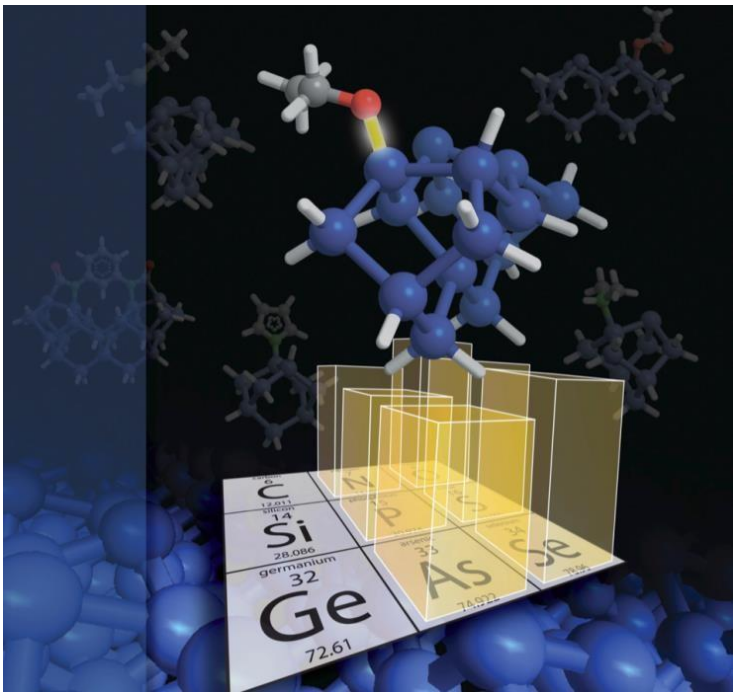
MASTERQO

MÁSTER UNIVERSITARIO EN QUÍMICA ORGÁNICA

XV Simposio del MQO
Universidad Autónoma de Madrid
14-16 de junio de 2023



www.masterqo.es

Colaboran

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

UAM Universidad Autónoma de Madrid

INFORMACIÓN GENERAL

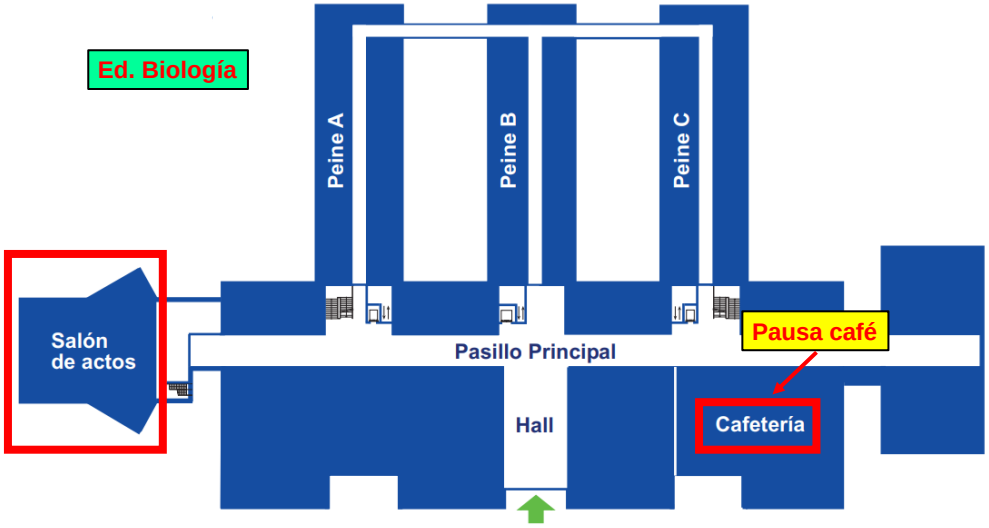
El XV Simposio del Máster en Química Orgánica se celebrará en la Facultad de Biología de la Universidad Autónoma de Madrid, Campus de Cantoblanco, 28049, Madrid.

Transporte:

- **Renfe:**
  - *Línea C-4a:* "Parla-Atocha-San Sebastián de los Reyes"
  - *Línea C-4b:* "Parla-Atocha-Colmenar Viejo"
- **Autobuses interurbanos (con parada dentro del Campus):**
  - *Línea 714:* Plaza Castilla-Cantoblanco-Comillas
  - *Línea 827:* Alcobendas-Cantoblanco
  - *Línea 827A:* San Sebastián de los Reyes-Alcobendas-Cantoblanco
  - *Línea 828:* Campo de las Naciones–Aeropuerto–Cantoblanco

Las conferencias se impartirán en la Salón de Actos de la **Facultad de Biología**.

Las sesiones de pósteres se realizarán en la Plata Baja de la **Facultad de Biología**.



PROGRAMA

Miercoles 14 de junio

12:45-13:00 Apertura (*Salón de Actos, Facultad de Biología*)

13:00-14:00 Conferencia Dr. Laura Lechuga (ICN2) (*Salón de Actos, Facultad de Biología*)

16:00-18:00 Sesión de Pósteres I (*Planta baja, Facultad de Biología*)

Jueves 15 de junio

9:30-11:30 Sesión de Pósteres II (*Planta baja, Facultad de Biología*)

11:45-12:30 Pausa café (*Planta baja, Facultad de Biología*)

12:30-13:30 Conferencia Dr. Lluis Montoliu (CNB-CSIC) (*Salón de Actos, Facultad de Biología*)

16:00-18:00 Sesión de Pósteres III (*Planta baja, Facultad de Biología*)

Viernes 16 de junio

10:00-12:00 Sesión de videos (*Salón de Actos, Facultad de Biología*)

12:30-13:00 Encuestas (*Salón de Actos, Facultad de Biología*)

13:00-13:30 Entrega de premios y Clausura (*Salón de Actos, Facultad de Biología*)

Dr. Laura Lechuga
Instituto Catalán de Nanociencia y Nanotecnología (ICN2)
"Dispositivos Nanobiosensores para el diagnóstico precoz y descentralizado de enfermedades"
Miércoles, 14 de junio, 13:00h
Salón de Actos
Facultad de Biología

Dr. Lluis Montoliu
Centro Nacional de Biotecnología (CNB-CSIC)
"*Aplicaciones actuales de la edición genética con las herramientas CRISPR*"
Jueves, 15 de junio, 12:30h
Salón de Actos
Facultad de Biología

ORGANIZACIÓN

Comité Organizador Local

Ramón Gómez Arrayás (UAM)

Mercedes Rodríguez Fernández (UAM)

Giovanni Bottari (UAM)

Ernesto Brunet (UAM)

Maria Montaña Jiménez García (UAM)

Jose García Calvo (UAM)

Comité Interuniversitario

Jesús Varela Carrete (USC)

Mercedes Torneiro Abuín (USC)

David García Fresnadillo (UCM)

Mar Gómez Gallego (UCM)

Silvia Ortega Gutiérrez (UCM)

PARTICIPANTES

Abellan Dumont, Mario	UAM	P1
Ávila Duran, Julian	UAM	P2
Balboa Lopez, Manuel	USC	P59
Ben Ahmed, Sophia	UAM	P3
Benito Gómez, Ignacio	UAM	P4
Bernabeu Rodríguez, Carlos	UCM	P32
Bouzán Cumplido, Fernán	USC	P60
Carrasco Alcaide, María	UCM	P33
Corral Hernando, César	UAM	P5
Crespo Veiga, Daniel	USC	P61
Cuadros Higueras, Carlos	UAM	P6
Díaz Mendoza, Carmen	UAM	P7
Duro Pérez, Emma	UAM	P8
Espejo Martín, Lucía	UCM	P34
Ferreira Alves, Joana Filipa	UCM	P35
Gallardo López, Sara	UCM	P36
García López, Patricia	UCM	P37
Goicuría Montoro, Marta	UAM	P9
Gomez Gomez, Marta	UAM	P10
González Martínez, David	UAM	P11
González Pinardo, Daniel	UCM	P38
Hortigón Ortega, Ricardo	UCM	P39
Hrehoret , Gabriel Alexandru	UCM	P40
Ibarra Sarango, Angela Belen	UAM	P12
Izquierdo Cachazo, Nerea	UCM	P41
Izquierdo Cazorla, Pablo	UCM	P42
Jiménez Bermudo, José Antonio	UAM	P13
Jiménez Rufo, David	UAM	P14
Jutglar Rigau, Sònia	UCM	P43
Lago Lorenzo, Laura	USC	P62
Landín González, Helena	USC	P63
Martín Garrido, Fernando	UCM	P44
Martín López, Ainhoa	UCM	P45
Martín Sáez, Nuria	UAM	P15
Martínez Fernández, Miguel	UCM	P46
Martínez Rodríguez, Aritz	UCM	P47
Marugán Benito, Sergio	UAM	P16
Mateo Del Río, Daniel	USC	P64
Maza Barón, Álvaro	USC	P65
Merino Díaz-Caneja, Paula	UAM	P17
Millán Miquel, Eugenio	UCM	P48
Molla Arroyo, Elio	UAM	P18

Morón Blanco, Adrián	UCM	P49
Muñoz Herranz, María	UCM	P50
Muñoz Rodríguez, Pedro	UCM	P51
Navarro Blanco, Maria Dolores	UAM	P19
No Gomez, Miguel	USC	P66
Oñate Martínez, Silvia	UAM	P20
Ordóñez Chacón, José Antonio	UAM	P21
Ortega Ruiz, Maria	UAM	P22
Pérez Sánchez, Carla	UAM	P23
Pernas Arias, Daniel	USC	P67
Pravos Gonzalo, Carla	UCM	P52
Ramos Aranda, Ignacio	UCM	P53
Rey Bello, Nicolás	USC	P68
Rodríguez Pérez, David	USC	P73
Rubio Ramiro, Pedro	UAM	P24
Rubio Ramón, Pablo Ignacio	UCM	P54
San Martín Loubet, Daniel	UCM	P55
Sánchez Casillas, Marina	UCM	P56
Sanchez De La Morena, Paula	UAM	P25
Sánchez García, Claudia	UCM	P57
Senent Romero, Alberto	UAM	P26
Seoane Míguez, Sara	USC	P69
Silva Gallardo, Víctor	UAM	P27
Solek Pondo, Claudia	UAM	P28
Taillandier, Gabriel	UAM	P29
Tapia Rodríguez Juan, Manuel	USC	P70
Torres Calvo, Beatriz	UAM	P30
Vale Gomez, Alejandra	USC	P71
Valverde Canuto, Alejandro	UCM	P58
Vázquez Viso, Juan	USC	P72
Vos Gracia, Miriam	UAM	P31

ABSTRACTS DE LOS PÓSTERES

Transition metal-free borylation reactions of C=N bonds

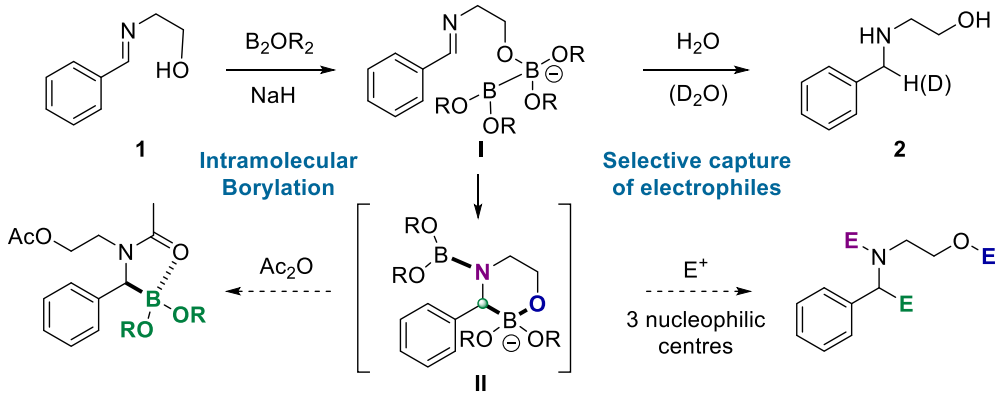
M. Abellán Dumont,[a] M. I. Alonso,[a] M. Tortosa,[a] M. B. Cid.[a]

[a]*Universidad Autónoma de Madrid*
e-mail: mario.abellan@estudiante.uam.es

Keywords: *Diboron compound, umpolung, intramolecular borylation*

The α-aminoboronic moiety is a valuable motif in organic synthesis and an interesting pharmacophore present in important drugs such as Bortezomib. They are commonly prepared from imines and diboron reagents in the presence of a transition metal.[1] It would be remarkable to find new strategies based on transition metal-free activation to form this kind of derivatives. Alkoxides are known to act as Lewis bases that react with diboron reagents to form trivalent nucleophilic boryl synthon that could lead to organoboron compounds under transition metal-free conditions.[2] However, the use of hydroxyl as a directed pseudo-intramolecular version has been scarcely explored.[3]

We have been focused on developing a simple strategy in which the imine contains a hydroxyl group (**1**), which after deprotonation could act as a Lewis base able to activate a diboron reagent, forming an intermediate type **I** and promoting **an intramolecular** borylation reaction. Nevertheless, when imine **1** was treated with NaH and B_2pin_2 the reaction evolved into the formation of amine **2**. We demonstrated that this formal reduction was due to the remaining water of the solvent by performing the reaction in the presence of D_2O. In this case, the deuterated amine **2** was observed (Scheme 1).



Scheme 1. Route proposed to the capture of electrophiles.

This result and theoretical calculations pointed out that this process could take place through the formation of the borate intermediate **II**. This intermediate opens a new route to invert the typical reactivity of imines (**umpolung**) and contains three possible nucleophilic centers (carbon, nitrogen and oxygen) to be selectively functionalized. We present herein a study to detect and understand the potential of borate **II**, evaluating a variety of imines and electrophiles using different conditions and diboron reagents.

References:

[1] Ming, W.; Liu, X.; Marder, T. B.; Soor, H. S.; Trofimova, A.; Yudin, A. K. *Chem. Soc. Rev.* **2021**, 50,12151−12188.
[2] Cuenca, A.B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.*, **2017**, *46*, 415-430
[3] (a) Blaisdell, T.P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken. J.P. *J. Am. Chem. Soc.*, **2014**, 136, 9264. (b) Nagashima, Y.; Hirano, K.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2014**, *136*, 8532–8535.

Porous organic materials for applications in photocatalysis

J. Ávila Durán,[a] and M. Iglesias Hernández[a]

[a]*Instituto de Ciencia de Materiales de Madrid (ICMM)*
e-mail: julian.avila@estudiante.uam.es

Keywords: *Photocatalysts, Porous Organic Polymers (POPs) and Aromatic compounds*

Two new porous organic polymers are synthesized: first, a new covalent triazine framework (CTF) containing naphthalene units with amino groups is synthesized by microwave thermal activation [1]. Two chemical structures are combined in this polymer. Triazines, which are acceptor units, are combined with naphthalene units, which are aromatic donor groups. In addition, the importance of the substituents on the naphthalene core is reflected in the properties of the resulting polymer. On the other hand, a covalent organic framework (COF) is also synthesized by the condensation of carbonyl groups with amine groups forming imine bonds by solvothermal synthesis [2]. The resulting porous organic polymers are efficiently used as metal-free heterogeneous photocatalysts in various reactions, such as the selective aerobic oxidation of sulfides [3]. In addition, these polymers exhibit other excellent properties such as high chemical stability, high structural organization, and adsorption capacity.

