, post-synthesis, fluorescence*

Las redes orgánicas covalentes (covalent organic frameworks, COFs) comprenden una clase emergente de materiales poliméricos cristalinos, porosos, de baja densidad y gran área superficial. Las principales características que les diferencian de los polímeros covalentes clásicos es que son estructuralmente prediseñables, sintéticamente controlables y funcionalmente manejables[1]. Es decir, sus propiedades pueden ser moduladas mediante procesos de pre-síntesis o post-síntesis al introducir funcionalidades novedosas sin alterar la topología de la red[2]. A su vez, los COFs se clasifican en bidimensionales (2D), en los que el enlace covalente está restringido en el plano de la red, y tridimensionales (3D), en los que se extiende a lo largo de las tres dimensiones del espacio.

En el presente trabajo se realiza la síntesis de un COF 2D, el $COF_{0,17}$-Alquino, mediante el método solvotermal. Posteriormente, se lleva a cabo su modificación post-sintética mediante la cicloadición 1,3-dipolar de Huisgen catalizada por Cu (I) con objeto de introducir en cada poro un fluoróforo, la molécula de Nile Red, formando el $COF_{0,17}$-NR. Todos los compuestos sintetizados son caracterizados empleando las técnicas adecuadas en cada caso.

Además, se realiza el estudio de las propiedades luminiscentes del $COF_{0,17}$-NR. Para ello, con el fin de evitar el fenómeno de extinción causada por agregación (Aggregation-Caused Quenching, ACQ), se lleva a cabo el exfoliado del COF formando nano-láminas (CONs) mediante dos métodos diferentes, la exfoliación asistida por ultrasonidos (UAM) y la autoexfoliación ácida (ASE). Así, a partir del análisis de los espectros de UV-Vis y de fluorescencia del $COF_{0,17}$-NR en mezclas THF/H_2O en distintas proporciones se busca comprender su comportamiento luminiscente y, también, evaluar qué método de exfoliación resulta más eficaz. En colaboración con la Universidad Autónoma, el $COF_{0,17}$-NR se incorpora, a distintos pH, en films mediante composites con matrices poliméricas para conseguir trasladar la fluorescencia al estado sólido.

Por último, se lleva a cabo la síntesis de un nuevo compuesto que podrá ser empleado como monómero C3 en procesos de post-síntesis de COFs para futuros proyectos.

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Development of organic CPL emitters

A. Montón Vicente, B. Lora Maroto, S. de la Moya Cerero

Departamento de Química Orgánica, Facultad de Ciencias Químicas. Universidad Complutense de Madrid. Ciudad Universitaria s/n 28040-Madrid, Spain

***Keywords**: BODIPY, circularly polarized luminescence, bioimaging*

Circularly polarized (CP) light possesses higher degree of definition than linearly polarized or non-polarized light, due to the presence of two additional variables for the former: the degree of circular polarization and the handedness (sign) of such polarization. Both variables are respectively quantified by the module and the sign of the *luminescence dissymmetry factor*, g_{lum}.[1] The high-definition character of the CP light envisages the microscopy based on *circularly polarized luminescence* (CPL) as a novel, high-resolution bioimaging technique to be exploited.[2] Nevertheless, this new microscopy (CPL microscopy) is still in the stage of development, mainly due to difficulties in both the synthetic development of proper CPL-active bioprobes and the establishment of a handy optical instrumentation to detect the CPL signals coming from such biomarkers.[2]

This communication describes preliminary results regarding the synthetic development of a selected battery of organic CPL emitters acting as CPL-active bioprobes (see Figure 1) and aimed at future studies for advancing CPL microscopy. The battery was attained on the basis of engineering BODIPY dyes to specifically probe different cell organelles (mitochondria, lipid droplets, lysosomes, etc.), and to enable CPL with proper CPL bright,[3] in different spectral regions (from green to red) and with different circular-polarization handedness.

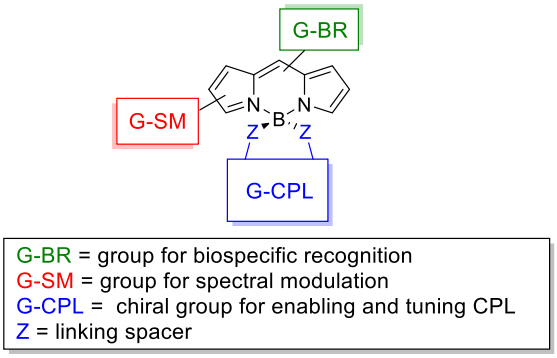

Figure 1. Schematic view of the structure of the developed BODIPY-based CPL bioprobes.

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Carbon nanostructures as multivalent platforms for biological applications

G. I. Nieto Ortiz,[a] J. Cabrera González,[a] B. M. Illescas Martínez,[a] and N. Martín[a]

[a]*Organic Molecular Materials Group, Facultad de Ciencias Químicas, UCM, Avda. Complutense s/n, 28040, Madrid, Spain*
e-mail: gemnieto@ucm.es

***Keywords**: DC-SIGN, nanostructures, porphyrin.*

DC-SIGN is a lectin expressed in the plasma membrane of certain cells that recognizes carbohydrates through multivalent interactions. This receptor is involved in the first stages of the infection process by some viruses, such as Ebola, Dengue, Zika and HIV.[1]
In this context, multivalent systems based on hexakis adducts of [60]fullerene decorated with carbohydrates have been reported. These glycomimetic nanostructures named glycofullerenes have shown a remarkable response to inhibit the viral infection process of Ebola, Dengue and Zika.[2]
Along this project, a synthetic route to obtain new asymmetric mannose-functionalized glycofullerenes, and their chemical binding to a porphyrin scaffold is described. It is hoped that these porphyrin-cored conjugates will have potential biomedical applications as fluorescent probes with antiviral activity.

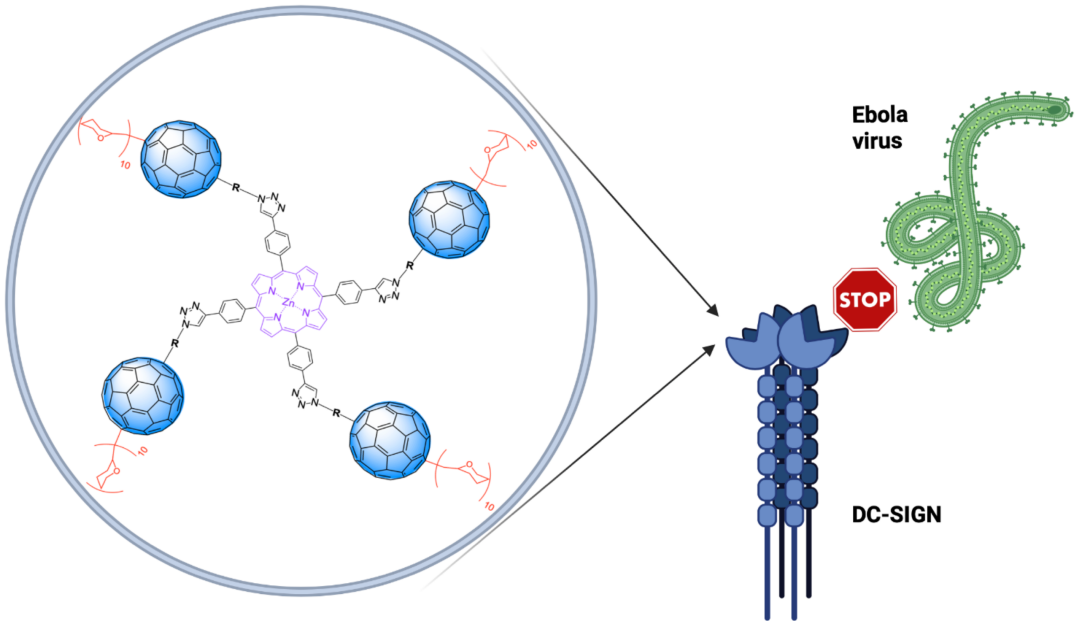

Figure: Glycofullerenes coupled to a central porphyrin scaffold as efficient inhibitors of Ebola virus.

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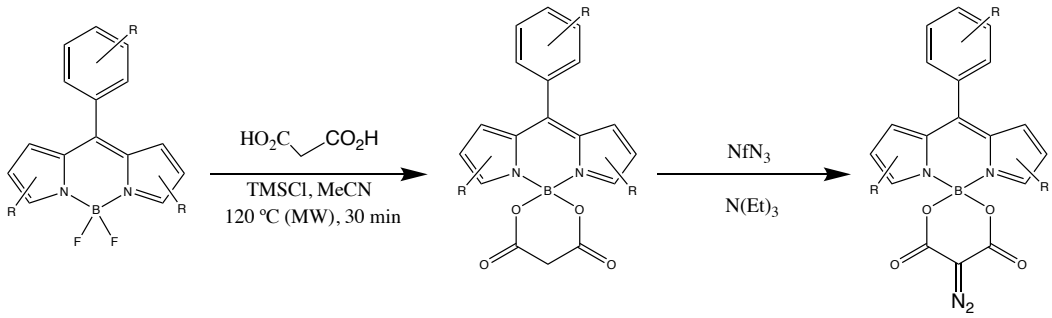
Synthesis and Functionalization of new Diazo BODIPY dyes.

L. Pastor, L. Maierhofer, J.L. Chiara

Instituto de Química Orgánica General, CSIC, Madrid.
lapast02@ucm.es

***Keywords**: BODIPY, diazo compounds, biolabeling.*

The main objective of this project is the design of new reactive fluorescent dyes for biolabeling and for the preparation of multichromophoric molecular nanoparticles based con fullerene. This work describes the synthesis of the first examples of diazo-BODIPY dyes via a two-step process involving the exchange of 2F on boron to a malonate group, followed by a highly efficient diazo transfer reaction with nonaflyl azide[1] in the presence of a base. Subsequent functionalization of the 2-diazomalonic group under rhodium catalysts, allowed us to obtain new chromophores with different attached groups.[2] The photophysical properties will be studied.



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New synthetic methodologies based in allenes, alkynes and bioactive heterocycles

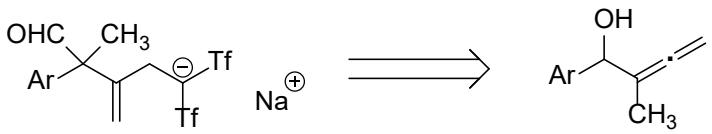
B. Peñín del Río,[a] T. Martínez del Campo,[a] P. Almendros[b]

[a]*Grupo de Sistemas Insaturados y Heterociclos Bioactivos, Departamento de Química Orgánica, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid;* [b]*Instituto de Química Orgánica General, IQOG, CSIC, Juan de la Cierva 3, 28006-Madrid.*

e-mail: beapenin@ucm.es

Keywords*: allene, β,γ-unsatured aldehyde, synthetic methods.*

The search for new synthetic routes to obtain β,γ-unsatured aldehydes is of interest due to be versatile intermediates in organic synthesis.[1] On the other hand, the presence of fluorine-containing groups in an organic compound confers it unique chemical and pharmaceutical properties.[2] In this context, increasing attention is being given to the SO_2CF_3 (Tf) group due to its strong electron-withdrawing ability coupled to a mild lipophilicity, which resulted in a bioavailability improvement.[3] Recently the use of allenes has increased to prepare advanced materials and for the beginning of lots of synthetic routes.[4] The use of metal catalysis helps to have an exquisite selectivity in terms of chemo-, site-, and stereo-selectivity. In continuation of our interest in allene chemistry,[5] we decided to examine the reactivity of α-allenols with Yanai's reagent to obtain a new protocol for the synthesis of β,γ-unsatured aldehydes.