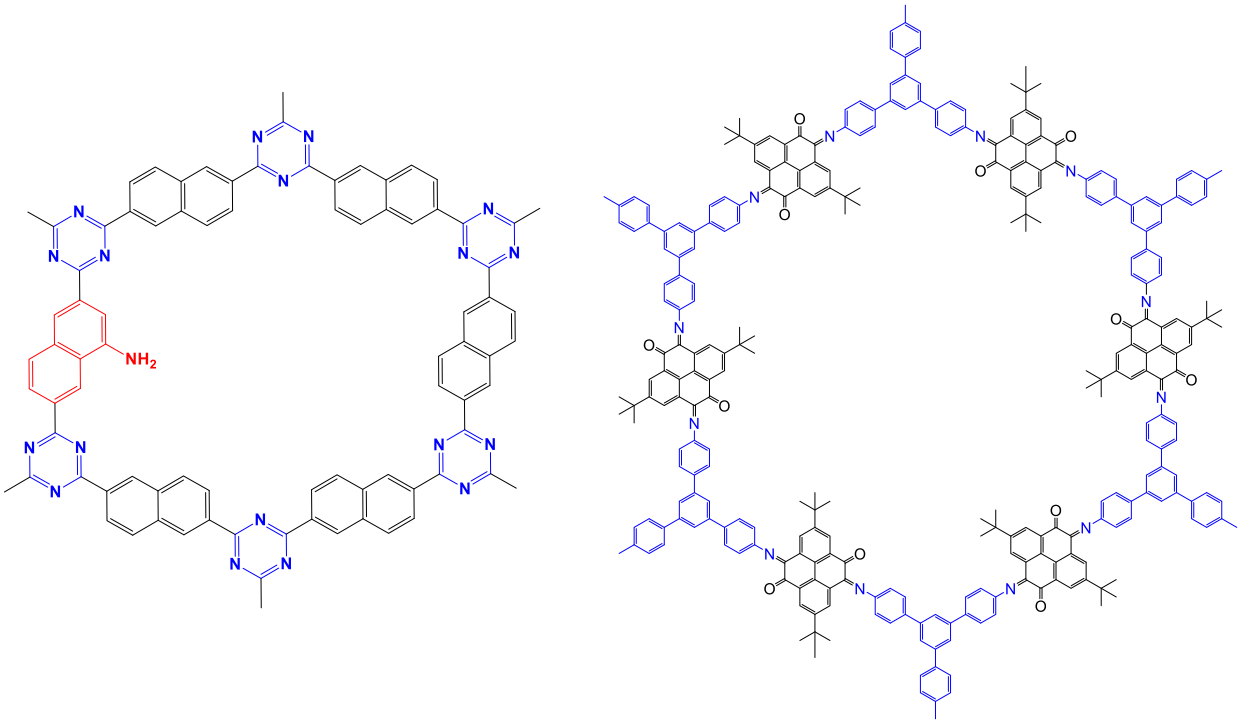


Figure 1. Structure of naphthalene dinitriles and CTFs synthetized by microwave activation (left) and structure of COF with imine bond synthesized by solvothermal synthesis (right).

References:

[1] Ren, S., Bojdys, M. J., Dawson, R., Laybourn, A., Khimyak, Y. Z., Adams, D. J., & Cooper, A. I. *Adv. Mater*, **2012**, 24(17), 2357-2361.
[2] Keyu G., Ting H., Ruoyang L., Sasanka D., et al. *Chem. Rev*. **2020**, 120, 8814-8933.
[3] Chaubey, S., Yadav, R. K., Tripathi, S. K., Yadav, B. C., Singh, S. N., & Kim, T. W.. *Photochem. Photobiol.*, **2022**, 98(1), 150-159.

Synthesis of amphiphilic subporphyrinoids as potential photosensitizers for photodynamic therapy and fluorophore markers

S. Ben Ahmed,[a] M. S. Rodríguez-Morgade.[a]

[a]*Organic Chemistry Department, Universidad Autónoma of Madrid, Madrid, Spain.*
e-mail: sophia.benahmed@estudiante.uam.fr

Keywords: *Subporphyrazines, singlet oxygen, fluorescence*

Photodynamic therapy (PDT) is a non-invasive, selective, and repeatable therapy against cancer relying on the photogeneration of active oxygen species know as singlet oxygen $^1O_2$ by a photosensitizer. Amongst the most common sensitizers for PDT, porphyrinoids are still nowadays the most extensively studied.[1] Subporphyrazines (SubPzs) are contracted porphyrinoids composed of 3 pyrrole rings linked by aza bridges through their 2 and 5 positions.[2] These macrocycles bear 14 conjugated π electrons and are only known as boron complexes due to their small central cavity. Owing to the trigonal geometry of boron's orbitals, SubPzs display a conical shape creating an axial position on said central boron atom. SubPzs tend to show peculiar photophysical and photochemical properties with outstanding tunability related to that of other porphyrinoids. Notable properties of the bare SubPz structure comprise its absorption at 500 nm, its fluorescence and its ability to generate singlet oxygen, which makes these compounds potentially useful for diagnosis and PDT. The latter is possible based on the strong modification of the SubPz absorption profile via peripheral functionalization.[3] Contrarily, axial functionalization usually does not alter the absorption properties of SubPzs but it is a powerful tool to tune singlet oxygen production in other porphyrinoids.[4] Within SubPzs, axial functionalization has been limited so far to the substitution of the original chlorine atom, arising from the cyclotrimerization reaction conditions, by hydroxy, aryloxy or fluorine groups. This project aimed at establishing general synthetic protocols for the axial functionalization of SubPzs. The preparation of amphiphilic compounds, able to cross cell membranes by simple diffusion, is among the objectives. To this end, a variety of nucleophiles was tested to be introduced on the boron atom (Figure 1), either directly, or through newly generated synthetic intermediates such as triflates. The effects of the axial ligand in the fluorescence quantum yields and singlet oxygen generation of the dyes was systematically evaluated. Until now the effects of axial substitution on these parameters has not been studied, not only in SubPzs but in any other subporphyrinoid.

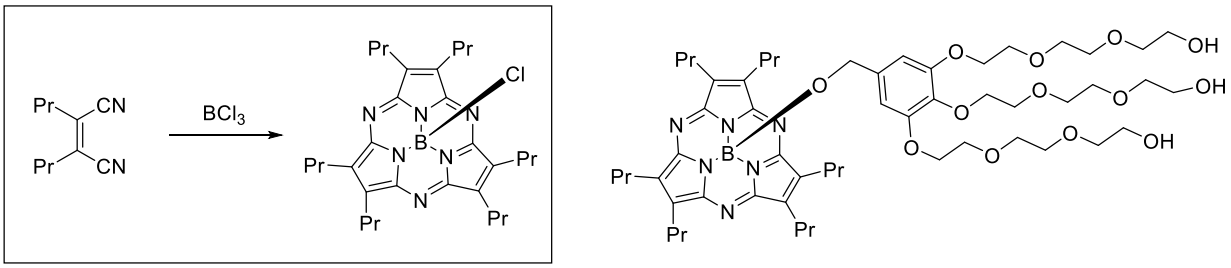


Figure 1. Cyclotrimerization reaction scheme (left) and example of amphiphilic axially substituted SubPz (right).

References:

[1] Lo, P; Rodríguez-Morgade, M. S.; Pandey, R.K.; Ng, D.K.P.; Torres, T.; Dumoulin, F. *Chem. Soc. Rev.*, **2020**, *49*, 1041-1056.

[2] Lavarda, G.; Labella, J.; Martínez-Díaz, M.V.; Rodríguez-Morgade, M.S.; Osuka, A.; Torres, T. *Chem. Soc. Rev.*, **2022**, *51*, 9482-9619.

[3] Caballero, E.; Guzmán, D.; Torres, T.; Rodríguez-Morgade, M. S. *J. Org. Chem.* **2020**, *85*, 1948-1960.

[4] Ferreira,T.; Pina, J.; Ribeiro, A.F.; Fernandes, R.; Tomé, J.P.C.; Rodríguez-Morgade, M.S.; Torres, T. *ChemPhotoChem* **2018**, *2*, 640-654.

Novel approaches for the efficient conjugation and release of therapeutic oligonucleotides from nanoparticles

I. Benito Gómez,[a] M. Martínez-Mingo,[a] Á. Somoza.[a]

[a]*Nanobiotechnology research group, IMDEA Nanociencia, C/ Faraday 9, Cantoblanco, Madrid (Spain)*
e-mail: ignacio.benitog@estudiante.uam.es

Keywords: *Oligonucleotide, nanoparticle, release*

Therapeutic oligonucleotides (TONs) are promising tools for treating numerous diseases since they can inhibit the expression of specific genes with extraordinary efficacy and selectivity.[1] However, TON-based therapies present several challenges due to the intrinsic properties of nucleic acids. Naked oligonucleotides are very unstable in blood serum due to exonuclease activity, show little ability to permeate into cells, are very keen to be excreted by the organism before reaching their target, or can activate an immune response.[2]

One approach to solve these issues involves using nanoparticles as delivery vectors to improve their properties and increase their selectivity towards the tumoral environment, taking advantage of the enhanced permeability and retention (EPR) effect. In this context, gold nanoparticles (AuNPs) are very versatile due to their easy and tunable synthesis, interesting optical properties, and high biocompatibility.[2,3]

In this work, the conjugation of TONs with AuNPs is mediated by linkers presenting a dithiolane moiety that allow efficient binding to the gold surface. For that purpose, *controlled pore glass* (CPG) solid supports are prepared with this moiety. After that, TONs are obtained through the standard solid-phase DNA/RNA synthesis based on phosphoramidite chemistry. During this process, different elements will be introduced in the TONs to improve the final stability of the system and control their release from AuNPs.

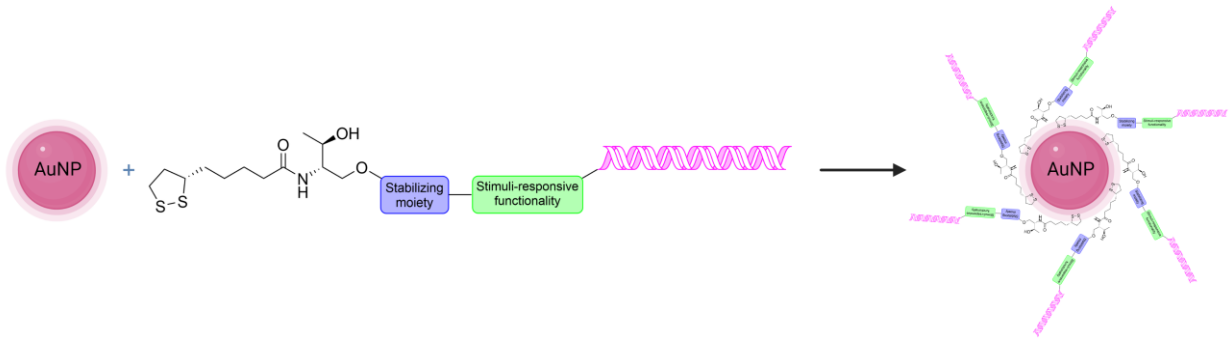


Figure 1. Conjugation of TON with AuNPs by a linker with a dithiolane moiety.

References:

[1] Sridharan, K.; Gogtay, N. J. *Br. J. Pharmacol*. **2016**, *82*, 659-672.

[2] Lafuente-Gómez, N.; Latorre, A.; Milán-Rois, P.; Rodriguez Díaz, C.; Somoza, A. *Chem. Commun.* **2021**, *57*, 13662-13677.

[3] Latorre, A.; Posch, C.; Garcimartín, Y.; Ortiz-Urda, S.; Somoza, A. *Chem. Commun*. **2014**, *50*, 3018-3020.

Enantioselective BODIPY functionalization through catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides

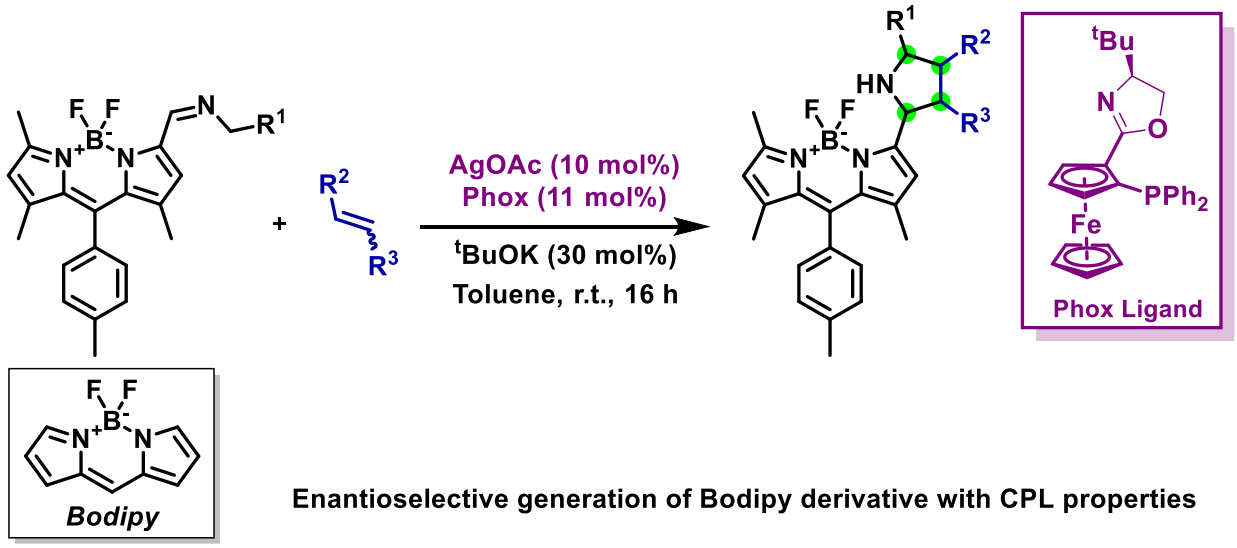
C. Corral[a], C Cristóbal[a], M. Ribagorda*[ab] and J. Adrio*[abc]

[a] *Departamento de Química Orgánica, Facultad de ciencias, Universidad Autónoma de Madrid (UAM), 28049 Madrid (Spain),* [b] *Institute for Advanced Research in Chemical Sciences (IAdChem), UAM, 28049 Madrid (Spain),* [c] *Center for innovation in AdvancedChemistry (ORFEO-CINQIA, UAM, Cantoblanco 28049 Madrid (Spain))*
e-mail: cesar.corralh@estudiante.uam.es

Keywords: *BODIPY, 1,3-dipolar, cycloaddition*

Borondipyrromethenes (BODIPY) are of particular interest due to their photophysical properties[1]. These characteristics make them suitable to be used in high valued applications such as photodynamic therapy or fluorescence imaging. BODIPY´s derivatization had been widely studied in the past years. However, as far as we are concerned, catalytic asymmetric transformations in BODIPY´s framework have been scarcely studied.