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Síntesis de nuevos derivados selenados y evaluación 'in silico' de sus propiedades farmacológicas.

J. Prado Rodríguez,[a] E. Domínguez-Álvarez[a]

[a]*Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas (IQOG-CSIC).*
e-mail: jjprado1996@gmail.com

***Keywords**: selenoesters, chemopreventive, antibacterial*

In recent decades, the number of diseases caused by drug-resistant bacteria and cancer cells has increased considerably. This, together with the increase in the mortality rate caused by cancer[(1)] and the arising of the non-tratable bacterial infections, has forced the scientific community to explore new ways to obtain drugs with enhanced antitumor activity and with the ability to inhibit bacterial resistance mechanisms.

The objective of this project is to design and synthesize new selenoesters that can be used as antitumor and/or antibacterial agents from various α-haloketones and styrene oxide. Several studies realised by our team have shown the potential of various selenoesters for the treatment of diseases, showing chemopreventive activity, anticancer, inhibitor of the tumor mechanisms of drug and antibacterial resistance[(2; 3)].

In this work, twenty-eight new selenoesters with a wide variety of halogenated substituents have tried to be synthesized using a previously optimized synthetic process; obtaining seventeen of them with an appropriate purity to carry out an evaluation of their biological activity. Additionally, pharmacological activity of the obtained products were evaluated by computational simulation.

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Synthesis of tau protein ligands for the early diagnosis and treatment of tauopathies

P. Ramírez Veliz,[a b] F. Sánchez-Sancho,[a] S. Roscales García,[b] A. García Csákÿ[b]

[a]*Medicinal Chemistry Institute, Spanish National Research Council (CSIC), Juan de la Cierva 3, 28006, Madrid, Spain*

[b]*Pluridisciplinar Institute, Complutense University of Madrid, Paseo Juan XXIII 1, 28040, Madrid, Spain*

pabramir@ucm.es

***Keywords**: Tau, EIS/QCM, Alzheimer*

Tau is a protein bonded to microtubules that helps to stabilize such neuronal structures under physiological conditions. However, specific neuropathologic events can lead to abnormal aggregation of tau, and therefore, causing neurodegenerative diseases called tauopathies, which affect millions of people around the world. Alzheimer's disease (AD) is a well-known case of tauopathy where tau hyperphosphorylates, causing it to aggregate in insoluble forms, generating helical filaments (PHF) and neurofibrillary tangles (NFT). These aggregates promote neuron and connectivity loss, overall affecting our capability to remember, think and understand.

Taking advantage of such aggregates, in previous research projects we were able to identify different chemical structures with high affinity for those pathological forms of tau protein. In this project, we functionalize an oxindole-derived nucleus that showed affinity for tau protein aggregates via Surface Plasmon Resonance (SPR) analysis, in order to use it in voltammetry methods and modern electrochemical techniques like Electrochemical Impedance Spectroscopy (EIS) and/or Quartz Crystal Microbalance (QCM) techniques, with the objective of discovering new sensitive methods for the early diagnosis of AD alternative to the current postmortem histopathological methods.

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Synthesis and characterization of new derivatives of BODIPYs for optical and/or biomedical applications.

M. San Eusebio Álvaro[a], M. J. Ortiz[a], A. R. Agarrabeitia[a].

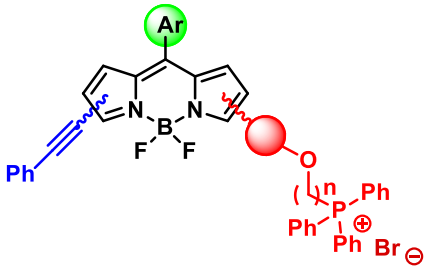
[a]*Departamento de Química Orgánica, Facultad de CC. Químicas, Universidad Complutense de Madrid, Ciudad Universitaria s/n, 28040, Madrid, Spain.*
e-mail: mirisane@ucm.es

***Keywords**: BODIPY, Bioimagen probes, Mitochondrias.*

Mitochondria are organelles present in almost all eukaryotic cells responsible for the production of energy in the form of ATP through cellular respiration. The set of mitochondria in the cell has a dynamic character that is regulated by complex mechanisms of cellular communication, so their damage is involved in numerous pathological processes, including cancer.[1] Although a wide variety of fluorescent probes are currently known for the specific visualization of mitochondria,[2] they have numerous limitations. Therefore, the development of new fluorescent probes as specific markers for these organelles is very important.

New probes should fulfill several criteria: low toxicity in the absence of light, selective accumulation in mitochondria, high stability to favor removal from tissues, high absorption in the red region (λ_{abs} > 620 nm, within biological window) to maximize light penetration[3] and should also good water solubility, possessing at the same time a hydrophobic moiety to facilitate their penetration in membranes.

BODIPY (boron dipyrromethene) dye is a privileged fluorescent scaffold to fulfil of the demanded requirements and design improved probes for bioimaging of mithocondria in living cells,[4] owing to the excellent photophysical and chemical properties of these stable fluorophores,[4] as well as their easy functionalization.[6] In the present work, we carried out the synthesis of three new probes based on this chromophore that have: 1) A mesityl group or a hydroxymethylphenyl group in the meso position has been carried out. 2) Styryl groups in positions 3 and 5 of BODIPY and phenylethynyl groups in positions 2 and 6, that allow absorption / emission in the red zone of the visible spectrum. 3) Hydrophobic chains with triphenylphosphonium groups that facilitate membrane penetration and specific labeling of mitochondria. Photophysical and biological studies will allow to validate the synthetic design of these systems as probes or even as mitochondrial teragnostic agents.



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Supramolecular polymerization of cyano-substituted luminogens

C. Sánchez Santos, C. Naranjo Calderón, R. Gómez Aspe, L. Sánchez Martín

Departamento de Química Orgánica, Facultad de CC. Químicas,
Universidad Complutense de Madrid, Madrid (Spain)
e-mail: cecisa02@ucm.es

***Keywords**: CN-OPV, Supramolecular polymers, Self-assembly*

In this project, the synthesis of a chiral cyano-substituted oligo-*para*-phenylenevinylene derivative (**(*R*)-CN-OPV**, Figure 1a) has been accomplished. The chemical structure of this compound allows an efficient self-assembly yielding helical supramolecular polymers by the operation of H-bonding interactions between the amides, π-stacking of the aromatic units and Van der Waals forces between the peripheral side chains.[1] The self-assembling features of **(*R*)-CN-OPV** have been investigated by different spectroscopic techniques, namely FT-IR, ^{1}H-NMR, UV-vis and circular dichroism (CD).

^{1}H-NMR experiments at different concentrations disclose the self-assembly of **(*R*)-CN-OPV**, as evidenced by the modifications of the chemical shifts of the aromatic and amide protons. Meanwhile, UV-vis and CD studies suggest the operation of a cooperative supramolecular polymerization mechanism, that involves nucleation and elongation steps.[2] The CD spectra demonstrates that the incorporation of stereogenic centers in the monomeric species leads to helical structures with a preferred handedness. Thus, whilst **(*R*)-CN-OPV** yields *P*-type helical aggregates, its enantiomer [**(*S*)-CN-OPV**], previously prepared in our research group, forms *M*-type helices (Figure 1b). Importantly, these helical aggregates afford highly emissive supramolecular structures as demonstrate the corresponding Circularly Polarized Luminescence (CPL) measurements. In short, the self-assembling and emissive features of the described CN-OPV derivatives hold great potential as luminogens for optoelectronic applications.[3]

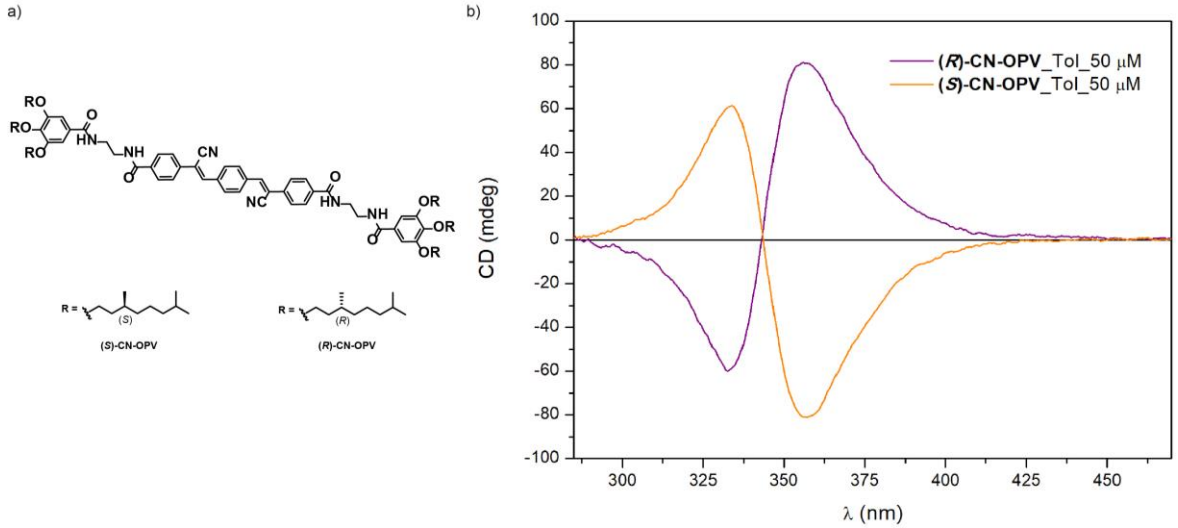

Figure 1. a) Chemical structures of the described **CN-OPV** derivatives. b) CD spectra of chiral **(*R*)-CN-OPV** (purple line) and their enantiomeric analog **(*S*)-CN-OPV** (orange line), 5 ·10^{-4} M in toluene.

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Allenes and bioactive heterocyclic compounds: Preparation of spiroindolenines

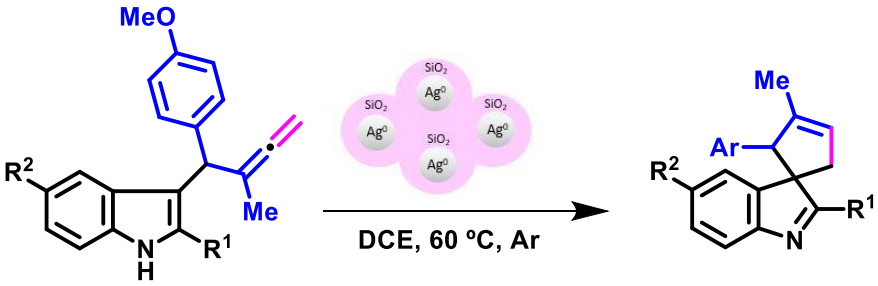
M. Tiemblo Martín,[a] P. Almendros,[b] A. Luna[a]

[a]*Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, España;* [b]*Instituto de Química Orgánica General, IQOG, CSIC, Juan de la Cierva 3, 28006-Madrid, España*

martatie@ucm.es

Keywords*: allenes, catalysis, silver nanoparticles*

Allenes are a class of unique compounds with two π-orbitals perpendicular to each other.[1] They also exist in many natural products with interesting biological activities, which together with their ability to undergo a variety of transformations using a wide variety of transition metals, makes them highly valuable synthetic precursors in preparative organic chemistry.[2] On the other hand, the indole nucleus is an important component of many natural and synthetic molecules with significant biological activity.[3] Attention to metallic nanoparticles has been increasing in the recent years due to their effective reactivity as catalysts. In this document, we report a controlled carbocyclization reaction of different C3-allene-tethered indoles in the presence of silver nanoparticles supported in silica achieving access to uncommon C3-spirocyclic indolenines.



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Nuevos diseños de nanotubos peptídicos tipo Venturi

B. Alvariño Ferreiro,[a] M. Amorín,[a] J.R. Granja*, [a]

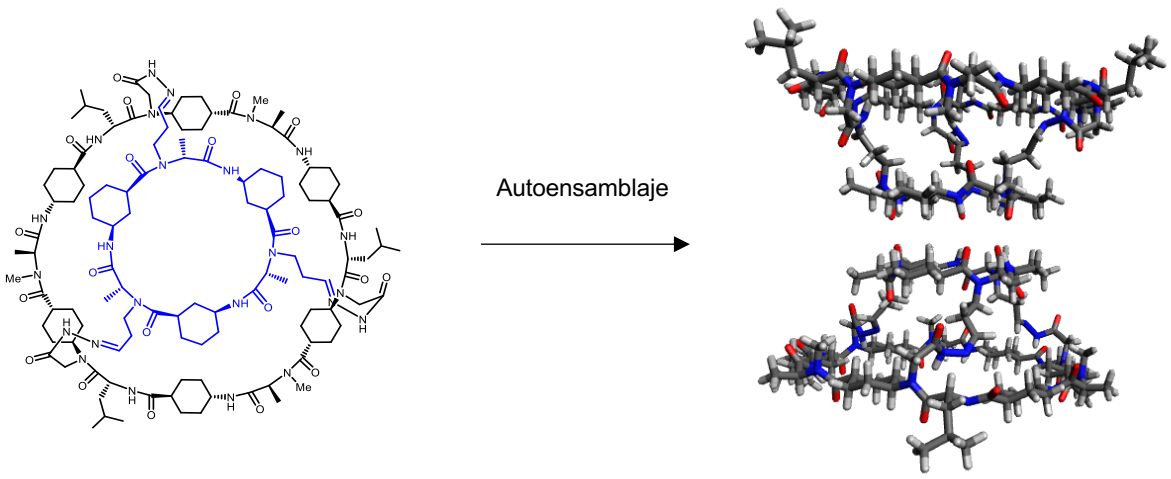
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

borja.alvarino@rai.usc.es

***Keywords**: Nanotubo, ciclopéptido, autoensamblaje.*

En los últimos años, ha ganado un mayor protagonismo la investigación centrada en el estudio de materiales de dimensiones nanométricas similares a los componentes básicos de los seres vivos, como el desarrollo de canales artificiales.[1] Sin embargo, hasta la actualidad no se ha podido emular la eficacia de los procesos biológicos, por lo que estudios en este campo siguen siendo de gran interés. En este contexto, nuestro grupo de investigación ha desarrollado previamente nanotubos tipo Venturi que presentan una zona interna de menor dimensión imitando la estructura y las propiedades de algunos canales iónicos.[2] Además, estos nanotubos podrían actuar como filtros seleccionando el paso de moléculas o remplazar canales proteicos dañados.

Este trabajo se centra en el diseño y en el desarrollo de una estrategia sintética para la construcción de nanotubos peptídicos tipo Venturi formados por dos ciclopéptidos de diferentes tamaños, un α,δ-ciclopéptido[3] y un α,γ-ciclopéptido. Estos ciclopéptidos estarán unidos entre sí mediante enlaces covalentes dinámicos que permitan mantener la capacidad de autoensamblaje.



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Enantioselective synthesis of chiral derivatives of bicyclo [1.1.1] pentane via copper-catalyzed asymmetric allylic alkylation

Sergio Barbeira Arán, Eva Rivera Chao, Martín Fañanás Mastral

Centro de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento en Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela
sergio.barbeira.aran@rai.usc.es

***Keywords**: bicyclo[1.1.1]pentanes, copper, asymmetric catalysis.*

The structural modification of biologically active molecules to improve their physicochemical properties is highly relevant and represents an important strategy for the design of new drugs.[1] Aromatic rings are ubiquitous structures in bioactive compounds. However, several studies suggest an existing correlation between the high number of aryl moieties in a molecule and bioavailability and toxicity problems.[2] A common strategy to tackle these difficulties lies on the replacement of planar aryl groups by three-dimensional cyclic rings. Among the bioisosteres of aryl groups, bicyclo[1.1.1]pentanes (BCPs) represent a promising alternative to replace 1,4-disubstituted aromatic rings, allowing the positioning of the substituents in a similar dihedral angle with an improvement of the physicochemical profile of the corresponding bioactive molecules.[3]

Previous work reported by other groups had shown that BCP−metal species, generated in situ from [1.1.1]propellane and organometallic reagents, can react in palladium and copper-catalyzed cross-couplings.[4] Here, we report a synthesis of α-chiral allylic BCPs by 1,3-difunctionalization of [1.1.1]propellane with Grignard reagents and allylic systems using copper catalysis (Figure 1). This mild protocol proceeds via initial addition of a Grignard reagent to [1.1.1]propellane followed by an asymmetric allylic substitution of the resulting organometallic intermediate. After studying the performance of various types of ligands, we found that a Cu NHC complex containing a sulfonate group provided the best results. Also, the solvent, copper salts and the leaving group play an important role in the outcome of the reaction.

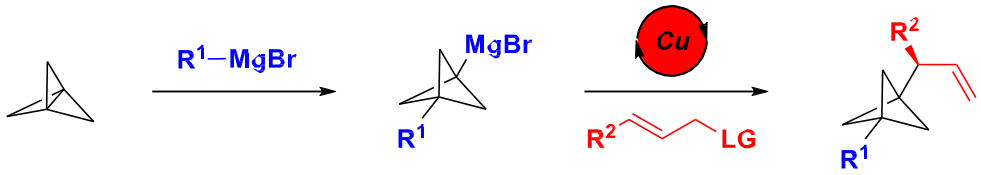

Figure 1.

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Development of Catalytic Pd(II)-WW domains

Sandra Baúlde, Soraya Learte-Aymamí, José L. Mascareñas,* M. Eugenio Vázquez

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Departamento de Química Orgánica. Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
sandra.baulde@rai.usc.es

***Keywords**: Metallopeptides, peptide engineering, catalysis*

The generation of artificial metalloenzymes with catalytic properties in living cells is a major research challenge at the interface between catalysis and cell biology. These new hybrid metal/protein systems increase the selectivity of the metal catalysts and allow new chemical transformations in cellular environments.1

In this project, we have studied a set of catalytic metallopeptides based on a short β-sheet scaffold derived from the WW domains. WW domains are small protein modules of about 30 amino acids, involved in the regulation of many cellular processes through protein-protein interactions. Structurally, these domains consist of triple-chain of antiparallel β-strands. Their small size, compact fold, and lack of disulphide bridges, have made WW domains an ideal model for study protein fold and stability, and a convenient scaffold for our engineering purposes.2

Taking as a reference the natural sequence of WW domain, we have designed, synthesized, and studied a series of rational mutants that contain two His residues in different positions to create a chelating site for Pd(II) (Fig. 1, left). Finally, in vitro reactivities were studied using the depropargylation of the fluorogenic probe HBTPQ as reaction model (Fig. 1, right).

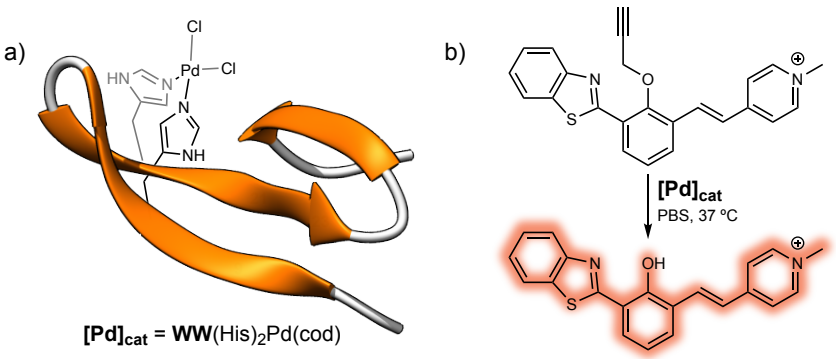

Figure 1. Left: Representation of the engineered mutant with the His pairs linked to Pd (II). Right: catalytic uncaging of HBTPQ and formation of the emissive fluorophore

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Towards the synthesis of molecular wires based on oligoacenes containing cyclobutadiene rings

Rebeca Calviño, Dolores Pérez

Centro Singular de Investigación en Quimica Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela

rebeca.calvino@rai.usc.es

***Keywords**: Arynes, cycloaddition reactions, CB-oligoacenes.*

Conjugated polycyclic hydrocarbons that incorporate cyclobutadiene (CB) rings have unique electronic properties, derived from the combination of aromatic and antiaromatic currents in their structure.[1] Derivatives with linear fusion, which can be considered as analogues of acenes (*CB-oligoacenes*) are of special interest due to their potential use as "molecular wires" (Fig 1). In the last few years, our research group has developed convergent methods for the construction of linear HPAs using aryne chemistry,[3] including the synthesis of oligoacenic molecules with CB rings through [4+2] cycloaddition reactions of an aryne derived from benzo[*b*]biphenylene.[4] In this context, this project has focused on the study of alternative routes for the synthesis of various CB-oligoacenes. In the first part, the study of the [2+2] cycloaddition of arynes has been carried out through the generation of these unstable species under photochemical irradiation conditions, using both the well-known *o*-(trimethylsilyl)aryl triflates **I** as aryne precursors or the new photolabile esters **II** or **III**. In the second part, we have also addressed the synthesis of bistriflates **IV**, as potential precursors of the biphenylene-based bisaryne **V**.