In this context, we set as main objective of this work the development of a catalytic asymmetric 1,3-dipolar cycloaddition using BODIPY-derived iminoesters as azomethine ylide precursors. In the presence of silver (I) and a *P*hox type ligand as catalytic system the corresponding pyrrolidines were obtained with good yields and excellent diastereo and enantioselectivities. Finally, these derivatized products display Circularly Polarized Luminescence (CPL) properties[2], which give them an additional interest.



Scheme 1. *Synthetic route for the enantioselective synthesis of Bodipy-derived pyrrolidines.*

References:

[1] (a) Loudet, A.; Burgess, K. *Chem Rev.* **2007**, *107* (11), 4891-932. (b) Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Chung, L. Y.; Burgess, K. *Chem. Soc. Rev.* **2013**, *42* (1), 77–88. (c) Boens, N.; Leen, V.; Dehaen, W. *Chem. Soc. Rev.* **2012**, *41* (3), 1130–1172. (d) Rigotti, T.; Asenjo-Pascual, J.; Martín-Somer, A.; Milán Rois, P.; Cordani, M.; Díaz-Tendero, S.; Somoza, Á.; Fraile, A.; Alemán, J. *Adv. Synth. & Catal*. **2020**, *362* (6), 1345–1355.

[2] Sánchez-Carnerero, E. M.; Moreno, F.; Maroto, B. L.; Agarrabeitia, A. R.; Ortiz, M. J.; Vo, B. G.; Muller, G.; Moya, S. d. l. *J. Am. Chem. Soc.* **2014**, *136* (9), 3346–3349.

Linkers development for advanced applications of DEL technology

Carlos Cuadros Higueras, María Dolores Martín-Ortega,[a] Jesús Blas.[a]

[a] Eli Lilly and Company- Centro de Investigación Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid
e-mail: carlos.cuadros@estudiante.uam.es

Keywords: *"DNA Encoding Libraries", "Photoactivated Covalent Capture", "Next Generation Sequencing"*

One of the key stages in the Drug Discovery process is to find small molecules with biological activity to modulate the pharmacology of a target of interest. The toolkit for this endeavor includes in-silico tools as virtual screening or DeNovo design using neural networks, and real compound sources like natural products, fragments and high throughput screening. During the past decade, DEL (DNA Encoded Libraries) has become a potent strategy for hit generation in the Pharma industry. The ability to cover a huge chemical space together with the advances in Next Generation Sequencing (NGS), provide this technology with an extraordinary power for new chemical matter generation to be screened versus the most relevant therapeutic targets.
DEL concept was established in 1992 by Novel laureates Brenner and Lerner as a combination of chemistry and biochemistry disciplines: by using pool and split methodology, vast number of chemical entities may be produced and then individually encoded by a unique DNA sequence. These DELs are screened using Affinity Selection and the molecules that bind to a specific target are then analyzed by NGS, thus disclosing the identity of the new binders. The development of DEL technology has grown exponentially both academy and Pharmaceutical Industry in last ten years. This evolution goes beyond chemistry production or affinity selection conditions but looking for a broader scope to fragment screening modalities or protein degraders.
One of the limitations of the technology is their application to fragments (typically weak binders) due to the lack of strong binding interactions. In this work, we will incorporate photoaffinity assisted capture for DEL fragments. This methodology will broaden the detection margin of the affinity selection, thus augmenting the versatility of the DEL technology.

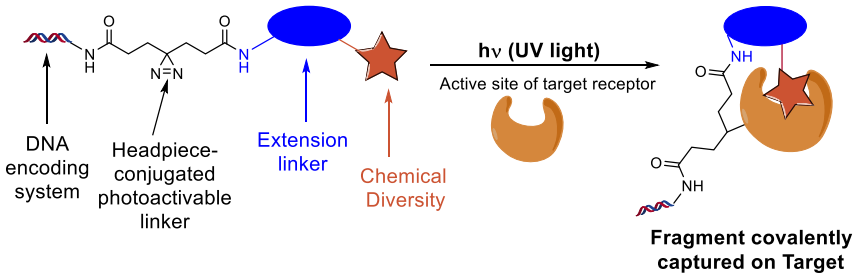


Figure 1. The PAC-FragmentDEL process. Covalent binding of PAC-FragmentDEL to the target receptor.

Recent developments for chemical biology prove photoactivated fragments to identify and characterize binding sites. For this purpose, PAC DELs (Photoaffinity Capture) requires three elements: the DNA encoding system that records the chemistry at each cycle, the linkers and the fragments. Linkers involve a hydrocarbon chain containing a photoactivable diazirine moiety and different lengths extensors to allow an optimal approach of the fragment and the diazirine system towards binding pocket to ensure the covalent capture of the fragment through carbene insertion. Herein we will develop a variety of linkers which contains a photoactivable diazirine. Furthermore, these linkers will be employed in the production of a DEL for later screening in target proteins.

References:

[1] Brenner, S.; Lerner, R. A. Proc. Natl. Acad. Sci. U.S.A. **1992**, 89 (12), 5381–5383.
[2] Hubbard, R. E.; Liu, G. RSC Med. Chem. **2022**, 13 (11), 1341–1349.

Autocatalysis of molecular chimeras composed of amino acids, fatty acids and nitrogenous bases.

C. Díaz Mendoza, [a] S. Vela Gallego, [a] A. de la Escosura Navazo.[a]

[a] Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid (UAM), 28049 Madrid (Spain)
e-mail: carmen.diazmendoza@estudiante.uam.es

Keywords: *Systems chemistry, replication, kinetic reactions.*

Systems chemistry search for emergent properties that arise in mixtures, in and out of equilibrium, when their components interact and/or interconvert. [1] In relation to this, a previous study designed a nucleobase replication network that operated by thiol oxidation of a cysteine residue and disulphite exchange of monomers. [2] In this work, two complementary objectives will be developed. The first is to improve the rate of the thymine reaction, which is slow to be brought into a flow-through system. To meet this objective, the ionic strength of the medium will be increased by introducing a certain amount of NaCl (Figure 1A). The second objective is to form a new replication network by including hydrophobic strengths to the hybrid system, using oleic acid and thymine (Figure 1B); similarly, the introduction of these strengths is intended to increase the speed of replication and the formation of new supramolecular structures. The kinetic behaviour of the newly formed network, which includes 2 different biological blocks, will also be studied.

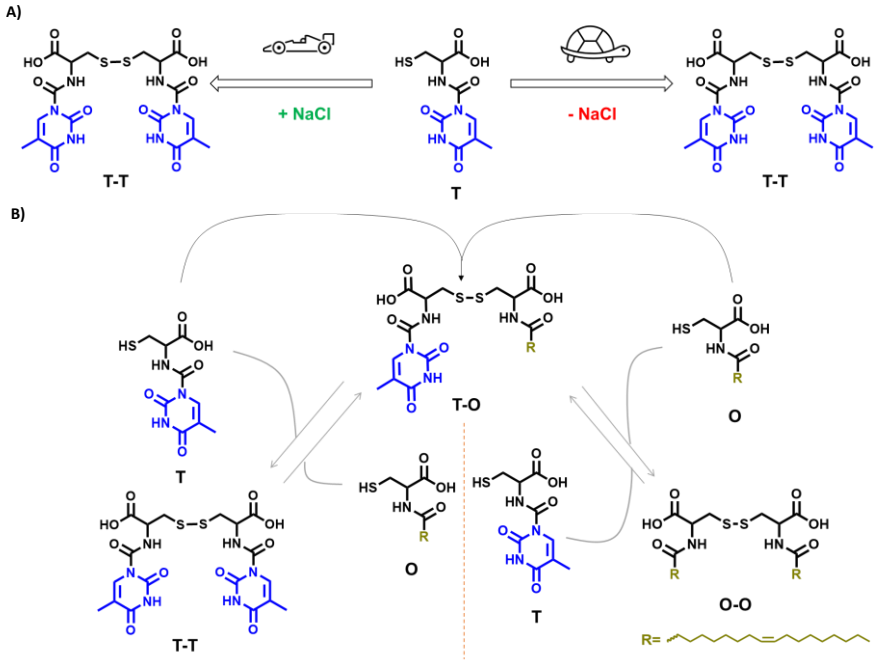


Figure 1. A) Thymine oxidation in a medium with higher ionic strength. **B)** Scheme of replication network that could be formed with the cysteine monomers T (containg thymine) and acid oleic.

References:

[1] Ashkenasy, G.; Hermans, T. M.; Otto, S.; Taylor, A. F. *Chemical Society reviews* **2017**, *46*, 2543-2554.

[2] Vela-Gallego, S.; Pardo-Botero, Z.; Moya, C.; de la Escosura, A. *Chemical Science (Cambridge)* **2022**, *13,* 1715-1724.

Cobalt-catalyzed C(sp^3)–H functionalization of carbonyl compounds

E. Duro,[a] A. García-Viada,[a] J. C. Carretero,[a,b,c] I. Alonso,*[a,b,c] N. Rodríguez,*[a,b,c] J. Adrio*[a,b,c]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid (UAM), 28049 Madrid (Spain),* [b]*Institute for Advanced Research in Chemical Sciences (IAdChem), UAM, 28049 Madrid (Spain),* [c]*Center for innovation in Advanced Chemistry (ORFEO-CINQIA, UAM, Cantoblanco 28049 Madrid (Spain)).*
e-mail: emma.duro@estudiante.uam.es

Keywords: *Cobalt catalysis, C(sp^3)–H functionalization, decarboxylative cross-coupling*

Functionalization of carbonyl compounds is one of the cornerstones in organic synthesis. Numerous synthetic strategies take advantage of the inherent electrophilic nature of carbonyl compounds and the acidity of α-C(sp^3)–H bonds to introduce functionalities in the *ipso* and *alpha* positions, respectively. However, functionalization of the β-position is not so easy, with the β-C(sp^3)–H bond being considered an "inert bond" due to its reduced acidity.

Therefore, the functionalization of this position is a remaining challenge that is being intensively addressed by evaluating the activation of this C–H bond by metal catalysis. In fact, great progress has been achieved using catalysts based on noble metals (Pd, Rh, Ru and Ir).[1] However, with the interest of developing methods in the line of sustainable chemistry, our research has focused on the development of protocols using metals of the first transition series.[2]

In this context, we herein present our preliminary results in the synthesis of pyrrolidinones through a high-valent cobalt-catalyzed decarboxylative cross-coupling/cyclization tandem process starting from aliphatic amides and alkynylcarboxylic acids. Mechanistic studies are allowing us to rationalize this reactivity and to understand the observed selectivity. This knowledge is necessary for the development of increasingly efficient catalysts that allow the application of this synthetic strategy to the preparation of structurally complex products, using carboxylic acids of different nature.

In addition, the mechanistic information obtained has allowed us to launch other lines of research. Among them, we would like to highlight the reactivity achieved with isonitrile derivatives using cobalt catalysis in high oxidation state. In this case, the method allows access to 1,4-dicarbonyl compounds, retrosynthetically challenging due to their dissonant nature.

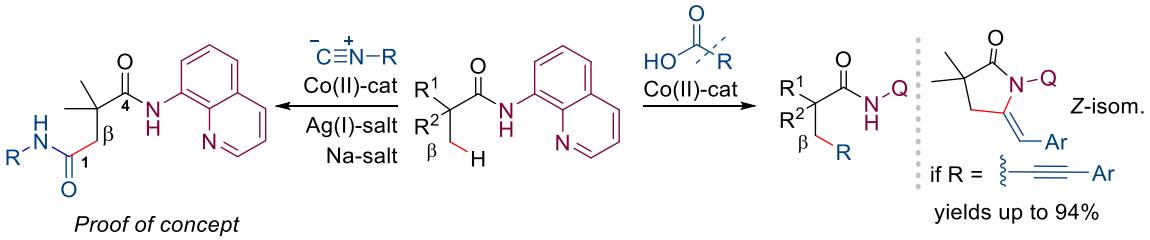


Figure 1. *8*-Q-assisted Co-catalyzed β-C(sp^3)–H functionalization of aliphatic amides.

References:

[1] Carvalho, R.L.; Dias, G.G.; Pereira, C.L.M.; Ghosh, P.; Maiti, D.; da Silva Júnior, E.N. *J. Braz. Chem. Soc.* **2021**, *32*, 917.

[2] (a) Ge, H.; Li, G.; Sun, H.; Zhao, Y.; Yang, K.; Wu, X. *Nat. Commun.* **2015**, *6*, 6462. (b) Barsu, N.; Bolliand, S. K.; Sundararaju, B. *Chem. Sci.*, **2017**, *8*, 2431. (c) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wangand, C.; Zhang, C. *J. Am. Chem. Soc.*, **2015**, *137*, 12990. (d) Cizikovs, A.; Grigorjeva, L. *Inorganics* **2023**, *11*, 194. (e) Lukasevics, L.; Cizikovs, A.; Grigorjeva, L. *Chem. Commun.* **2021**, *57*, 10827. (e) Williamson, P.; Galván, A.; Gaunt, M.J. *Chem. Sci.*, **2017**, *8*, 2588. (f) Zeng, L.; Tang, S.; Wang, D.; Deng, Y.; Chen, J.L.; Leeand, J.F.; Lei, A. *Org. Lett.*, **2017**, *19*, 2170.

PCET ring opening of unstrained cycloalkanols through EDA complex formation

M. Goicuría[a], L. Marzo.[a]

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

Keywords: *EDA complex, PCET, cycloalkanols oxidation*

An electron donor-acceptor (EDA) complex is formed when an electron-rich substrate and an electron-accepting molecule are associated generating a new molecular aggregate in the ground state. Upon light absorption this complex generates a radical ion pair that can evolve through different reaction pathways. EDA complexes offer the possibility of using less energetic light sources to activate substances that would not absorb in this region of the spectrum.[1]
Knowles described a redox-neutral isomerization of cyclic alcohols to linear ketones through a photocatalytic reaction where the oxidation of an arene generates a radical cation that, in the presence of a base, promotes a proton-coupled electron transfer (PCET). In this process, the deprotonation of the hydroxyl group and the reduction of the radical cation befalls in a concerted step, generating an alkoxy radical. Finally, a β-C-C bond scission occurs, opening the cycle and forming the corresponding ketone and an alkyl radical.[2]

Last year our group described the racemic and the enantioselective addition of the remote alkyl radical formed upon PCET activation of cycloalkanols to Michael acceptors. Both approaches employed blue light, a base and an external organic photocatalysts to perform the PCET activation.[3] Herein, we present the formation of an EDA complex between cycloalkanols and Michael acceptors that promotes the PCET activation and consecutive ring opening without the need of an external photocatalyst or base (Figure 1). The method is applicable to different types of alcohols, and it works effectively with electron-deficient double bonds. Furthermore, mechanistic studies were carried on successfully.

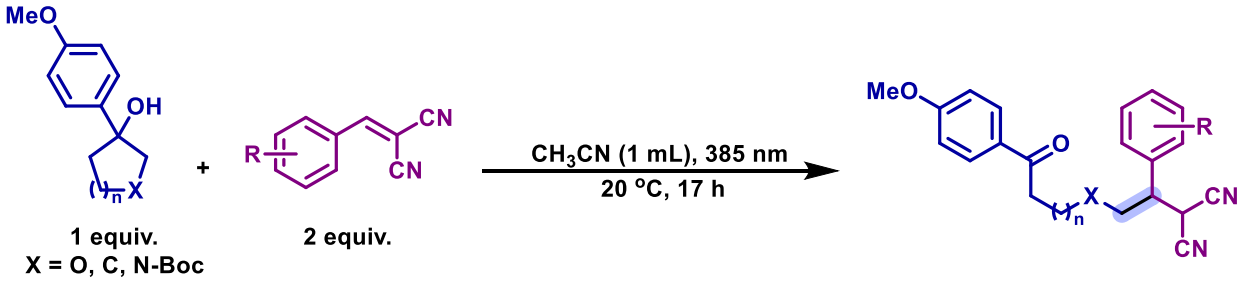


Figure 1. General rection of ring openings in activated cycloalkanols by the formation of an EDA complex and subsequent intramolecular PCET.

References:

[1] G. E. M. Crisenza, D. Mazzarella, P. Melchiorre. *J. Am. Chem. Soc*. **2016**, *138*, 10794−10797.
[2] H. G. Yayla, H. Wang, K. T. Tarantino, H. S. Orbe, R. R. Knowles. *J. Am. Chem. Soc*. **2020**, *142*, 5461−5476.
[3] a) N. Salaverri, B. Carli, S. Díaz-Tendero, L. Marzo, J. Alemán. *Org. Lett*. **2022**, *24*, 3123-3127. b) N. Salaverri, B. Carli, P. B. Gratal, L. Marzo, J. Alemán. *Adv. Synth. Catal*. **2022**, *364*, 1689-1694.

Peripheral functionalization of subphthalocyanines: From in solution to on-surface chemistry

M. Gómez Gómez,[a] J. Lobo Checa,[b,c] J. Labella,[a] T. Torres.[a,d,e]

[a] *Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain.,* [b] *Instituto de Nanociencia y Materiales de Aragón (INMA), CSIC-Universidad de Zaragoza, Zaragoza 50009, Spain,* [c] *Departamento de Física de la Materia Condensada, Universidad de Zaragoza, E-50009 Zaragoza, Spain* [d] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain.,* [e] *Instituto Madrileño de Estudios Avanzados (IMDEA)-Nanociencia C/ Faraday, 9, Cantoblanco, 28049 Madrid, Spain.*

e-mail: marta.gomez02@estudiante.uam.es

Keywords: *subphthalocyanines, borylation, on-surface chemistry.*

Subphthalocyanines (SubPc, Figure 1) hold a privileged position among the most employed organic semiconductors.[1] These unique non-planar aromatic macrocycles exhibit exciting properties easily tailored by functionalization. In particular, the peripheral substituents (Figure 1), which are in π-conjugation with the aromatic skeleton, control aspects as fundamental as the supramolecular organization, the absorption-emission range or the band-gap. However, only few methods have been developed for the peripheral functionalization of SubPcs, which hampers the development of novel systems with potential applications, such as oligomeric species. Along this line, herein we are focused on developing two novel methodologies by means of both in solution and on-surface chemistry.

The peripheral borylation of porphyrinoids has become a key step to prepare advanced functional materials. Therefore, we describe a method for the efficient peripheral borylation of SubPcs via Suzuki-Miyaura reactions (Figure 1, left). We explore the utility of these borylated SubPcs as synthons for several cross-coupling reactions, as well as for the preparation of SubPc-SubPc dimers linked by single C-C bonds.

On the other hand, on-surface chemistry has enabled the synthesis of complex systems otherwise impossible to prepare using conventional in solution chemistry.[2] In this work we aim to "toposelectively" prepare SubPc-based oligomeric species by means of on-surface C-X activations (X= Br, Cl or F; Figure 1, right). One step further, chiral systems are at reach when employing C_3-symmetric SubPcs, which is known to be very appealing for molecular spintronics.[3] Accordingly, we also study SubPc precursors for the fabrication of 2D π-polymers combining chirality and porosity into a single molecular framework.

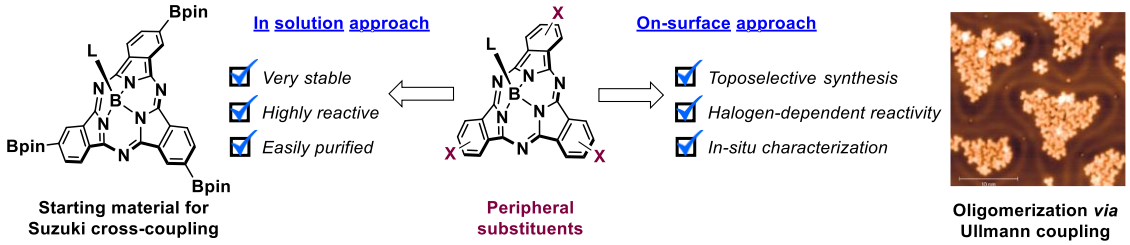


Figure 1. In solution (left) and on-surface (right) approach for the peripheral functionalization of SubPcs.

References:

[1] Labella, J.; Torres, T. *Trends in Chemistry* **2023**, *5*, 353-366.

[2] Labella, J.; Lavarda, G.; Hernández-López, L.; Aguilar-Galindo, F.; Díaz-Tendero, S.; Lobo-Checa, J.; Torres, T. *J. Am. Chem. Soc.* **2022**, *144*, 16579-16587.

[3] Labella, J.; Bhowmick, D. K.; Kumar, A.; Naaman, R.; Torres, T. *Chem. Sci.* **2023**, *14*, 4273-4277.

Synthesis of azoderivatives as hypoxia-like sensors

D. González Martínez,[a] A. Jaafar Arias,[a] M. Ribagorda.[a,b]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049, Madrid, Spain;* [b] *Institute for Advanced Research in Chemical Sciences (IAdChem), UAM, 28049, Madrid, Spain*
e-mail: david.gonzalezmartinez@estudiante.uam.es

Keywords: *Azobenzene, hypoxia, biosensor.*

Azobenzenes are a family of organic compounds with outstanding photophysical properties that recently have found use as temporal fluorescent quenchers for biosensing and bioimaging studies. The azo moiety is able to extinguish the emission of several fluorophores by a non-radiative process. Moreover, these azo dyes can turn on their emission properties under reductive conditions that trigger the azo bond cleavage, leading to fluorescent amino fluorophores.[1]

Our group have recently reported an azo-based OFF/ON fluorescent biosensor of hypoxia-like conditions using BODIPYs as the fluorophore unit.[2] In this work, we report a new family of azo-based hypoxia sensors composed by an azobenzene group linked to a dipyridophenazine unit. The dypiridophenazine group can be used not only as a masked fluorophore, but also to coordinate different metals like iridium or ruthenium to get larger stokes shift, anti-photobleaching, tunable phosphorescence and long phosphorescence time.[3]

Herein, we present the synthesis and photophysical properties of the azo and the corresponding amino derivative obtained upon reductive N=N bond cleavage. The synthetic route used is based on operationally simple protocols that allows a direct access to azo-substituted dipyridophenazines, through palladium catalyzed cross-coupling processes and Mills reactions. The initial biologic studies, including the dark toxicity, localization and phototoxicity are also detailed.

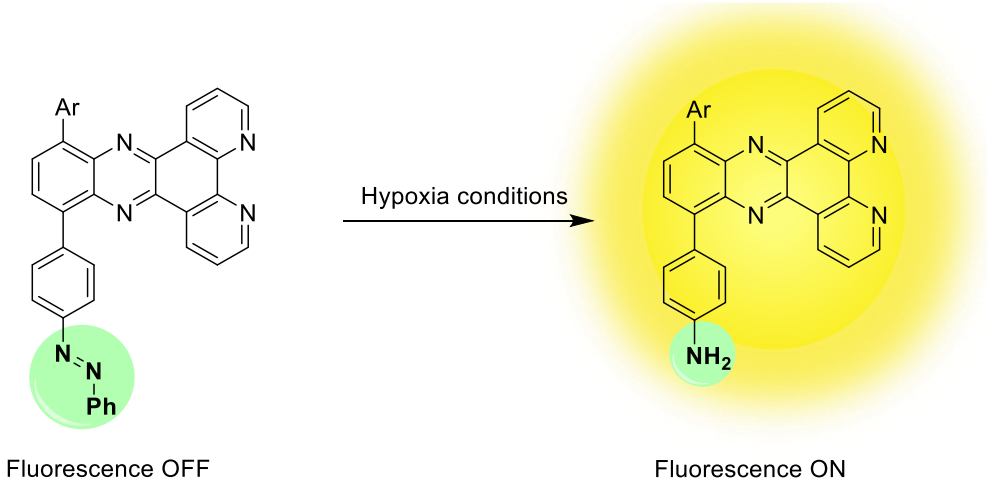


Figura 1. Reductive cleavage of the azo-derivative to the amino-derivative turning on the fluorescence.

References:

[1] Kiyose, K.; Hanaoka, K.; Oushiki, D.; Nakamura, T.; Kajimura, M.; Suematsu, M.; Nishimatsu, H.; Yamane, T.; Terai, T.; Hirata, Y.; Nagano, T. *J. Am. Chem. Soc.* **2010**, *132*, 15846.
[2] Guisan-Ceinos, S.; Rivero, A. R.; Romeo-Gella, F.; Simón-Fuente, S.; Gómez-Pastor, S.; Calvo, N.; Orrego, A. H.; Guisán, J. M.; Corral, I.; Sanz-Rodríguez, F.; Ribagorda, M. *J. Am. Chem. Soc*. **2022**, *144*, 8185-8193.
[3] Sun, L.; Li, G.; Chen, X. et al. *Sci. Rep.* **2015**, *5*, 14837.

Heterocyclic cores from cascade reactions between internal alkynes and gem-diborylalkenes

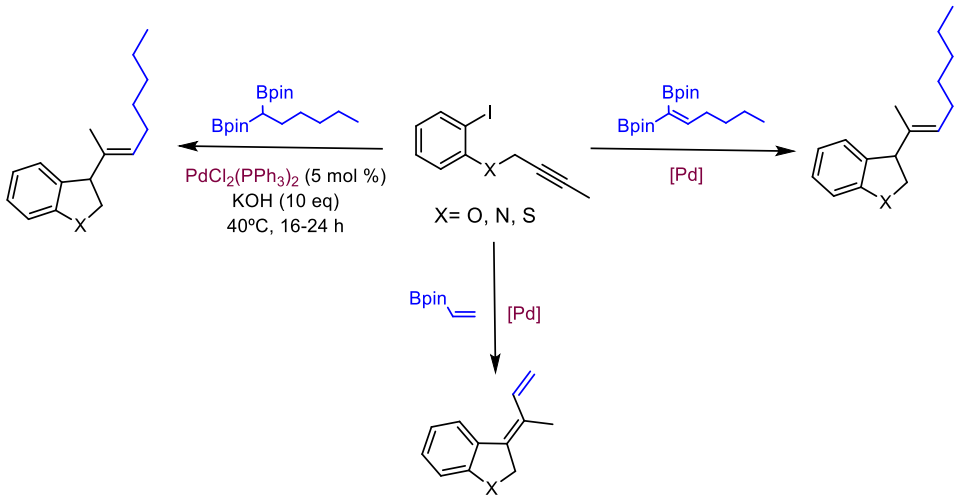
B. Ibarra Sarango,[a] N. Pascual,[a] P. Mauleón,[a] R. Gómez-Arrayás.[a]

[a]*Departamento de Química Orgánica, Facultad de ciencias, Universidad Autónoma de Madrid, 28049, Madrid*
e-mail: angela.ibarra@estudiante.uam.es

Keywords: *cascade reactions, gem-diborylalkenes, Palladium*

Organoboranes compounds are useful synthetic intermediates in organic synthesis with utility in C-C and C-X bond forming reaction. Different methodologies have been developed in which their catalytic efficiency has been demonstrated with transition metals such as Cu or Pd.[1] Recently, gem-diborylalkenes have emerged as efficient reagents for selective cross-coupling reactions as the Suzuki-Miyaura that in combination with cascade reactions, it offers the possibility to rapidly build up molecular complexity.[2]

Our research group has been involved in the mechanistic study and reactivity of different organoboron derivatives such as gem-diborylalkanes and 1-monoborylakenes against aryl iodides containing a C-C triple bond. In this project, we investigate the reactivity of gem-diborylalkenes. In this context, we initially expected a different reactivity subject to the boron derivate. It was observed that in the same conditions as a result of the catalysis (Scheme 1), gem-diborylalkanes and 1-monoborylakenes formed diferent products, while gem-diborylakenes formed the same product as with gem-diborylalkanes. The ultimate aim of the project is to be able to propose a mechanism that justifies the unexpedted reactivity of gem-diborylalkenes.



Scheme 1. Catalytic scheme for the products obtained.

References:

[1] (a) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (b) Whyte, A.; Burton, K.; Zhang, J.; Lautens, M. *Angew. Chem. Int. Ed*. **2018**, *57*, 13927.

[2] (a) *Eur. J. Org. Chem*. DOI: 10.1002/ejoc.201701786. (b) Willems, S.; Toupalas, G.; Reisenbauer, J.; Morandi, Bill. *Chem. Commun.* **2021**, *57*, 3909.