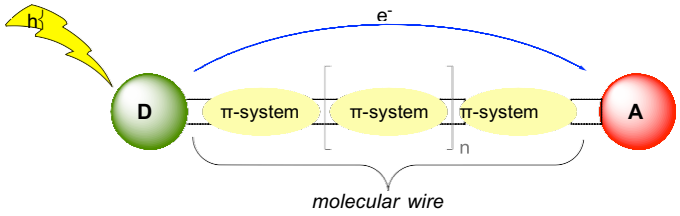
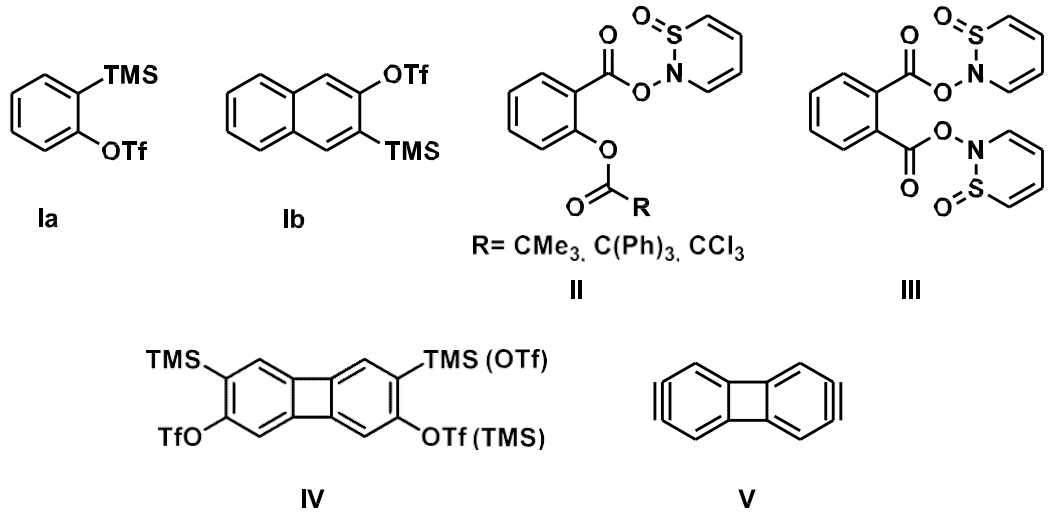


Figure 1



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New Chiral Inductors in the Remote Control of PPAs

P. Cid Prieto,[a] E. Quiñoá Cabana,[a] F. Freire Iribarne[a]

[a]*Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Universidade de Santiago de Compostela. C/Jenaro de la Fuente s/n; 15782, Santiago de Compostela, Spain*
e-mail: pablo.cid.prieto@rai.usc.es

Keywords: *PPAs, teleinduction*

Over the last years, the scientific community has achieved great progress in the field of helical polymers with a predominant helix sense due to their attractive properties. Consequently, design, synthesis and structural elucidation studies have been carried out, allowing the application of this compounds in different fields such as material science, chemical sensing, asymmetric synthesis and separation of enantiomers. Poly(phenylacetylene)s (PPAs) are a type of dynamic helical polymers[1] that can be defined by two parameters: the helical sense of the helix, determined by AFM and Circular Dichroism (CD), and the helical pitch, that make the polymer more or less extended, easily determined by CD/UV-Vis. The main goal of this research is to evaluate the impact of the teleinduction phenomenon when an achiral flexible spacer (glycine) is introduced between the PPA backbone and the chiral amino acid. In order to test the effectiveness of this phenomenon have been modified the chiral amino acids (L-phenylalanine and L-valine) thus creating a new category of polymers derived from PPA.

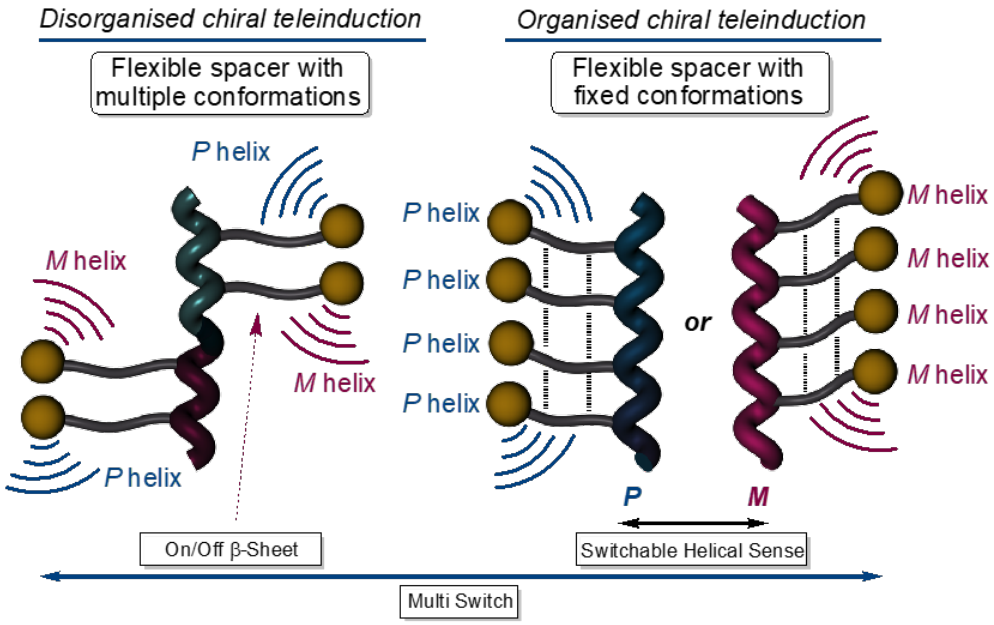

Figure 1. *Conceptual representation of the chiral teleinduction produced in a helical polymer when an achiral flexible linker is fixed by internal supramolecular interactions.*[2]

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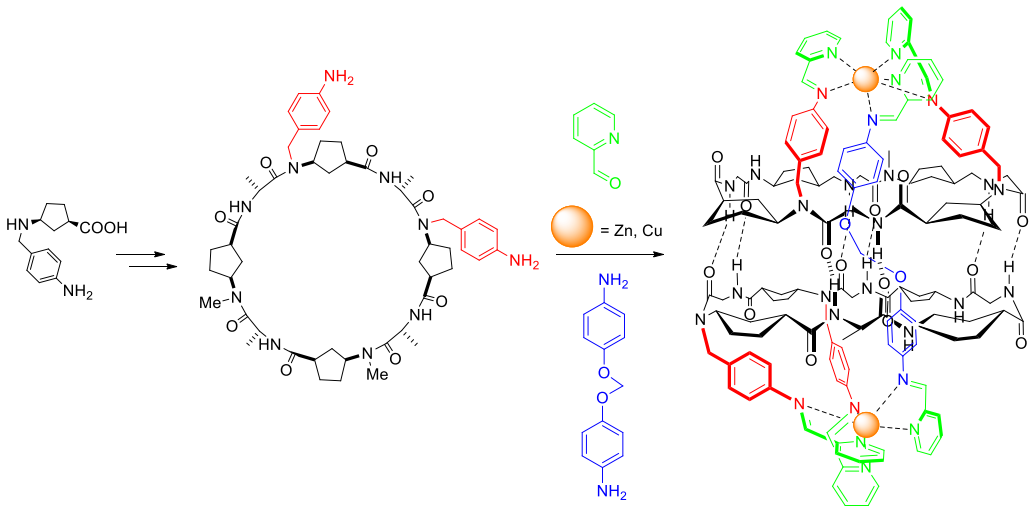
Supramolecular capsules based on cyclic peptides with caps

A. de Manueles, [a] V. López, [a] M. Amorín, [a] J. R. Granja

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Dpto. de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
alejandro.de.manueles@rai.usc.es

Keywords: *Capsules, Metal Recognition, Self-assembly.*

Supramolecular polymers can be constructed by stacking macrocycles formed by flat-shaped peptides rings.[1] The strategy is based in the self-assembly of the components by hydrogen bonds between amide groups.
Using this approach, our group has been able to synthesize different supramolecular structures such as nanotubes, nanoreactors or capsules by functionalizing their cyclic peptides.[2] The capsules are composed by two self-assembled peptides rings that are enclosed by caps in both ends.[3] The properties of the dimeric capsules depend on the type of molecular cap and the cyclic peptide used, as well as the empty space generated that can be occupied by diverse types of molecules modifying its properties and reactivity.
Herein, we present a strategy based on a metallo-supramolecular self-assembly.[4] Our objective is to synthesize a novel functionalized aminoacid to introduce two residues in a cyclic octapeptide. The aniline ends in presence of six pinacolinaldehydes and two metals would induce the self-assemble forming both imine bond and coordinative nitrogen-metal bond during the same process, resulting in the capture of a dianaline chain in the center of the capsule when the metal has octahedral coordination. In addition, the other objective is to study the equilibrium between octahedral and tetrahedral coordinations of the metal to pursue the release of the captured molecule.



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OLIGO (*p*-FENILENETINILENO) DERIVATIZADO CON ALENO COMO INDUCTOR QUIRAL EN POLÍMEROS HELICOIDALES

N. Fiz Alvar, [a] F. Freire Iribarne, [a] E. Quiñoá Cabana

[a] *Departamento de Química Orgánica, Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Universidad de Santiago de Compostela, 15782, Santiago de Compostela, Spain.*
e-mail: noemi.fiz@rai.usc.es

Keywords: *Allene, helicoidal polymers, rigid achiral spacers.*

The helix is a structural motif responsible for the function of biological-relevant molecules such as proteins or DNA. This structure–function relationship has prompted us to study other non-natural helical materials. More specifically, dynamic helical polymers, such as poly(acetylene)s (**PA**)s have attracted the attention of researchers in recent year, because they are formed by a chain of polyenes (π conjugates) whose helical sense and/or elongation of the helical structure can be modulated by the presence of external stimuli. [1]

In helical polymers, the induction of a specific helix sense is due to the chiral center of the monomeric units.[2] In this project, we will investigate how the axial chirality of 1,3-diethynylallene (DEA) units will be transmitted to the polyene backbone and the effect of the introduction of rigid achiral spacer, the oligo (*p*-phenyleneethynylene) (OPE).

These DEAs have been selected as they are increasingly used as building blocks due to their unique chiroptic properties and configurational stability. DEAs have been incorporated into chiral macrocycles, acyclic oligomers, as well as supramolecular structures.[3]

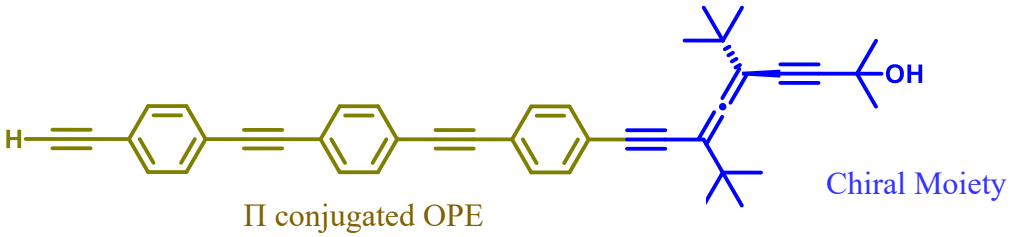

Figura 1. Structure of the monomer.