Catalyzed reactions optimization using ChemBeads-supported reactants and its applicability in automated synthesis

J. A. Jiménez Bermudo,[a] C. Alhambra Jiménez,[a] M. Cifuentes García[a]

[a]*Eli Lilly and Company, Centro de Investigación Lilly S.A, Alcobendas, Madrid, España.*
e-mail: joseantonio.jimenezb@estudiante.uam.es

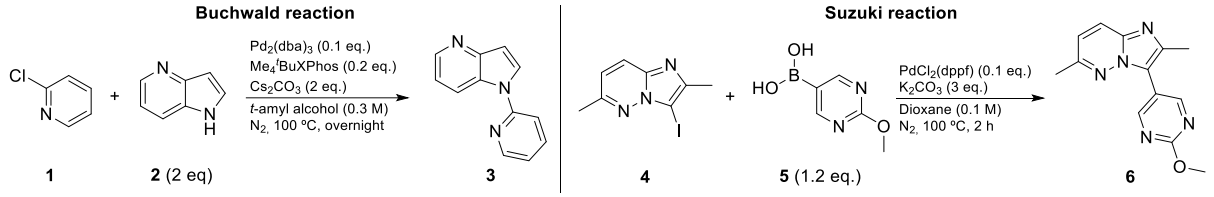
Keywords: *ChemBeads, catalysis, HTE*

Microscale high-throughput experimentation (HTE) is considered as one of the most important synthetic technologies in drug discovery programs, as it enables the accelerated and effective development and optimization of reaction conditions in parallel for novel compounds discovery at a submilligram scale, minimizing highly valuable intermediates consumption.[1] However, accurate and efficient dispensing of different solid reactants on this scale remains a major issue. The different physical properties among these solids and the small mass required for each transformation, make either the use of automatic dispensing robots or manual weighting difficult and unpractical.[2]

Recently, ChemBeads (glass beads coated with solid chemical reagents) strategy has emerged as the solution to this problem.[3] In ChemBeads, solid reagents are adhered to the surface of the inert glass beads until they reach the reaction solution, where reactants separate from the beads to take part in the reaction. The principal benefits from this strategy are that ChemBeads have (i) a superior gross weight than the neat reactants and (ii) glass beads physical properties, allowing and easier and more accurate manual or automatic weighting process.

Metal catalyzed reactions are essential synthetic transformations in medicinal chemistry. Its main limitations for microscale HTE are the insolubility, handling and weighting of the metal catalyst at a submilligram scale. This project aims to evaluate the Chembeads strategy performance when catalysts are the guest particles in the glass beads surface in a microscale content.

In order to validate the ChemBeads strategy, various catalyzed reactions were studied (examples in Scheme 1). Catalyst ChemBeads were prepared mixing 212-300 µm glass beads and 5%wt. of catalyst in a Resodyn Acoustic Mixer at 100 G for 30 seconds. Once required ChemBeads were prepared, miniaturization and optimization of the reactions were carried out, along with a comparative between Bead-supported and neat-catalyst reaction.



Scheme 1. Model reactions for ChemBeads validation.

According to the results obtained in this project, it can be concluded that catalyst-ChemBeads make the process of miniaturization and optimization of the studied reactions much easier and more practical at micromolar scale. Results were analogous to larger scale catalyst-neat reaction, showing cleaner LC-MS in most cases.

References:

[1] Perera, D.; Richardson, P.; Sach, N. W. *Science*, **2018**, *359,* 429-434.
[2] Tu, N. P. *Org. Process Res. Dev.* **2019**, *23,* 1900-1907.
[3] Tu, N. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 7987-7991.

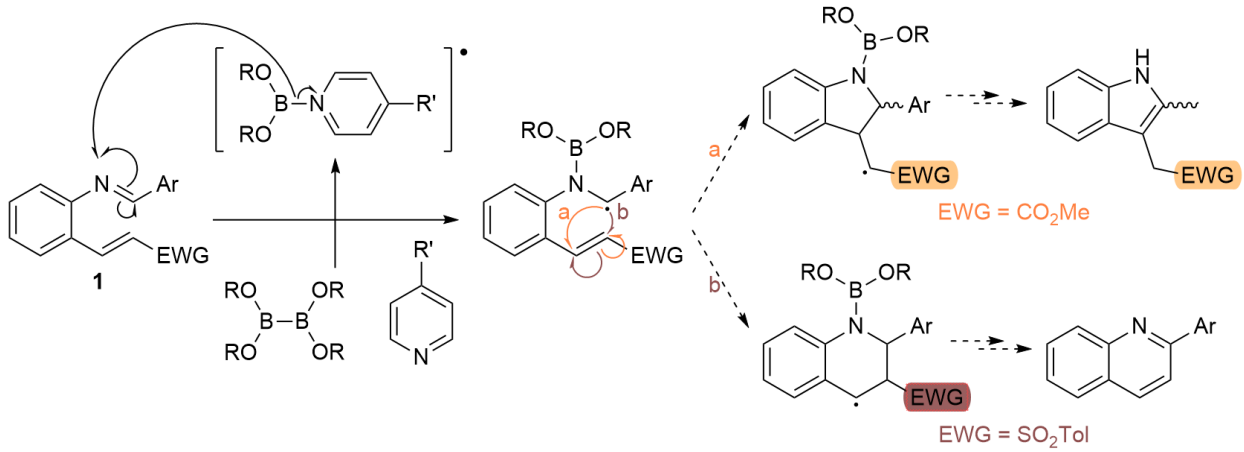
Intramolecular trapping of α-amino radicals by treatment of imines with pyridine-boryl radicals

D. Jiménez Rufo,[a] R. Valderrama,[a] M. Tortosa,[a] M. B. Cid.[a]

[a]*Universidad Autónoma de Madrid*
e-mail: david.jimenezrufo@estudiante.uam.es

Keywords: *Diboron compound, α-amino radical, cyclization*

Diboron compounds are non-toxic, readily available, versatile, and valuable reagents in a wide range of organic transformations, particularly in borylation reactions.[1] Boron reagents act as Lewis acids with moderate, yet remarkably interesting, reactivity. As evidenced by their ability to react with substituted pyridines, diboron compounds generate pyridine-boryl radicals, which serve as useful intermediates capable of promoting diverse reactions under very mild conditions.[2] Previous studies in our group were focused on demonstrating the applicability of these intermediates on various imines. In the presence of pyridine and diboron reagents, imines dimerized easily to provide diamines, presumably via α-amino radicals.[3] The main objective of this work is to assess the ability of imines to generate α-amino radicals and subsequently undergo intramolecular trapping. Cyclization of imines **1** can lead to the formation of either five- or six-membered rings, yielding indol or quinoline structures, respectively, which are very common scaffolds of pharmaceutical and biologically active entities (Scheme 1).



Scheme 1. Previous studies and current work

Herein, we present the preparation and cyclization studies of a variety of substrates containing different electron-withdrawing groups (EWG) substituents at the double bond, such as ester and sulfone, as well as different aromatic substituents at the imine moiety. Preliminary results showed that the reaction of the unsaturated ester resulted in a complex mixture in which the indolic structure was detected. Interestingly, the cyclization of the vinyl sulfone evolved to the corresponding quinoline through aromatization, attributed to the elimination of sulfinic acid.

References:

[1] Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem.Rev.* **2016**, *116*, 9091-9161.
[2] Misal Castro, L .C.; Sultan, I.; Tsurugi, H.; Mashima, K. *Synthesis,* **2021**, *53*, 3211-3226.
[3] Franco, M. **2022** "Novel Applications of Diboron Reagents through Graphene-Based Cu(I) Catalysis and Lewis Base Activation", PhD thesis, Universidad Autónoma de Madrid, Madrid.

Copper-catalyzed carboboration enabled by hydrogen atom transfer

N. Martín Sáez,[a] C. Lendínez,[a] G. Marcos-Ayuso,[a] P. Mauleón,[a] R. Gómez Arrayás.[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, UAM, 28049 Madrid (Spain).*
e-mail: nuria.martinsaez@estudiante.uam.es

Keywords: *Copper catalysis, carboboration, vinylboronates, C−H functionalization, Hydrogen Atom Transfer (HAT).*

The Cu-catalyzed carboboration of internal alkynes using diboron reagents and carbonated electrophiles has emerged as an innovative strategy for the synthesis of tri- and tetrasubstituted vinylboronates with a fully defined stereochemical configuration.[1,2] The use of alkanes as carbon source is a powerful tool in synthetic chemistry, providing minimal residues and avoiding substrate pre-functionalization. Hydrogen Atom Transfer (HAT) has proved to be a successful methodology in the activation of alkanes,[3] requiring in many cases an external oxidant as radical source. In this work the merge of carboboration with C−H functionalization through HAT is explored.

The feasibility of the hydroboration reaction in the presence of different oxidants was evaluated, obtaining the best results when using di-tert-butyl-peroxide (DTBP). However, no product was observed when the carboboration reaction was tested, even under similar conditions to those described by Chang's group.[4] In an attempt to simplify the system, the borylation of alkanes was run both under thermal conditions and under light irradiation, but was not satisfactory. This promising strategy for the generation of borylated species is still being studied.

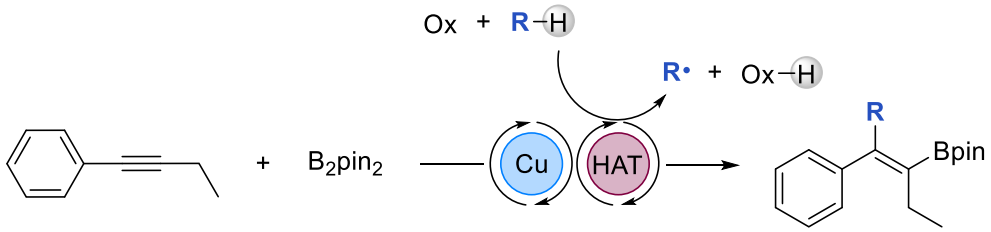


Figure 1. General reaction for the Cu-catalyzed carboboration of internal alkynes enabled by HAT.

References:

[1] Alfaro, R.; Parra, A.; García Ruano, J.L.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165-15168.
[2] Kim-Lee, S. H.; Mauleón, P.; Gómez Arrayás, R.; Carretero, J. C. *Chem* **2021**, *7*, 2212-2226.
[3] a) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. *Science* **2016**, *353*, 1014-1018.
b) Zheng, Y. W.; Nabore, R.; Donabaeur, K.; Yakubov, S.; König, B. *ACS Catal.* **2020**, *10*, 8582-8589.
[4] Xie, W.; Heo, J.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2020**, *142*, 7487-7496.

Removal of perfluorinated water contaminants using chemically modified metal-organic frameworks

S. Marugán-Benito,[a] A. E. Platero-Prats.[a,b]

[a]*Dept. of Inorganic Chemistry, Universidad Autónoma de Madrid, Madrid, Spain,* [b]*Condensed Matter Physics Centre (IFIMAC), Madrid, Spain.*
e-mail: sergio.maruganb@estudiante.uam.es

Keywords: *Metal-organic frameworks, perfluorinated substances (PFAS), water treatment.*

Perfluorooctanoic acid (PFOA) is an emerging water pollutant with harmful effects for the environment due to its toxicity, bioaccumulative nature, high persistence and degradation resistance.[1] As a result, one of the most efficient methods for PFOA removal is through capture by porous materials. In this context, metal-organic frameworks (MOFs) have shown potential for this purpose due to their high surface areas and permanent porosity.[2] To expand on this, the objective of this work is to study the potential of chemical functionalizations in MOFs as a method to improve the PFOA capture performance. Specifically, two different families of functionalized materials of the zirconium(IV)-based MOF-808 were prepared and evaluated for adsorptive PFOA removal from aqueous solution (Figure 1). The frameworks were modified with different fluorinated ligands (2-fluorobenzoic acid, 2,6-difluorobenzoic acid and trifluoroacetic acid) or metals (iron(II), copper(II) and nickel(II)) to evaluate the effect of various interactions in the capture performance, compared to the pristine MOF. The adsorbents show high surface areas (575-1678 m^2/g) and are highly crystalline and stable in aqueous media for several days under biological pH conditions. PFOA capture capacity was measured at 1972 mg/g for pristine MOF-808 and 2036 mg/g for Fe-MOF-808 using 1000 ppm as the initial pollutant concentration. These results show the high aptitude of pristine and functionalized MOF-808 materials for the removal of PFOA. Possible capture mechanisms for the two different families are also proposed.

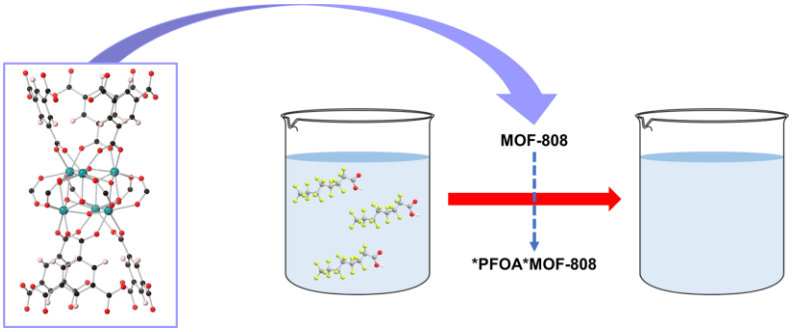


Figure 1. (left) Structural model of a repetition primary unit of MOF-808 (Zr atoms colored blue, O red, C black and H pink). (right) PFOA removal from water using MOF-808 scheme.

References:

[1] Li, R.; Alomari, S.; Stanton, R.; Wasson, M. C.; Islamoglu, T.; Farha, O. K.; Holsen, T. M.; Thagard, S. M.; Trivedi, D. J.; Wriedt, M. *Chem. Mater*. **2021**, *33*, 3276–3285.

[2] Chang, P. H.; Chen, C. Y.; Mukhopadhyay, R.; Chen, W.; Tzou, Y. M.; Sarkar, B. *J. Colloid Interface Sci*. **2022**, *623*, 627–636.

Subphthalocyanine cages as photoreactors for the functionalization of fullerenes

P. Merino Diaz-Caneja,[a] I. Paramio,[a] G. de la Torre.[a,b]

[a] Department of Organic Chemistry, Universidad Autónoma de Madrid, [b] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid*
e-mail: paula.merinod@estudiante.uam.es

Keywords: *Subphthalocyanine, photocatalysis, fullerenes*

Metallo-organic ensembles built with porphyrinoids offer defined spaces for the encapsulation of large organic guests such as fullerenes. Some authors have taken advantage of the space confinement in these host:guest complexes to carry out organic transformations that do not proceed outside the cage.[1] Subphthalocyanines (SubPcs) are 14-π electron aromatic chromophores with a bowl-shaped structure. The internal cavity formed by a dimeric SubPc capsule ($SubPc_2Pd_3$), ensembled by coordination of pyridines at the periphery of C_3-symmetry SubPc to Pd centers, has proved an optimal, shape-complementary space for the complexation of C_{60} fullerene.[2] Taking advantage of the intense absorption of green light of the SubPc components of the capsule, and their ability to transfer energy/electrons from the excited state, our group has recently described the unprecedented use of SubPc cages as molecular photoreactors to perform photoredox addition reactions over the double bonds of guest C_{60}.[3] Unfortunately, the reaction could only be performed using stoichiometric amounts of the SubPc cage due to product inhibition (Fig. 2). In this work, we describe the preparation of a more flexible SubPc cage, built with a related C_1-symmetry tris-pyridyl SubPc (Fig. 1), which facilitates the exchange between the complexed addition compound and pristine fullerene, thus allowing to use it in catalytic amounts (Fig. 3). Interestingly, under these conditions, a different reaction pathway is favored, which renders a cyclopropanated fullerene in very high yields.