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Design and synthesis of pH sensitive sensor probes

P. Fulias Guzmán[1], A. Rioboo Vidal[1], I. Lostalé Seijo[1], J. Montenegro García[1]

[1] Departamento de Química Orgánica, Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Universidade de Santiago de Compostela, 15782, Santiago de Compostela, Spain
e-mail: patricia.fulias@rai.usc.es

***Keywords**: fluorophors, ratiometric, cells*

The use of fluorescence as a characterization technique has many advantages due to its low cost, simplicity and sensitivity. Furthermore, within the biological field, it has multiple applications such as the study of the environment where a molecule is locate based on its anisotropy or viscosity, the energy transmition between two molecules (FRET, Förster Resonance Energy Transfer) or the visualization of the route of internalization of a drug.[1] Regarding this last approach, pH-sensitve and ratiometric fluorophores are especially usefull for *in vivo* tests in a harmless way to the organism under study. By having two or more wavelengths of fluorescence emission or absorption, a more precise characterization of the pH value of the medium is achiving, avoinding changes in intensity due to instrumental or dilution factors. With these molecules, the internalization pathway can be tracked to know their target and the effects it causes. Thus, these molecules provide valuable information about the internalization pathways and target areas of new therapeutic agents.[2]

Herein, we describe the synthesis and characterization of a pH-sensitive ratiometric fluorophore, 5 and 6 C.SNARF-1, and its coupling with Mastoparan X, an antimicrobial peptide naturally found in wasp venom. Subsequently, the peptide behaviour and internalization pathway has been studied in HeLa cells thanks to SNARF fluorescence properties. [3]

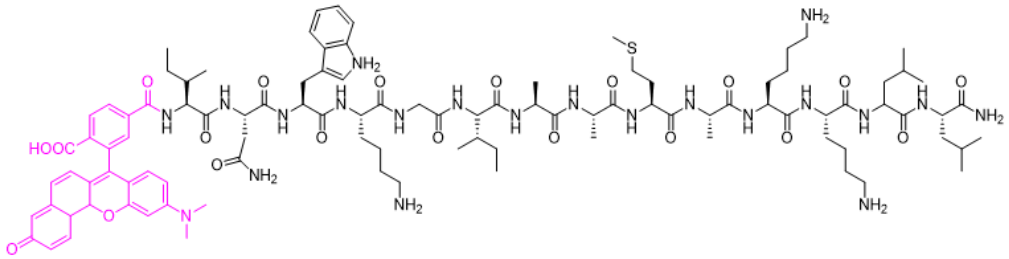

Figure 1. Mastoparan X peptide (black) and C.SNARF-1 (pink)

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Peptide coiling through non-canonical chromophoric amino acids

C. Gullón Conde, J.M. Martínez Parra, J. Bergueiro Álvarez, J. Montenegro García

Departamento de Química Orgánica, Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CiQUS), Universidad de Santiago de Compostela, Campus Vida s/n, E-15782 Santiago de Compostela, España
e-mail: cayetana.gullon@rai.usc.es

***Keywords**: Self-assembly, Alpha helix, Coiled-coil*

The alpha helix is the most abundant secondary structure in natural proteins.[1] Therefore, this structural motive offers new design opportunities of high importance to mimic and control the protein biological functions.[2] In detail, the alpha helix topology can fold into coiled-coils structures stabilized by the leucine zipper, which can be rationalized by the extended knobs into holes (KIH) model.[3-6] Particularly, the KIH model allows the prediction of supercoiling by hydrophobic interactions between two helixes resulting in a helical supramolecular aggregate.
We herein propose the extension of the KIH motif with non-canonical amino acids that will allow us to spectroscopically follow and determine the folding of alpha helical peptide into coiled-coil structures. For this purpose, we selected a small hydrophobic chromophore such as nitrobenzfurazan (NBD), which we have positioned in polyglutamic acids scaffolds. The chiro-optical properties of the resulting supramolecular assemblies were tracked by UV and CD of giving insights into the peptide secondary structure and the coiled coil folding.

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Pd(II)-catalyzed formal cycloaddition between alkenyl amines and dienes via C(sp2)-H activation

I. Huertas Morales[a], M. Font[a], M. Gulías[c]

[a]*Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS),* [b]*Departamento de Química Orgánica*
e-mail: ivanhuertas16@gmail.com

***Keywords**: C-H activation, Cycloaddition, Asymmetric*

Transition metal-catalyzed cycloaddition reactions, by allowing the formation of two bonds and one cycle in a single step, are very appealing from a synthetic point of view.[1,2] In line with our research group efforts to develop new methods for the assembly of heterocycles by means of metal-catalyzed in cycloaddition reactions via C–H activation processes, we report an intensive study of the Pd-catalyzed reaction between allyl amines or 2-alkenylanilides and dienes. Preliminary studies revealed the viability of the asymmetric version of this transformation.

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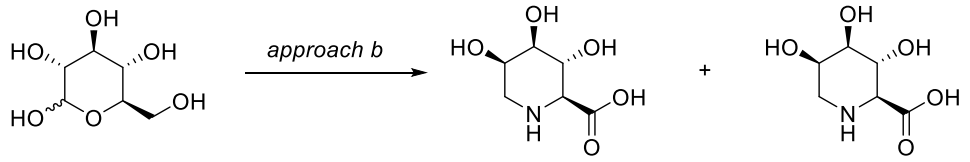
Divergent syntheses of iminocyclohexitols and polydroxylated pipecolic acids

Paula Martín González, Ramón J. Estévez and Juan C. Estévez*

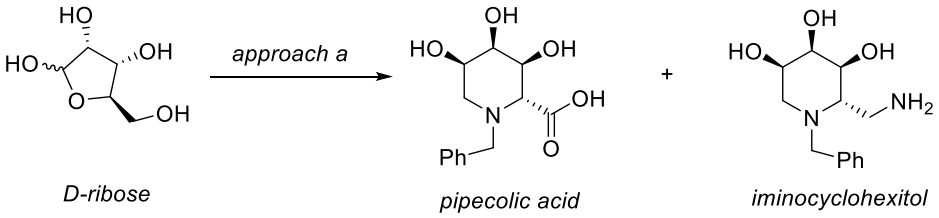
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares, Universidade de Santiago de Compostela, Spain
e-mail: paula.martin.gonzalez@rai.usc.es

***Keywords**: iminosugars, sugar imino acids, glycosidase inhibition*

Carbohydrates are an abundant source of useful scaffolds for the stereoselective synthesis of functionalized carbo- and heterocycles.[1] Two approaches have been dessigned for this purpose. Thus, the new ring can be generated from an open chain carbohydrate derivative (*approach a*). The alternative approach (*approach b*) involves the generation of a bicyclic derivative constituted by the original sugar ring and a new ring, and the ulterior opening of the sugar ring. In recent times, the generation of the carbo- or heterocyclic ring has been approached by an inter- or intramolecular a double displacement of a sugar ditosylate, dimesylate, ditriflate or dibromide by a properly nucleophile. Specifically, the *approach b* has only been applied to the preparation of azetidine iminosugars [2] and tiosugars [3].
Here we report a new contribution to this field, which consists of two novel divergent syntheses of iminocyclitols and polyhydroxylated pipecolics acids, starting from D-glucose (Scheme 1) and from D-ribose (Scheme 2), respectively.



Scheme 1



Scheme 2

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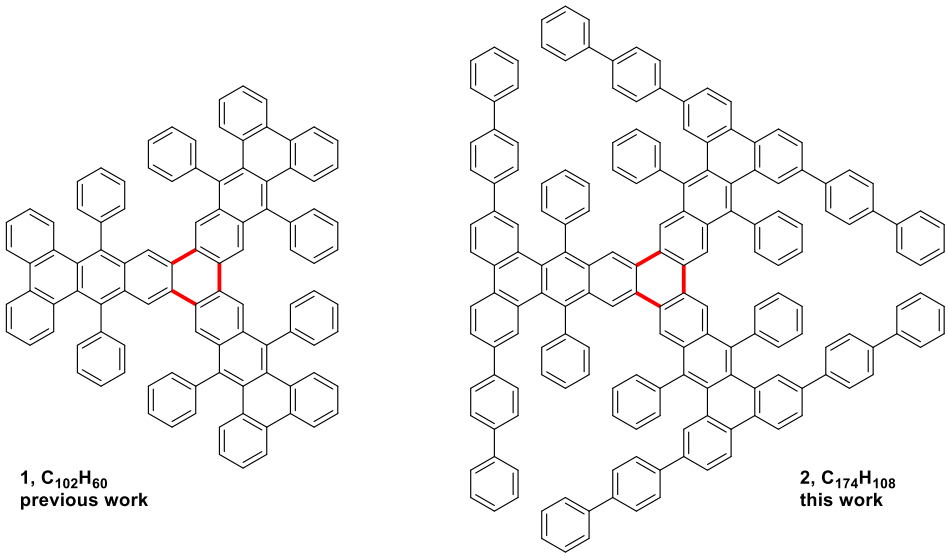
Synthesis of new nanoporous graphene precursors

A. Martínez Abelairas, Dolores Pérez, Diego Peña

[a]*Centro de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela,15782-Santiago de Compostela (Spain)*
e-mail: adrian.martinez.abelairas@rai.usc.es

Keywords: *(nanopore,graphene,arynes)*

Graphene derivatives are interesting carbon-based materials which have attracted a lot of attention in recent years. In particular, graphenes which include well-defined nanosize pores in their structure are appealing because can be used as molecular filters and sensors[2]. In 2019, our group prepared the hydrocarbon $C_{102}H_{60}$, which was used as a precursor of a triporous nanographene obtained by on-surface synthesis[1].In this work, we report our efforts to prepare compound $C_{174}H_{108}$, a precursor for a larger hexaporous nanographene with two different pore sizes. We synthesized this molecule by means of aryne chemistry, in particular by a Pd-catalyzed cyclotrimerization reaction.



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GREEN CHEMISTRY: ACCELERATED DENDRIMER SYNTHESIS PROCESSES

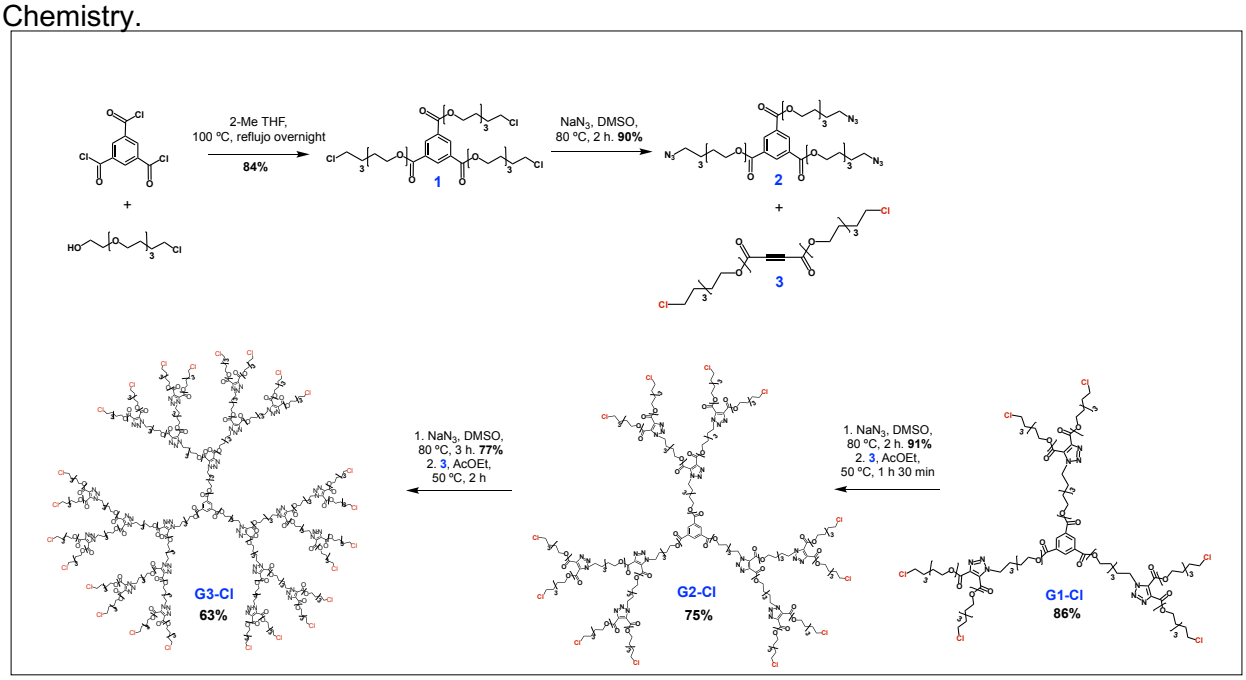
L. Martínez Reiriz, J.F. Correa Chinea, E. Fernández Megía*

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Universidad de Santiago de Compostela, C/ Jenaro de la Fuente s/n, 15782, Santiago de Compostela

lucia.martinez.reiriz@rai.usc.es

***Keywords**: Dendrimers, Click Chemestry, AAC*

Dendrimers[1,2] are highly branched polymeric macromolecules composed of repetitive layers (generations) from a repeating unit and the central core. So, a globular structure of nanometric size is formed, which has a well-defined and monodisperse structure. These characteristics make dendrimers to have multiple applications in different fields such as catalysis, biomedicine, materials science, etc., reason why it is necessary to approach its synthesis on a large scale. In this project, it was intended to develop a divergent gram-scale dendrimer synthesis with high generation, using thermal [3 + 2] azide-alkyne cycloadditions, in a reduced number of stages, with high yields and based on the principals of Green and Click Chemistry.



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Towards amphiphilic 2-aminomethylcyclopentanecarboxylic acid based α,β-peptides

Jorge Millán Lema, Ramón J. Estévez and Juan C. Estévez*

Centro de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento en Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela
e-mail: jorge.millan.lema@hotmail.com

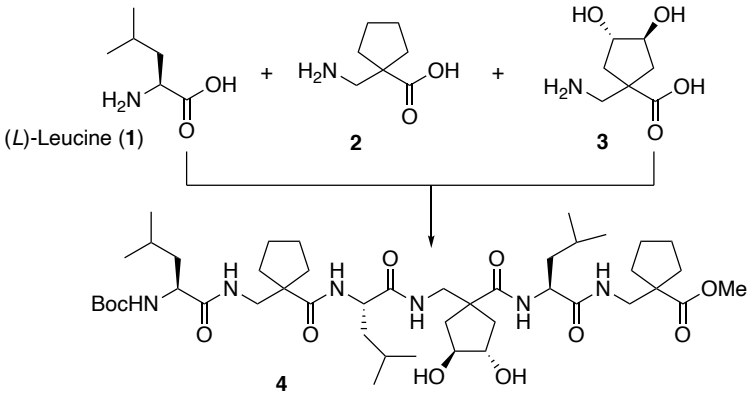
Keywords: *β-amino acids, peptidomimetics, amphiphiles*

Peptidomimetics are chemical structures capable of interacting with the same receptors and enzymes as natural peptides,[1] and although their structure does not necessarily have to be peptide in nature, most of them are modified peptides that incorporate a non-proteinogenic amino acid or are made up mostly or entirely of non-proteinogenic amino acids.[2] Therefore, there is currently great interest in the stereoselective synthesis of non-natural amino acids, mainly β- and γ-amino acids.[3] This is the first step towards access to conformationally restricted peptidomimetics (foldamers), which may improve the pharmacological limitations of α-peptides, mainly due to their conformational flexibility (side effects) and metabolic instability (low bioavailability).[4]

The search for versatile and efficient syntheses of β-amino acids is a very active area of research at present, most especially that of β-carbocyclic amino acids, because of the possibilities they offer for modulating the conformational rigidity of the β-peptides and α,β-peptides incorporating them.

As a contribution to an ongoing project aimed at the synthesis and structural studies of type **4** hybrid peptides, we now present the synthesis of the dihydroxylated 2-aminomethylcyclopentane carboxylic acid **3** and its incorporation into oligomer **4**.

Scheme 1



Preliminary studies on the folding and amphiphilic properties of this peptide will be also discussed.

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Synthesis of new porous materials for their use as absorbents in CO_2 capture.

M. Outeiral Valiño, A. Rumbo and M. Torneiro.

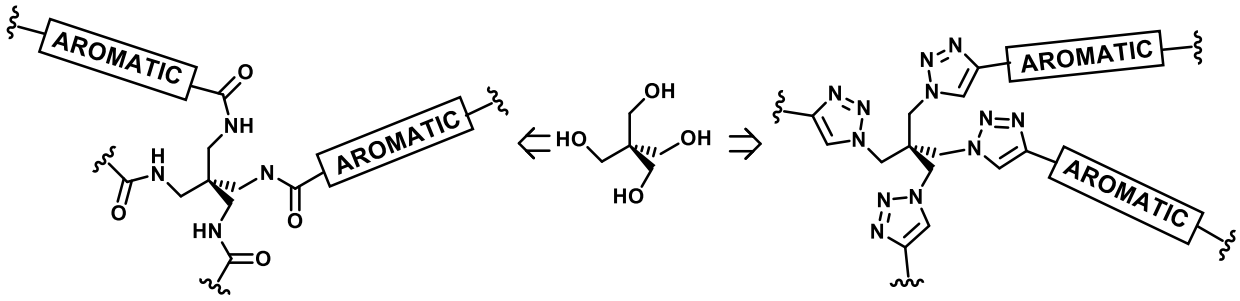
Organic Chemistry Department, Universidad de Santiago de Compostela, Galicia, Spain.
E-mail: mariacarmen.outeiral@rai.usc.es

***Keywords**: greenhouse effect, CO_2 absorption, microporous polymers.*

Porous aromatic structures, known as PAFs [1,2] (porous aromatic frameworks) are a class of materials with a diamond-like structure formed by tetrahedral centers to which multiple aromatic rings are attached through covalent bonds. The strong carbon-carbon bond network makes them stable under adverse chemical treatments showing characteristics such as their extreme hydrophobicity; additional existence of nitrogen-carbon or oxygen-carbon bonds originates dipolar-dipolar, hydrogen-bond and metal-coordination interactions for bonding of small organic molecules or metallic cations.

During the last decade microporous and mesoporous organic polymers are being used to selective adsorption and absorption of different media pollutant (gases as carbon dioxide, small aromatics as antibiotics, transitions metals as Hg^{+2}). The selective absorption/adsorption capacity of these materials is adjusted by the size of the pore and the chemical structure of the monomers that constitute it.[3]

PAFS have a rigid core of tetraphenylmethane, however, in the literature there can be found examples of porous materials with enhanced properties which benefit from certain flexibility in their structure. In our laboratory we aim to explore the role of flexibility and heteroatom content in PAFs for their use in the capture of carbon dioxide. In this context, we have designed new polymers containing the rather flexible tetrametylenemethane core in combination with rigid aromatic building blocks of different sizes and amide or triazol linkers that will serve as anchors for the pollutant molecules. In this communication, we will report our preliminary results towards the synthesis of these materials



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Post-synthetic superficial modification of gold nanoparticles

N. Pérez García, M. Paz Castañal, C. Vázquez Vázquez

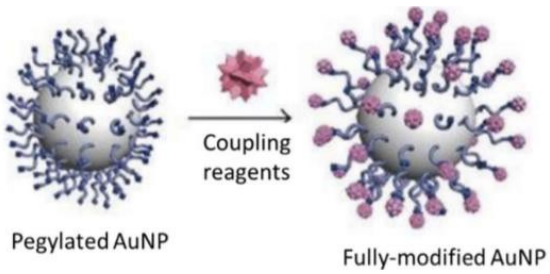
Facultad de Química, Universidad de Santiago de Compostela
Laboratorio NANOMAG, Universidad de Santiago de Compostela
AEMAT (Agrupación estratéxica de Materiais da USC)
e-mail: natalio.perez@rai.usc.es

***Keywords**: gold nanoparticles, post-synthetic modification, mixed-charge nanoparticles.*

The chemical, physical and biological properties of gold nanoparticles (AuNPs) strongly depend on the gold core shape and size and its surface stabilizing ligands functionalization [1]. Although the common way to diversify those ligands involves employing a wide range of modified thiols with the chemical groups of interest and other methods [2], our research group has recently developed a new methodology to diversify the chemical functionality from one single thiol ligand through coupling reactions, what allows a quantitative post-synthetic superficial modification of these gold nanoparticles (results pending publishing). With this new methodology, a new assay to evaluate the efficiency of the modifications carried is also developed and tested within this project.

In this research project was carried the successful functionalization of pegylated AuNPs using anhydrides as coupling reagents leading to their corresponding amides, allowing the successful modification of the superficial charges from its original cationic amino groups (from the polyethylene glycol ligands) to neutral (formal or zwitterionic) even anionic. This property was found to be susceptible of being modified as desired. In addition, these reactions could be carried out in water, cutting down the need of organic solvents.

The importance of being able of modifying the superficial charge of nanoparticles lays in its interaction with biological media and its efficiency in certain therapeutic approaches [3].