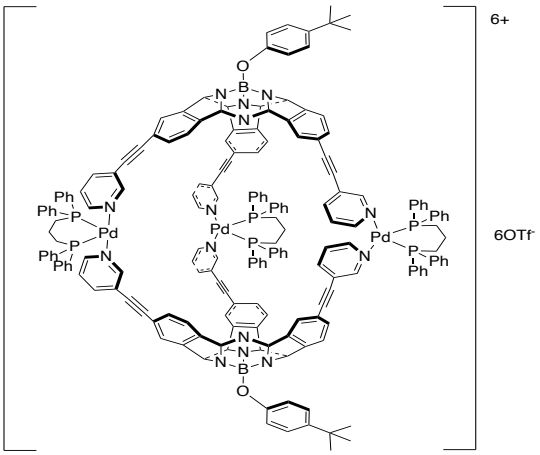


Fig. 1 C_1 symmetry SubPc cage

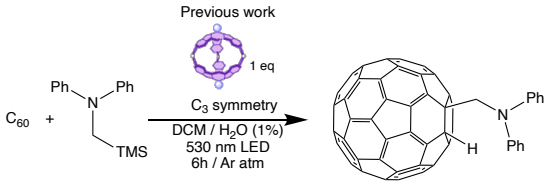


Fig. 2 Stoichiometric reaction with C_3 SubPc cage

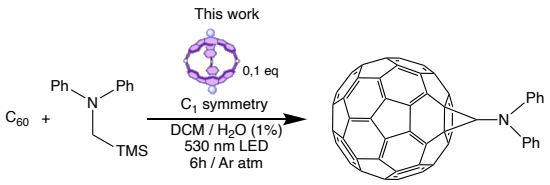


Fig. 3 Catalytic reaction with C_1 SubPc cage

References:

[1] Fuertes-Espinosa, C.; García-Simón, C.; Castro, E.; Costas, M.; Echegoyen, L.; Ribas, X.; Chang, X.; Lin, S.; Wang, G.; Shang, C.; Wang, Z.; Liu, K.; Fang, Y.; Stang, P. J.; *J. Am. Chem.* Soc. **2020**, *142*, 15950–15960.

[2] Claessens, C. G.; Gonzalez-Rodriguez, D.; Salomé Rodriguez-Morgade, S.; Medina, A.; Torres, T.; *Chem. Rev.*, **2014**, *114*, 2192–2277.

[3] Moreno-Simoni, M.; Torres, T.; de la Torre, G.; *Chem. Sci.* ***2022***, *13*, 9249–9255.

Synthesis of boronic esters derived from 3 and 4 member rings

E. Mollá Arroyo,[a] A. Viso,[a] R. Fernández de la Pradilla,[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.*
e-mail: elio.molla@estudiante.uam.es

Keywords: *Cyclobutanes, boronic esters, metal-free borylation.*

The cyclobutane skeleton displays various key properties that make them very useful both in catalysis[1] and medicinal chemistry.[2] Concerning the later field, its inclusion in drugs normally leads to a better binding with some biological receptors, mainly due to the increased conformational restriction that this group imposes. As a result, there is a high demand for new synthetic pathways to produce these cycles, which may open the way to optimize the synthesis of current drugs and especially to develop new ones.

In this project, the challenge was tackled by using boronic esters, due to the numerous advantages that this functional group offers. Boronates are stable and easy to handle, environmentally friendly, and can undergo multiple kinds of transformations, including oxidation, homologation, and coupling reactions to name a few, which make them ideal as synthetic scaffolds.[3] Their utility has already been proven for synthesizing 1,2-functionalized small-ring compounds using vicinal bisboronates.[4] The current project aims to synthesize geminal bisboronates in four-membered cycles and test if the synthetic usefulness they have displayed in aliphatic chains[5] can be translated onto these rings. The methodology developed consists of the transformation of commercial *exo*-alkenes into hydrazones, by a simple three-reaction procedure,[6] which undergo transition-metal-free gem-bisborylation to produce the desired 1,1-bisboronate with a fair scope for the substituents in the 3 position. To illustrate the possible uses of such compounds, further transformations were also tested.

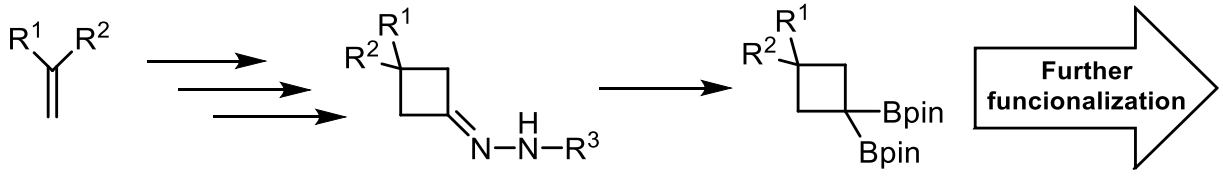


Figure 1. Synthetic sequence

References:

[1] Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50,* 7740-7752.
[2] van der Kolk, M. R.; Janssen, M. A. C. H.; Rutjes, F. P. J. T.; Blanco-Ania, D. *ChemMedChem* **2022**, *17*, e202200020.
[3] Leonori, D.; Aggarwal, V. K. *Angew.Chem. Int. Ed.* **2015**, *54*, 1082-1096.
[4] (a) Nóvoa, L.; Trulli, L. Parra, A.; Tortosa, M. *Angew. Chem.* **2021**, *133*, 11869-11874. (b) Teresa, J.; Velado, M.; de la Pradilla, R. F.; Viso, A.; Lozano, B.; Tortosa, M. *Chem. Sci.* **2023**, *14*, 1575-1581.
[5] Miralles, N.; Maza, R. J.; Fernández, E. *Adv. Synth. Catal.* **2018**, *360*, 1306-1327.
[6] Ning, X.; Chen, Y.; Hu, F.; Xia, Y. *Org. Lett.* **2021**, *23*, 8348-8352.

Synthesis of a CTF based material with highly reducing properties

M. D. Navarro,[a] L. Marzo.[a]

[a]*Organic Chemistry Department, Universidad Autónoma de Madrid, 28049 Madrid (Spain)*
e-mail: mariad.navarro@estudiante.uam.es

Keywords: *Materials, photocatalysis, heterogeneous catalysis*

Photocatalysis appeared more than a decade ago as an alternative capable of overcoming many of the limitations of photochemistry.[1] Most of the molecules are not able to absorb in visible region of the spectrum, therefore, the use of a coloured intermediator (photocatalyst) able to absorb in this region and to transmit the energy to the desired substrates has allowed the development of new synthetic methods.

The use of covalent triazine frameworks (CTFs) have gained much attention as a promising new class of polymer-based, metal-free, visible light active heterogeneous photocatalysts.[2] In this project we present the synthesis of a new covalent triazine framework (CTF) that contains a photocatalyst with high photoreductive activity. The CTF material shown in figure 1 will be prepared from the two monomers **A** and **B**, the latest containing a photoactive 9-anthrol based fragment. 9-Anthrol derivatives have been employed as photocatalysts, due to their high reduction power, in the photocatalytic C-H carboxylation of arenes and styrenes.[3] This fragment will be introduced as a defects in the material in different percentages with the aim to prepare a material with highly reductive properties.

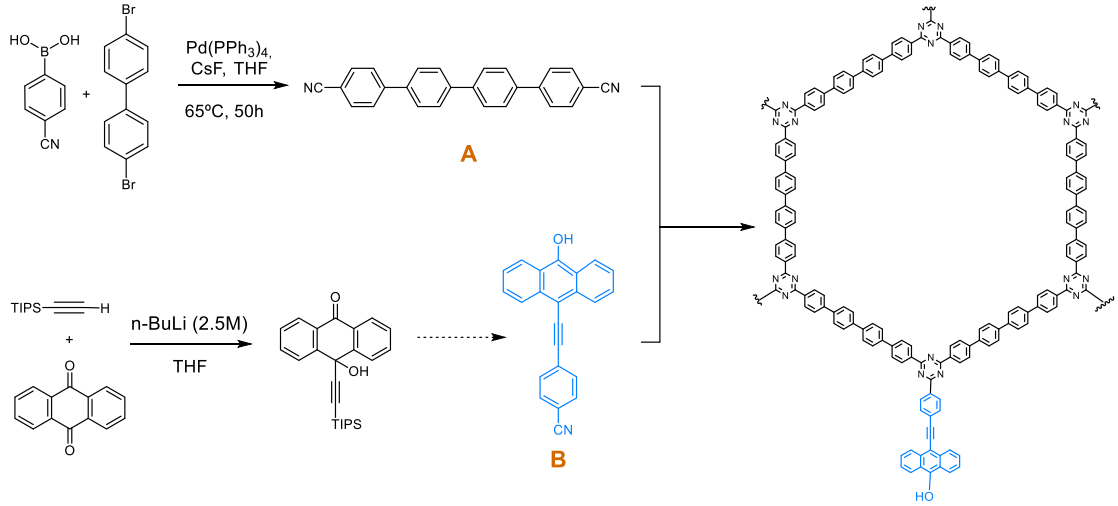


Figure 1. Synthesis of the material and subsequent photocatalytic reaction for substrate reduction.

References:

[1] Marzo, L.; Martinez-Haya, R. *An. Quim.* **2018**, *114*, 142–147.
[2] Qian, Z.; Wang, Z. J.; Zhang, K. A. I. *Chem. Mater.* **2021**, *33*, 1909–1926.
[3] Schmalzbauer, M.; Svejstrup, T. D.; Fricke, F.; Brandt, P.; Johansson, M. J.; Bergonzini, G.; König, B. *Chem*. **2020**, *6*, 2658–2672.

Infrared-induced carbene generation followed by C, H-insertion crosslinking of polymers

Silvia Oñate Martínez,[b] Alexander Bleiziffer,[a] Jürgen Rühe.[a]

[a]*Chemistry & Physics of Interfaces (CPI) - Institut für Mikrosystemtechnik (IMTEK) - Freiburg Universitä,*
[b]*Universidad Autónoma de Madrid*
e-mail: silvia.onnate@estudiante.uam.es / silvia.onate@imtek.uni-freiburg.de

Keywords: *Infrared radiation, CHic reaction, Polymer science*

Coatings are a simple and practical way to slightly modify the surface properties of materials, making them protein-repellent or hydrophobic without changing the bulk properties.[1] Polymer coatings have been developed during the last years due to their versatility and simple activation by introducing a crosslinker. Durability is an important property of these coatings, to increase it compared to adsorbed mechanisms, polymers can be covalently attached to the surface by activating the cross-linking.

Most of the research done so far to activate the crosslinking is based on thermal or photochemical activation.[2] IR radiation can be used to heat the polymer to induce thermal activation of the crosslinker, leading to carbene formation and subsequent C, H insertion crosslinking (CHic), resulting in covalent surface bonding and therefore improving durability. CHic reaction allows to crosslink the polymer and covalently attached the polymer to the surface in one step and just C,H bonds are required

To make the polymer more absorbent, another layer is mandatory. Black coatings have been proven to be IR absorbents and good thermally conductive.[3] The whole process is summarized in Figure 1.

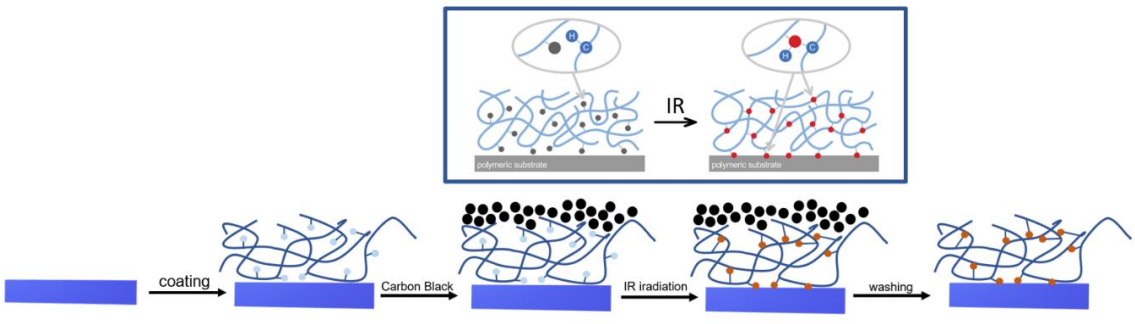


Figure 1:Scheme of the process of coating and Irradiation of the polymer to induce crosslinking

Using an innovative set up and 2 polymers, a low-power IR lamp (50-100 watts) can be used to achieve mild temperatures (30-60°C) sufficient to induce the CHic reaction and covalently bond the coating, resulting in more durable coatings using a more accessible and safer energy source.

References:

[1] Hönes, R. Rühe, J. *Langmuir*. **2018** *Jun 26; 34, 8661–8669.*
[2] Bleiziffer A, Kost J, Rühe J. *Macromol. Mater. Eng.* **2022** *Aug 20, 307, 2200345–5.*
[3] Mellouki,I. Bennaji, N. Yacoubi, *Elsevier.* ***2007*** *Mar50, 58–62.*

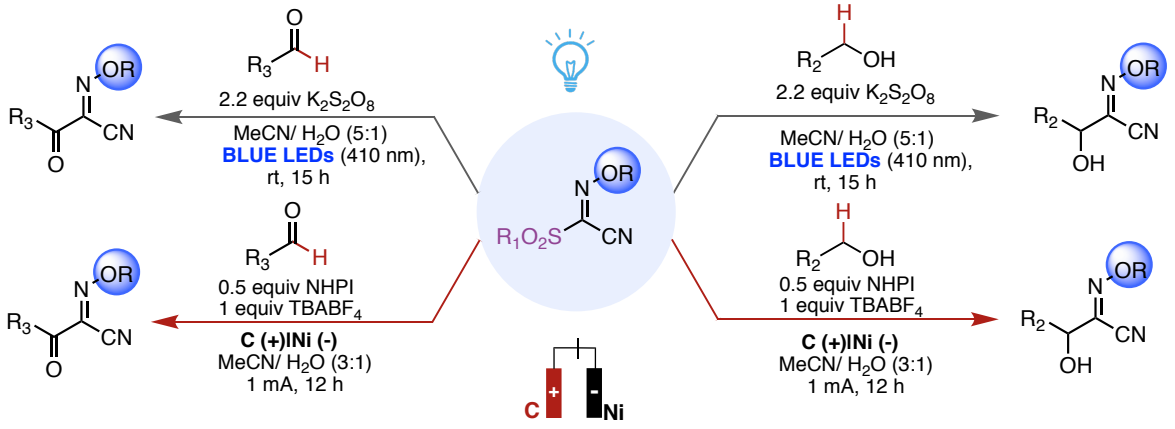
A cross-dehydrogenative process *via* photo-induced and electrocatalytic processes.