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Enantioselective copper-catalyzed borylative coupling between allenes and allylic dichlorides

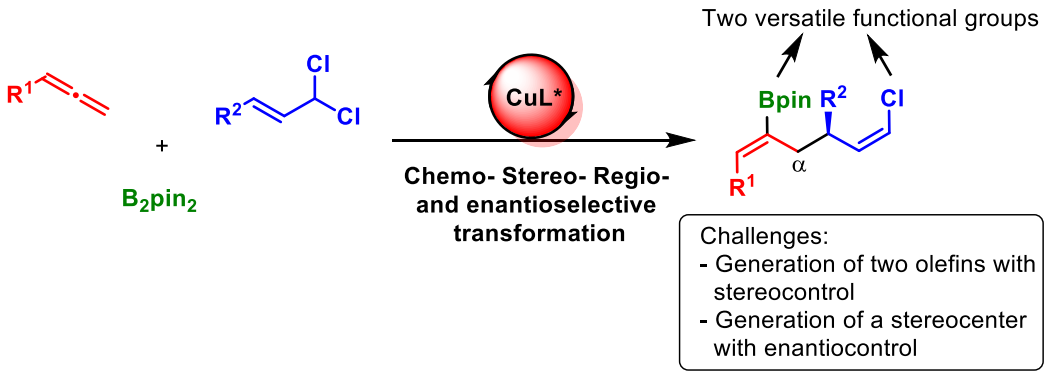
Martín Piñeiro-Suárez,[a] A. M. Álvarez-Constantino,[a] A. Chaves-Pouso,[a] M. Fañanás-Mastral [a]

[a] *Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain*
m.pineiro.suarez@usc.es

Keywords: *asymmetric catalysis, copper, multicomponent reactions*

Enantioselective catalytic methods, that allow simple and abundant starting materials to be converted into complex multifunctional chiral products in an easy and sustainable manner are in high demand.[1] In particular, access to chiral 1,5-diene structures is very important because they serve as building blocks in organic synthesis and are also found in many biologically active molecules.[2] However, the development of asymmetric strategies that provide these structures with high enantio- and stereoselectivity still remains a challenge. In 2014, Hoveyda reported a methodology to produce regio-, stereo-, chemo- and enantioselectively monofunctionalized 1,5-dienes based on a Cu-catalyzed multicomponent reaction of allenes, B_2pin_2 and allylic phosphates. This reaction involves the use of an allene as a precursor for a catalytic allyl copper reagent, which subsequently acts as a nucleophile in a S_N2' type substitution of the allyl phosphate.[3]

We envisioned that the use of allylic alpha-dichlorides in a related transformation would lead to the formation of chiral 1,5-dienes bearing both a boronic ester and an alkenyl chloride. This would represent a very versatile building block which could potentially open new synthetic pathways for the orthogonal functionalization of the diene structure.[4] We here present the development of a chiral catalytic system that allows the selective coupling of allylic diclorides, allenes and B_2pin_2 providing 1,5-dienes with excellent control of the regio- and stereoselectivity of the two olefins as well as the enantioselectivity of the generated stereocenter (Scheme 1).



Scheme 1.

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Ruthenium Promoted Deprotection Reactions in the Golgi Apparatus

J. Fernando Salgado Barca,[a] María Tomás Gamasa,[a] José Luis Mascareñas[a]

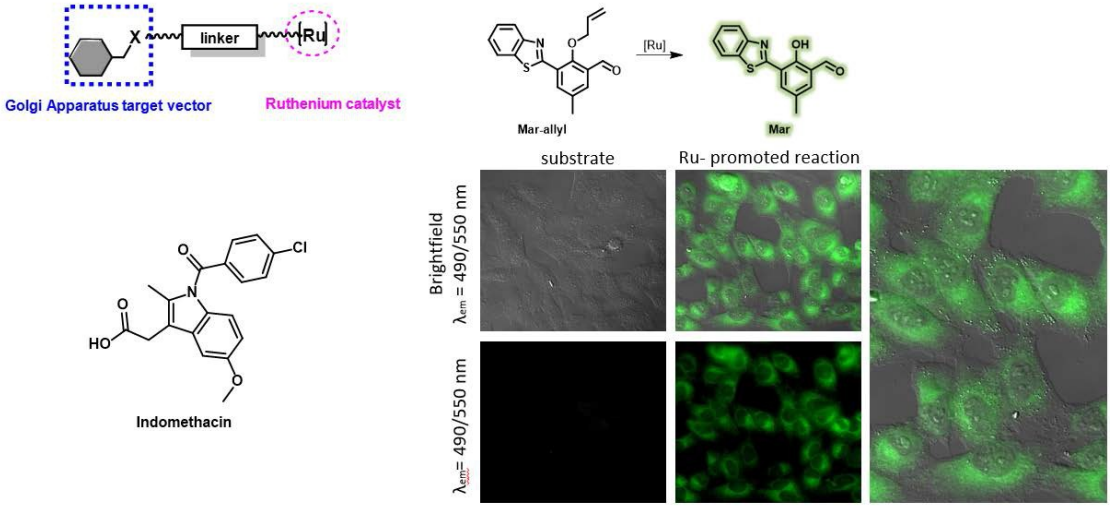
[a] *Dpto. De Química Orgánica, Centro de Investigaciones de Química Biológica y Materiales Moleculares (CIQUS), Universidad de Santiago de Compostela, 15782*
jesusfernando.salgado@rai.usc.es

***Keywords**: Bioorthogonal Chemistry, Transition metal catalysis, Organelle targeting*

Bioorthogonal chemistry refers to any chemical reaction that takes place within living systems without interfering with any native biochemical process.[1] In this context, our group has been involved in "on demand" synthesis of catalytic complexes and on the development of non-natural catalytic reactions that take place in such a hostile atmosphere as the cellular environment.[2]

A key factor to take into account in the development of bioorthogonal metal catalysis is controlling the localization of the desired process. Our group has been successful on preparing a ruthenium complex that accumulates in such an important organelle as mitochondria, promoting uncaging reactions inside this compartment.[3] However, targeting metal complexes to other organelles is a challenging task that remains to be overcome.

Herein we present the synthesis of a tailored catalytic system based on a ruthenium complex, designed to perform reactions in the Golgi apparatus. The targeting is achieved by an indomethacin molecule, unit that has proven to accumulate in the Golgi aparattus by inhibition of the COX-2 protein.[4] In addition to the synthetic development, we also present preliminar results of the reactivity of this system in live mammalian cells.



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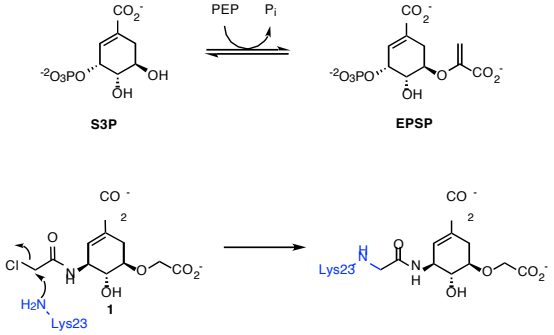
Development of Irreversible Ligands of EPSP Synthase for the Treatment of Tuberculosis

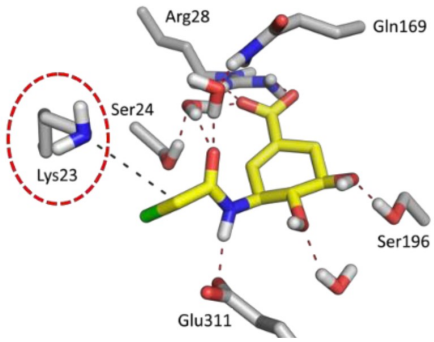
E. Sánchez Santos, E. Lence Quintana, C. González Bello

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Department of Organic Chemistry, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
estela.sanchez.santos@rai.usc.es

***Keywords**: tuberculosis, irreversible inhibition, EPSP synthase*

Despite the huge efforts recently made to fight against tuberculosis (TB), no major changes in its impact on human health have been achieved, since still 1.4 million people died from this disease in 2019. Even though the World Health Organization (WHO) established a milestone from 2015 to 2019 of 20% and 35% reductions in TB incidence and mortality, respectively, this goal has not been reached. This is mostly due to the increase and spread worldwide of multi-drug resistant strains of *Mycobacterium tuberculosis*, the causative agent of TB, which is also occurring faster as has been seen with delamanide and bedaquiline.[1] Therefore, it is urgent to search for new TB-drugs and approaches to face this global health challenge. In particular, it is vital to develop therapies with a new mechanism of action since bacteria have already developed sophisticated resistance mechanism against well-stablished and already exploited bacterial targets (cell-wall biosynthesis, protein biosynthesis, DNA and RNA replication and folate metabolism). Our research group is exploring the therapeutic potential of EPSP synthase (EPSPS), which is involved in the shikimic acid pathway in which chorismic acid is biosynthesized. This compound is the precursor in the synthesis of aromatic amino acids, folate cofactors, ubiquinone and vitamins E and K.[2] EPSPS is considered a good target for antibacterial drug discovery since: (i) the *aroA* gene, which encodes EPSPS from *A. baumannii* and *M. tuberculosis*,[2,3] proved to be essential *in vivo* and does not have any counterpart in human cells; and (ii) it may act as a virulence factor *in vivo* as the deletion of the *aroA* gene, which encodes EPSPS from *P. aeruginosa* and *S. typhimurium*, have been proven to afford satisfactory live oral vaccines in mices and calves, respectively.[4] EPSPS catalyzes the conversion of shikimate-3-phosphate and phosphoenolpyruvate into EPSP and phosphate. This project is aimed to develop an irreversible inhibitor capable of forming a stable covalent adduct, thus preventing the bacteria biological function. The target molecule, compound **1**, bears a "latent electrophile" that become activated towards covalent bond formation upon binding to EPSPS, being hidden to non-specifics targets.