J.A. Ordóñez Chacón,[a] R. García Enriquez,[a] J.A. Fernández Salas[ab]

[a] *Organic Chemistry Department, Universidad Autónoma de Madrid, Módulo 2, 28049 Madrid, Spain.*
[b] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, Madrid, Spain.*
e-mail: jose.ordonnez@estudiante.uam.es

Keywords: *CDC, HAT, Photochemistry*

There is a great need for developing new efficient "green processes" to create alternative sustainable methodologies to prepare valuable organic molecules. Cross-dehydrogenative coupling reaction (CDC) has been developed as environmentally-friendly and efficient strategy for building C-C bonds.[1] CDC has emerged as a powerful synthetic tool as it allows the direct coupling of unactivated C–H bonds. Therefore, this strategy circumvents the need for pre-functionalization, for example, through the conversion of a C–H bond to an electrophilic C–halogen bond, frequently utilized in synthesis, including in cross-coupling.[2] For the development of CDC reactions, viable methodologies for the cleavage of C–H bonds are crucial. In this context, one of the main strategies reported in the literature involves the abstraction of a hydrogen radical trough a hydrogen atom transfer (HAT) process. Photocatalysis have approached this challenging transformation by using a variety of different photoinduced HAT catalytic systems.[3] In this context, we discovered a general, simple and sustainable method for the selective functionalization of non-activated alcohols and aldehydes using oximes as radical acceptors, which represent privileged building blocks.[4] In the presented method, activated persulfate promotes a HAT process that give rise to hydroxyl or dicarbonyl derivatives in moderate to good yields (Scheme 1).[5] In addition, and looking for a more atom efficient systems, we have developed an electrocatalytic HAT process. The use of N-hydroxyphthalimide as HAT catalyst under electrochemical conditions triggers the C-C bond forming event in good yields (Scheme 1).



Scheme 1. Reactions studied

References:

[1] Tian, T.; Zhiping, L.; Chao-Jun, L. *Green. Chem.* **2021**, *23*, 6789-6862.
[2] Jan, R.; Pathak, P.T.; Sigma, S.M. *Chem. Rev.* **2011**, *111, 3,* 1417-1492.
[3] Capaldo, L.; Ravelli, D.; Fagnoni, M. *Chem. Rev.* **2022**, *122,2*, 1875-1924.
[4] (a) Zhu, Y.; Huang, K.; Pan, J.; et al. *Nat. Commun.* **2018**, *9*, 2625. (b) Zhu, Y.; Wen, X.; Song. S.; Jiao, N. *ACS Catalysis*. **2016**, *6, 10*, 6465-6472.
[5] Nova-Fernandez, J.L.; García, M, Mollari, L.; Pascual-Coca, G.; Cabrera, S.; Alemán, J. *Chem. Commun.* **2022**, *58*, 4611-4614.

Photo-electrochemical Minisci-type alkylation with α-silylalcohols

M. Ortega-Ruiz,[a] R. del Río-Rodríguez,[a] J. A. Fernandez-Salas.[a,b]

[a] *Organic Chemistry Department, Universidad Autónoma de Madrid, Módulo 2, 28049 Madrid, Spain.*
[b] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, Madrid, Spain.*
e-mail: maria.ortegar@estudiante.uam.es

Keywords: *Minisci-reaction, photochemistry, electrochemistry*

N-heterocycles have attracted the attention of organic chemists over the years as they are versatile intermediates in organic synthesis and common structures in natural and synthetic products with a wide range of biological properties.[1,2]
The venerable Minisci reaction stands as a powerful and attractive synthetic tool for the direct and rapid modification of *N*-heterocycles.[1] Both photoredox catalysis and electrochemistry, which is quickly becoming one of the most popular paths to access radical intermediates through single-electron activation of organic substrates, have attracted considerable attention to perform Minisci-type functionalization reactions employing different kinds of alkyl radical precursors.[2] Moreover, the combination of electrochemistry and photocatalysis have been recently demonstrated to provide alternative reaction pathways with excellent results.[3] In this context, we describe a general, facile and environmentally friendly Minisci-type alkylation of *N*-heteroarenes under simple photo-electrochemical conditions using alkyl α-silylalcohols as radical precursors (Figure 1). The presented method takes place in absence of any external promoter or photocatalyst as the photocatalytic cycle is autocatalyzed by the heterocyclic substrate itself. In addition, and by changing the electrochemical reaction conditions, the α-hydroxy alkylated (Figure 1, **A**) or the alkylated (Figure 1, **B**) products could be selectively achieved. A variety of different *N*-heterocycles have been successfully alkylated, and both products have been isolated in moderate to very good yields.

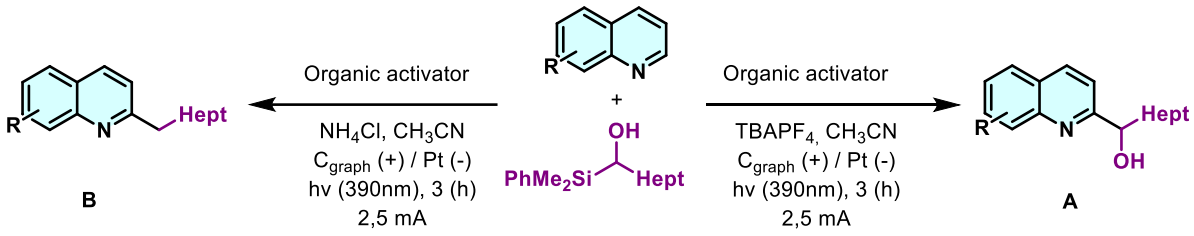


Figure 1. Reaction studied.

References:

[1] Proctor, R. S. J.; Phipps, R. J. *Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 13666.
[2] Heravi, M. M.; Zadsirjan, V. *RSC Adv.*, **2020**, *10,* 44247.
[3] (a) Photochemistry: S. Jin, X. Geng, Y. Li, K. Zheng, *Eur. J. Org. Chem*. **2021**, *2021*, 969. (b) Electrochemistry: Río-Rodríguez, R. D.; Fragoso-Jarillo, L.; Garrido-Castro, A.F.; Maestro, M. C.; Fernández-Salas, J.A.; Alemán, J. *Chem. Sci.* **2022**, *13*, 6512. (c) Photo-electrochemistry: J. P. Barham, B. König, Angew. *Chem. Int. Ed.* **2020**, *59*, 11732.

Visible light-mediated deaminative alkylation of primary amines via isonitrile formation

C. Pérez Sánchez,[a] T. Rigotti,[a] M. Tortosa.[a,b]

[a] *Organic Chemistry Department, Universidad Autónoma de Madrid (UAM), Cantoblanco, 28049-Madrid, Spain.*

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

e-mail: carla.perezsanchez@estudiante.uam.es

Keywords: *amines, isonitriles, photoredox*

Amines are ubiquitous molecules, abundant, and commercially available in a wide variety from simple to complex compounds. Therefore, they are an attractive feedstock as potential building blocks for the formation of more complex molecules. However, the selective catalytic cleavage of C-N bonds in amines is a difficult challenge, mainly due to the high dissociation energy of this bond compared to other carbon-heteroatom bonds. Pyridinium salts are an example of a simple amine derivative recently used in a photocatalyzed single-electron reduction process,[1] forming a carbon-centered radical capable of engaging in different bond-forming events.

Inspired by the early work reported by Barton,[2] we have envisioned that isonitriles could work as appropriate carbon-centered radical precursors in a silyl-mediated, photoredox-catalyzed process under visible light irradiation.

Using isonitriles as a redox-neutral precursor, silicon derivatives as radical initiators, and an organic photocatalyst, we have been able to optimize the homolytic cleavage of the C-N bond to generate primary, secondary, and tertiary alkyl radicals. These intermediates have undergone conjugate addition with electron-poor alkenes, forming $C(sp^3)$-$C(sp^3)$ cross-coupled products.

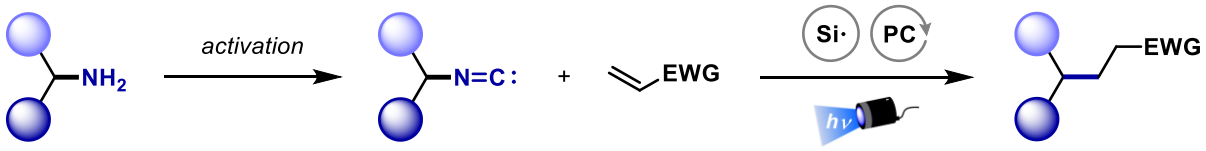


Figure 1. Activation of amines through isonitriles, and capture of the carbon-centered radical with an electron-poor alkene.

References:

[1] (a) Ociepa, M.; Turkowska, J.; Gryko, D. *ACS Catal.* **2018**, *8*, 11362-11367. (b) Correia, J. T. M.; Fernandes, V. A.; Matsuo, B. T.; Delgado, J. A.; de Souza, W. C.; Paixão, M. W. *Chem. Commun.* **2020**, *56*, 503-514.

[2] Barton, D. H. R.; Bringman, G.; Lamotte, G.; Motherwell, R. S. H.; Motherwell, W. *Tetrahedron Lett.* **1979**, *20*, 2291–2294.

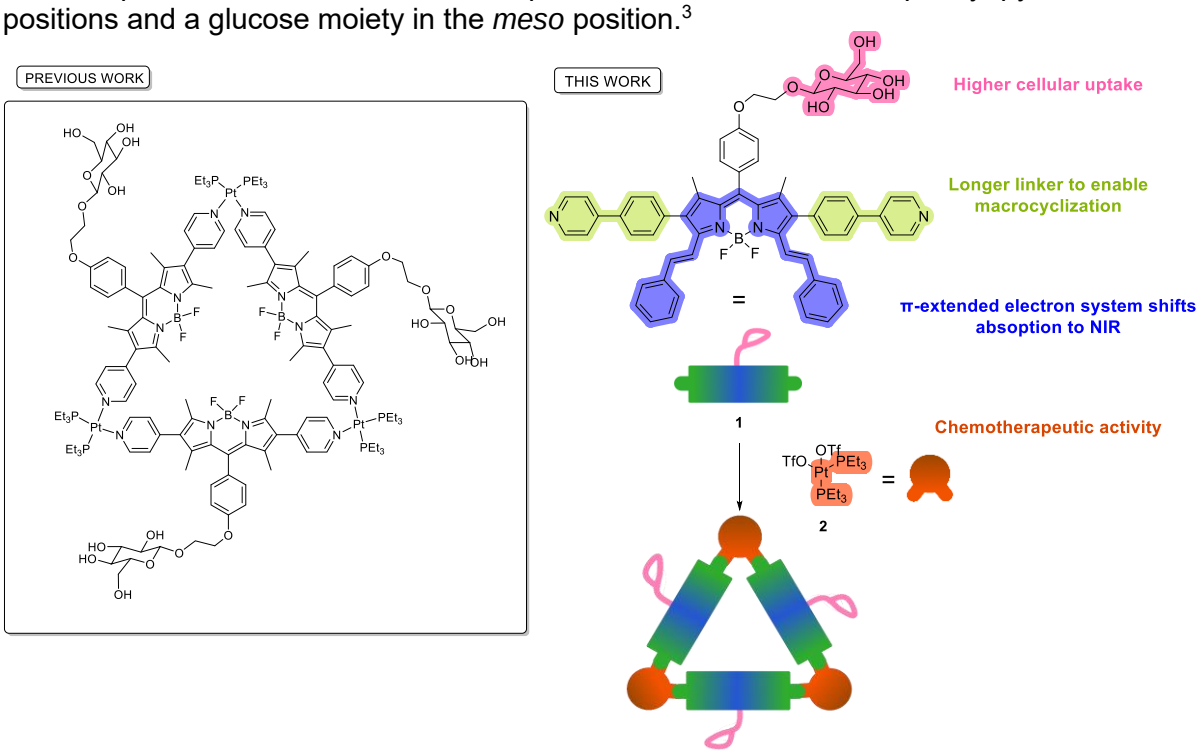
Synthesis of glycosylated Pt(II)-BODIPY metallacycle for combined chemo- and photodynamic therapy

P. Rubio Ramiro,[a] G. Durán Sampedro,[b] G. de la Torre.[a,c]

[a] *Department of Organic Chemistry, Universidad Autónoma de Madrid, Campus de Cantoblanco, Madrid. Spain.*
[b]*Organic Chemistry Department, Universidad Complutense de Madrid, Madrid 28040, Spain.*
[c]*Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, Campus de Cantoblanco, Madrid 28049, Spain*
e-mail: pedro.rubior@hotmail.com

Keywords: *BODIPY, metallacycle, PDT*

Photodynamic therapy (PDT) is a non-invasive form of phototherapy that utilizes harmless light to activate non- or minimally toxic photosensitive chemicals called photosensitizers (PS) to generate cytotoxic species for malignant cell eradication.[1] Pt(II)-BODIPY metallo-supramolecular complexes have proved appealing antitumoral agents that combine the chemotherapeutic activity of Pt(II) complexes with the photocytotoxicity of BODIPYs.[2] Our group has recently demonstrated that conjugation of these assemblies with tumor-targeting ligands (i.e. glucose) can boost the uptake by cancer cells that overexpress the corresponding receptors on the surface. However, the low absorption of the metallo-supramolecular complex in the therapeutic window have precluded the realization of in vivo studies. Herein, we report on the synthesis a Pt(II)-assembled metallo-supramolecular complex built by coordination-driven assembly of a π-extended electron BODIPY precursor with red-shifted absorption, functionalized with two phenyl-pyridines at the 2,6 positions and a glucose moiety in the *meso* position.[3]



Scheme 1: *Synthesis of Pt(II)-BODIPY metallomacrocycle.*

References:

[1] a) Hamblin, M. R.; Hasan, T. *Photochem. Photobiol. Sci.* **2004**, *3*, 436.
[2] Lin, X.; Chen, F.; Yu, X.; Stang, P. *Proc. Natl. Acad. Sci.* **2022,** *119*, 29.
[3] Duran-Sampedro G. et al. *J. Med. Chem.* **2023**, 66, *5*, 3448–3459.

Photochemical functionalization of carbon nanotubes

P. Sánchez de la Morena,[a] M. Blanco.[a]

[a] *Departamento de Química Orgánica, Facultad de ciencias, Universidad Autónoma de Madrid, 28049, Madrid*
e-mail: paula.sanchezd01@estudiante.uam.es

Keywords: *nanotubes, functionalization, photochemistry*

The tubular structure of carbon nanotubes (CNTs) gives them incredible mechanical and physical properties, very attractive in the area of nanotechnology.[1] However, their limited reactivity has motivated a great interest in their chemical modification, which is known as functionalization. Thus, new reactivities and properties of CNTs can be achieved. Due to the high stability of carbon nanotube walls, formed by C-C sp^2 bonds, the functionalization of nanotubes is still a synthetic challenge. The chemical functionalization methods used so far focus on thermal and electrochemical activation,[2] but it is hard to find any example of photochemical functionalization. Consequently, the objective of this work is to demonstrate the covalent functionalization of carbon nanotubes through the application of light-mediated chemical methods. To study the applicability of this new light-driven functionalization method, two types of reactions are carried out: a [4+2] annulation reaction of cyclobutylanilines[3] and a carbene addition reaction.[4] In both cases a new covalent bond is formed between the introduced organic material and the carbon nanotube, converting their aromatic carbons in reactant of the proposed reactivities. The resulting materials are fully characterized by solid characterization techniques, and as proof-of-concept, post-functionalization reactions with selected catalytic units has been tested as well as the potential employment of the hybrid materials as heterogeneous catalysts.