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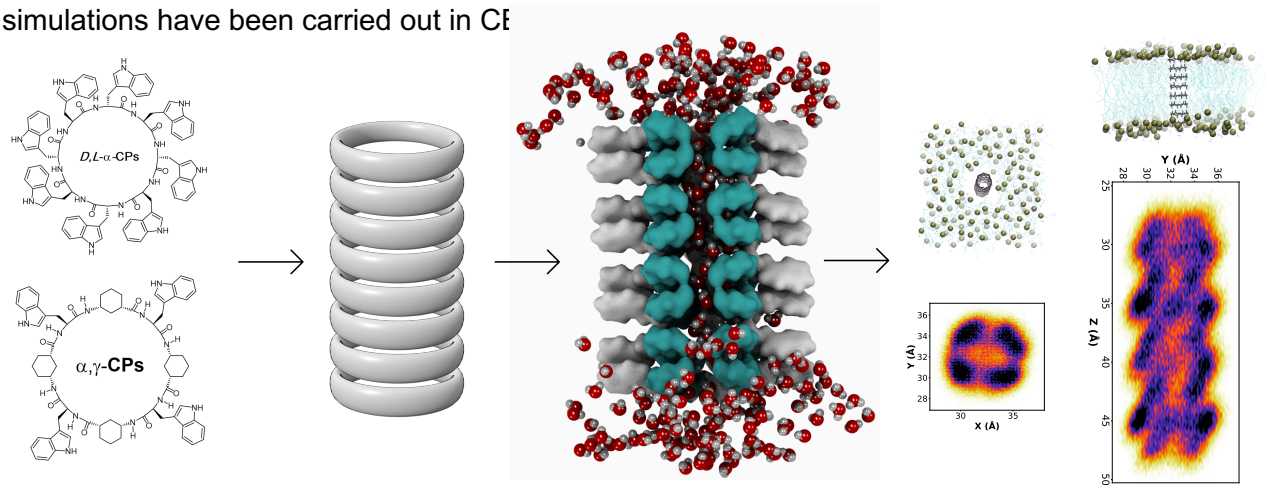
In-silico mutations of transmembrane peptidic nanotubes: impact on the inner channel properties

A. Seco,[a] D. Conde,[a] M. Calvelo,[a] Á. Piñeiro,[b] R. Garcia-Fandino[a]

[a]*Departamento de Química Orgánica, Center for Research in Biological Chemistry and Molecular Materials, Universidade de Santiago de Compostela, Campus Vida s/n, E-15782 Santiago de Compostela, Spain*
[b]*Departamento de Física Aplicada, Facultade de Física, Universidade de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*
e-mail: alejandro.seco@rai.usc.es

***Keywords**: Peptide nanotubes, Molecular Dynamics, Computational simulations*

Self-assembling cyclic peptide nanotubes (SCPNs) have been shown to function as synthetic, integral transmembrane channels.[1] The combination of natural and non-natural aminoacids in the sequence of the cyclic peptides (CPs) enables the control not only of their outer surface but also of the inner cavity behavior and properties, affecting for instance their permeability to different molecules including water and ions. Since the sidechains of the aminoacids in the CPs are directed towards the outside of the channel, it would be expected that a mutation in their sequence would not affect to the inner SCPN properties. However, preliminary results have suggested that the exterior of the channel can influence the internal water arrangement.[2]
In this work, and using Molecular Dynamics simulations, we have studied two different types of SCPNs acting as transmembrane channels: those based on the original CPs first synthetized by Ghadiri, *D,L*-α-SCPNs,[3,4] and those composed by the alternation of α-residues and cyclic γ-amino acids of appropriate chirality, α,γ-SCPNs,[5,6] where the β-carbon of the cycloalkane moiety is oriented towards the lumen of the cylinder. For each type of SCPN, we have investigated the effect of 5 different sets of mutations, analyzing their effect both in the stability of the ensemble and also in the disposition of the water confined in their cavities. All the MD simulations have been carried out in CE



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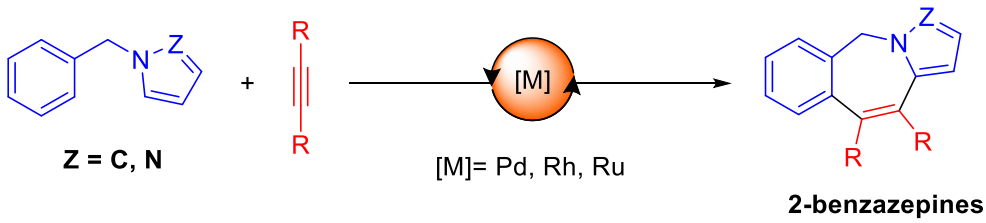
Azolic 2-Benzazepines by Metal-Catalyzed C-H Activation

Alejandro Suárez, Nuria Martínez, Álvaro Velasco, Sergio Otero, Jesús A. Varela, Carlos Saá*

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Dpto. de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela
alejandro.suarez.lustres@rai.usc.es

Keywords: *Benzazepines, C-H Activation, Catalysis,*

Benzazepines, benzofused seven-membered azaheterocycles, are privileged structures that are present in a large number of natural products which possess interesting biological properties that have aroused great interest in the chemical and pharmaceutical communities.[1] In classical synthetic approaches, annulation reactions (with loss of FG groups) are among the most efficient strategies. Nowadays, dehydrogenative annulations via metal-catalyzed C-H activation has emerged as an attractive step-economy and eco-friendly strategy. [2] In the field of benzazepines, metal-catalyzed [5 + 2] oxidative annulations have been successfully used to synthesize 1- and 3-benzazepines.[3] However, to our knowledge, [5 + 2] oxidative annulations to 2-benzazepines have not been reported. [4] Our approach to the synthesis of azolic 2-benzazepines *via* metal-catalyzed C-H activation will be discussed in this project.



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ORGANOMETALLIC CATALYSIS: NEW SUSTAINABLE ROUTES TO AMIDES AND MACROLACTAMS

José Valdivia Pinaque, Carlos Saá, Jesús A. Varela

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares e Dpto. de Química Orgánica
Universidade de Santiago de Compostela, 15782, Santiago de Compostela
jose.valdivia@rai.usc.es

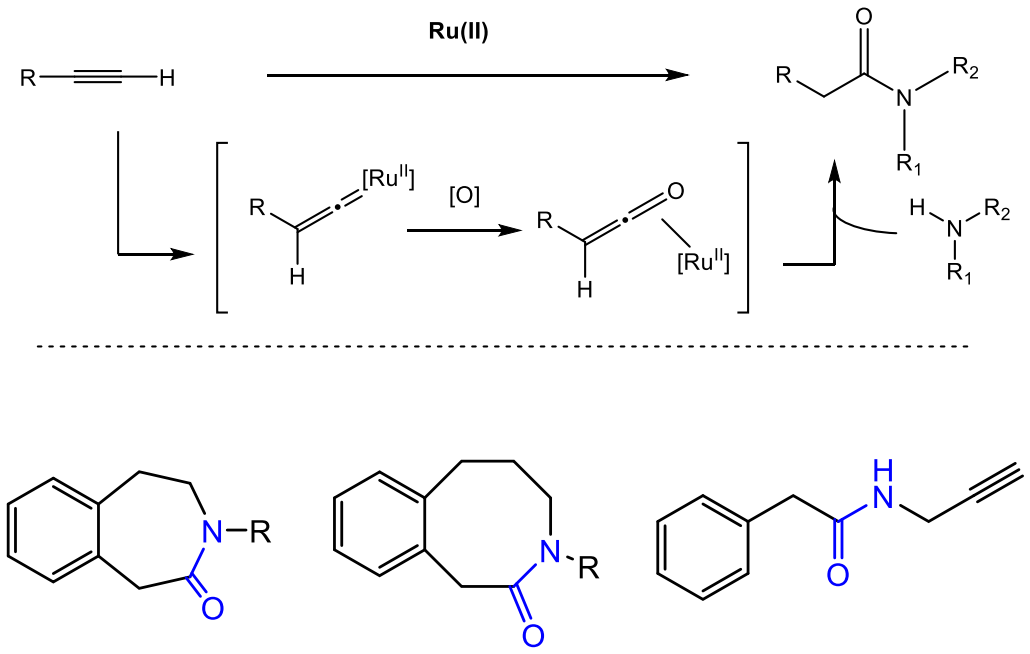
Keywords: *Ruthenium catalysis, Vinylidene intermediate, Oxidative amidation*

Amide bonds are present in numerous pharmaceuticals and play a capital role in living organisms. In addition, they are employed as synthetic materials like nylon, hydrogels, etc.[1]

Amide bond formation is an extensive organic chemistry field which remains to be one of the most important transformation methods. Typically, amide bonds are easily formed by condensation of an amine with a carboxylic acid via an active ester. Recently, new catalytic alternatives for selective amide bond formation have emerged to solve some of the limitations of the standard protocols. Oxidative amidations between ketenes (from terminal alkynes) and amines is one of the most promising protocol.[2]

In this project, applications of the Ru-catalyzed oxidative amidations to macrolactams (intramolecular reactions) and to foresee future solid phase synthesis will be discussed.

Figure 1. *General amidation mechanism and selected examples*



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Synthesis of new cyclopentadienones and thiophene oxides

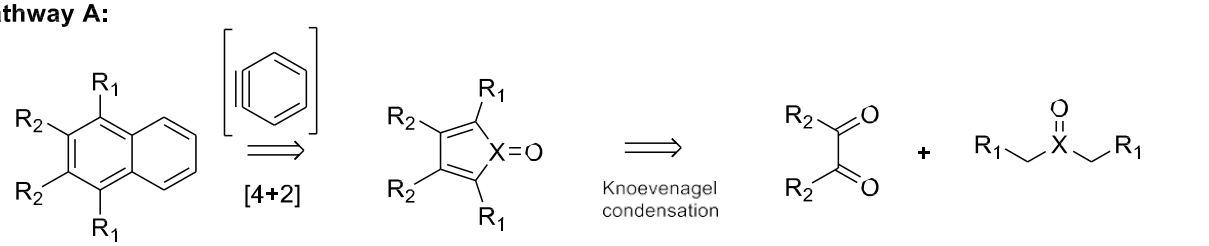
Daniel Villar, Jesús Castro-Esteban[a], Enrique Guitián[a], Dolores Pérez[a], Diego Peña[a]

[a]*Centro de Investigación en Química Biolóxica e Materiais Moleculares (*CiQUS), *Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782-Santiago de Compostela (Spain)*
e-mail: daniel.villar@rai.usc.es, enrique.guitian@usc.es, dolores.perez@usc.es

Keywords: *cyclopentadienones, thiophene oxides, aryne cycloadditions*

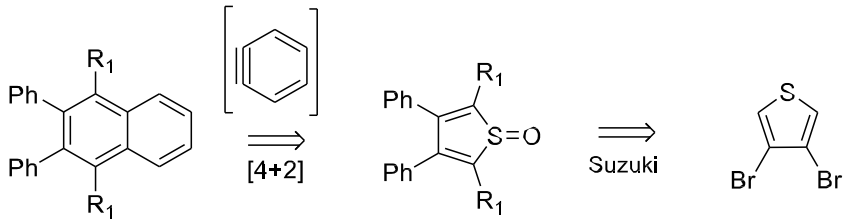
Polycyclic aromatic hydrocarbons (PAHs) form a big family of compounds which have generated interest during the last years due to their interesting optoelectronic properties, which make them promising materials for devices like light emitting diodes (LEDs), field-effect transistors (FETs) and photovoltaic cells.[1]
Nowadays, the synthesis of PAHs which behave like semiconductors is dominated by *p* type semiconductors. This is because there are not many building blocks which allow the synthesis of their *n* type analogues. However, DFT (*Density Functional Theory)* calculations shows that PAHs containing electron-withdrawing substituents are good candidates to have *n* type behavior.[2]
Having this in mind, the aim of this work is the synthesis of the cyclopentadienone **1**[3] as well as the thiophene oxides **2a** and **2b**[4] as new building blocks for the construction of *n* type semiconductors.

Pathway A:



1 X = C, R_1 = CN
2a X = S, R_1 = CN

Pathway B:



2b R_1 = Br

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