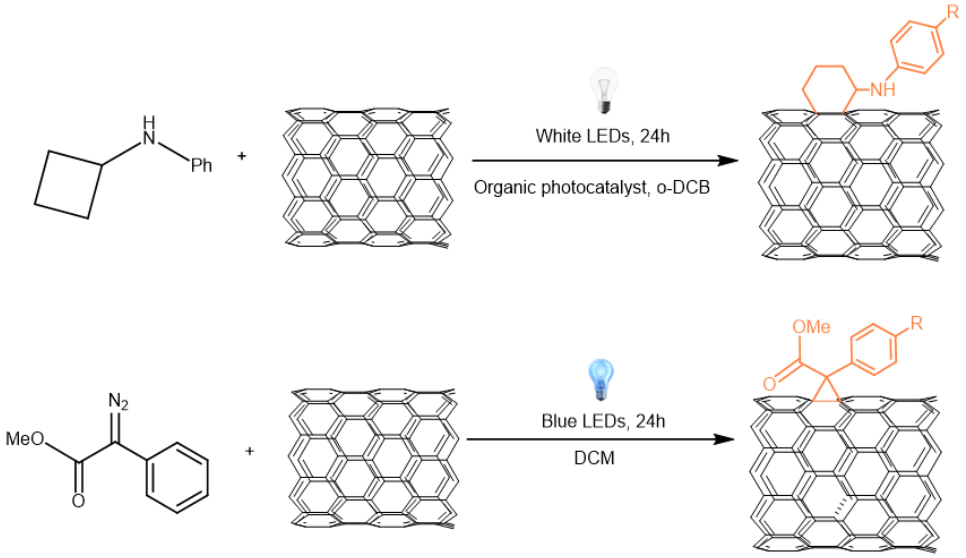


Figure 1. Reaction conditions via a) [4+2] annulation of cyclobutylanilines, b) carbene addition reaction.

References:

[1] Bernholc, J.; Brenner, D.; Buongiorno Nardelli, M.; Meunier, V.; Roland, C. *Annu. Rev. Mater. Sci*. **2002**, 32, 347-375.

[2] Balasubramnion, K.; Burghard, M. *Small* **2005**, 1, 180-192.

[3] Wang, J.; Zheng, N. *Angew. Chem. Int. Ed.* **2015**, 54, 11424-11427.

[4] Yang, Z.; Stivanin, M. L.; Jurberg, I. D.; Koenigs, R. M. *Chem. Soc. Rev.* **2020**, 49, 6833-6847.

Functionalization of imine-based COFs with proline-based organocatalyst through monomer truncation strategy

A. Senent Romero,[a] M. Blanco Fernández,[a] J. Alemán Lara.[a]

[a] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049, Madrid*
e-mail: alberto.senentr@estudiante.uam.es

Keywords: *COF, Monomer Truncation, (Photo)organocatalysis*

The heterogenization of catalysts in different materials have gathered increasing attention to achieve their fast and easy recyclability, as well as to improve the catalytic properties with respect to the homogeneous isolated molecular catalyst. Among all possible materials, imine-based covalent organic frameworks (COFs) are especially appealing to be functionalized due to their crystallinity, porosity, optical properties and their easy and tunable design and synthesis. They are synthetized by the acid condensation of aldehydes and amines, and this generality opens several functionalization methods up, being interesting the monomer truncation and post-functionalization strategy,[1] because it allowed the synthesis of a wide variety of materials with very different properties, for example decorated with metal catalysts among other functions. However, the introduction of organocatalyst by this approach has not been reported previously.

This work proposes the synthesis of a modified COF yielded by the monomer truncation strategy and postfunctionalization with a proline-based asymmetric organocatalyst. Especifically, this COF has been synthesized by imine chemistry in acidic medium and subsequently functionalized by click chemistry with an propargyl-decorated proline analogous to the Jørgensen-Hayashi catalyst.[2] The material has been characterized by different solid characterization techniques and its catalytic activity has been studied in organocatalysis and asymmetric photocatalysis.[3] In particular, the organocatalytic was tested in the Michael addition of aldehydes to β-nitrostyrene and the scope of the material was studied using different aldehydes and Michael acceptors. The catalytic material was also studied as photocatalyst in asymmetric α-alkylation reactions of aldehydes with bromoderivatives.

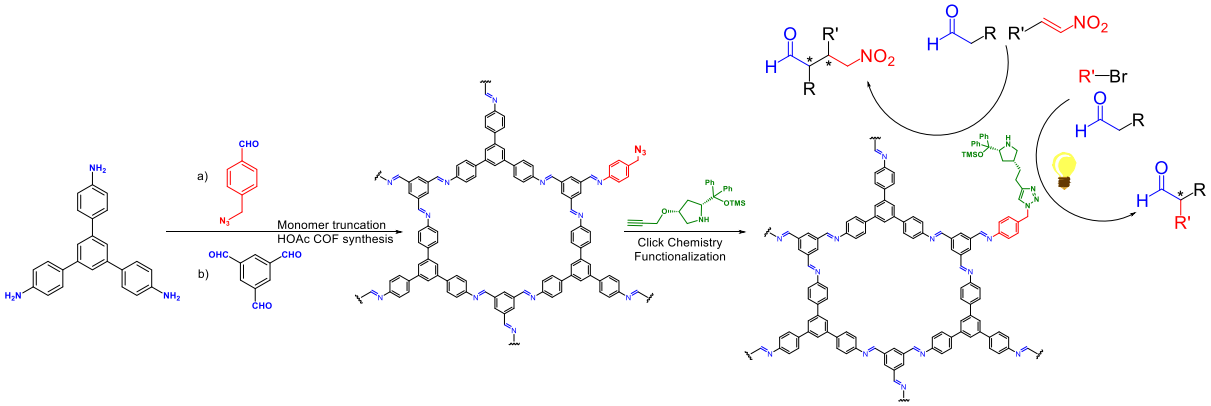


Figure 1. COF synthesis using a truncation, post-functionalization strategy and photo-organocatalytic application.

References:

[1] López-Magano, A.; Platero-Prats, A. E.; Cabrera, S.; Mas-Ballesté, R.; Alemán, J. *Appl. Catal. B.* **2020**, *272*, 119027.
[2] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.
[3] Jiménez-Almarza, A.; López-Magano, A.; Marzo, L.; Cabrera, S.; Mas-Ballesté, R.; Alemán, J. *ChemCatChem* **2019**, *11*, 4916-4922.

Novel catalytic methods for the selective functionalization of boronic esters

V. Silva,[a] B. Lozano,[a] J. Teresa,[a] R.M.Romero,[a] and M.Tortosa[a,b].

[a] *Organic Chemistry Department, Universidad Autónoma de Madrid, 28049, Spain.*
[b] *Institute for Advanced Research in Chemical Science (IAdChem), Universidad Autónoma de Madrid (UAM), 28049 Madrid, Spain*
e-mail: victor.silvag@estudiante.uam.es

Keywords: *cyclopropane ring opening, boronic esters, copper catalyst*

A new protocol for the synthesis of homoallylic derivatives has been succesfully achieved by the C-C bond cleavage of three membered rings. [1] Selective desymmetrization of an easily attainable cyclopropene followed by a Matteson homologation yields a methylcyclopropylboronic ester. [2] This isolable intermediate is activated as a borate complex, which undergoes a transmetallation reaction to copper species. Due to the high torsional tension of the system, the ring opening process is triggered, obtaining a homoallylic copper species. This highly reactive molecule can be trapped with an electrophile, allowing us to prepare homoallylic species with complete retention of configuration from the cyclopropane [3].

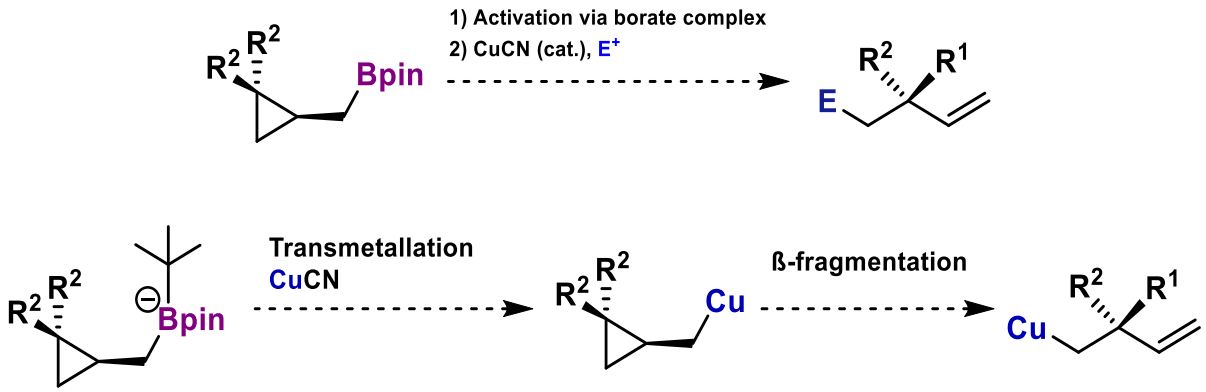


Figure 1. Scheme of borate complex activation and C-C bond cleavage

References:

[1] Cohen, Y.; Cohen, A.; Marek, I. *Chem. Rev.* **2021**, *121*, 140-161.

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

[3] *Unpublished results*

Automatic structural determination of organic compounds

Claudia Solek Pondo,[a] P. Vidal,[b] F. José Martínez,[b] J. F. Espinosa. [b]

[a] Organic Chemistry Department, Universidad Autónoma de Madrid, Módulo 2, 28049 Madrid, Spain

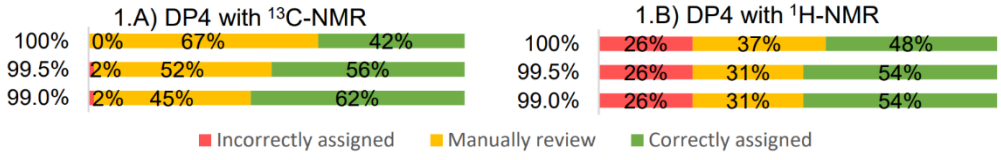
[b] *Eli Lilly and Company*- Centro de Investigación Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

e-mail: claudia.solek@estudiante.uam.es

Keywords: *nuclear magnetic resonance, statistical method, DP4/DP5.*

Time is now a precious resource, making research in process automation a key part in industry and science. Nuclear magnetic resonance (NMR) is a particularly important tool in the field of drug discovery and synthesis. Developing new NMR-derived methodologies to automate the structural elucidation process is essential. This project aims to evaluate automated methods for confirmation and structural elucidation of organic compounds from their resonance spectra (^{1}H-NMR, ^{13}C-NMR or 2D-HSQC).

For this purpose, statistical methods DP4[1] and DP5[2] developed by Prof. Jonathan M. Goodman will be used. DP4 method is a powerful tool for regiochemistry and sterochemistry assignment when having only one set of experimental data, providing the probability value of how well the experimental data fits the proposed structures; while DP5 goes one step further, quantifying the probability that single structure is correct with a ^{13}C-NMR spectrum. In addition, DP4 and DP5 are going to be compared with previous methods such as the mean absolute error (MAE) and the cumulative mean absolute error (CMAE). As both, DP4 and DP5, involve computational calculation for empirical chemical shift determination for each proposed structure to be compared with the experimental data, it is essential to establish optimal computational conditions beforehand. Results showed that the best condition for conformational search was using OPLS_2005 force field and taking the minimum energy conformer (using Maestro release 2019.4). Regarding Quantum mechanical calculations, they were carried out using Gaussian (2016.c02) using B3LYP functional and 6-31G (d,p) basis set for Geometry optimization. For the shielding constants calculations needed to determine the empirical chemical shift, it was observed that using mPW1PPW91 functional and 6-311+G(d,p) basis set yielded better results for ^{13}C-NMR (Graph 1A) while for ^{1}H-NMR better results were obtained using 6-31++G(d,p) basis set (Graph 1B). Graph 1A shows that DP4 accurately assigned the isomer with a 100% confidence level in 42% of the experiments, with no incorrect assignments. Therefore, a significant improvement was observed using DP4 method in contrast to earlier approaches (MAE and CMAE). However, unsatisfactory results were obtained for structure elucidation using DP5, indicating the need for in-depth studies to find the optimal computational conditions.



Graph 1. A) Results obtained using 13C-NMR and mPW1PPW91/6-311+G(d,p) when calculating shielding constants with DP4 in 66 experiments. B) Results obtained using 1H-NMR and mPW1PPW91/6-31++G(d,p) when calculating shielding constants with DP4 in 65 experiments.

References:

[1] Smith, S. G.; Goodman, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12946.

[2] Howarth, A.; Goodman, J. M. *Chem. Sci.* **2022**, *13*, 3507.

Computational screening of Viologens in Organic Redox Flow Batteries

Gabriel TAILLANDIER [a,b,c], Andreas MAVRANTONAKIS[c]

[a]*Universidad Autonoma de Madrid,* [b]*Université de Strasbourg,* [c]*IMDEA energy*
e-mail: gabriel.taillandier@estudiante.uam.es

Keywords: *Density Functional Theory (DFT), Viologens, Redox Flow Batteries*

Energy storage is one of the challenges of 21st century. The use of renewable energy, like solar and wind, has increased the demand for efficient energy storage. Since the energy production from renewable resources depends on the weather, which most of the time is not correlated to the consuming demands, it has become necessary to search potential ways to store energy from the renewable resources. Redox Flow Batteries (RFBs) offer a potential alternative for grid energy storage technology. The RFBs are a type of electrochemical cells that store the energy in liquid form. The reacting substances are localized in electrolyte solutions outside of the battery-cell in two tanks. More specifically, Organic Aqueous Redox Flow Batteries are one of the best alternatives as the they are composed of earth abundant elements and not on toxic and environmental unfriendly metals[1]. The organic molecule targeted is the Methyl-Viologen as it has interesting electrochemical properties. This molecule has two reduction processes, but the focus in this study is on the first process, especially because of the reversibility of the reaction in water [2]. The purpose of this project is to investigate the impact of introduced functional groups on the redox potential. The idea is to predict the first Reduction potential using high-throughput DFT [3], as it reduces significantly the time of screening of functionalized Viologens. Almost 150 viologen derivatives were calculated with 25 different functional groups, containing Electron Withdrawing and Donating Groups (EWGs & EDGs).

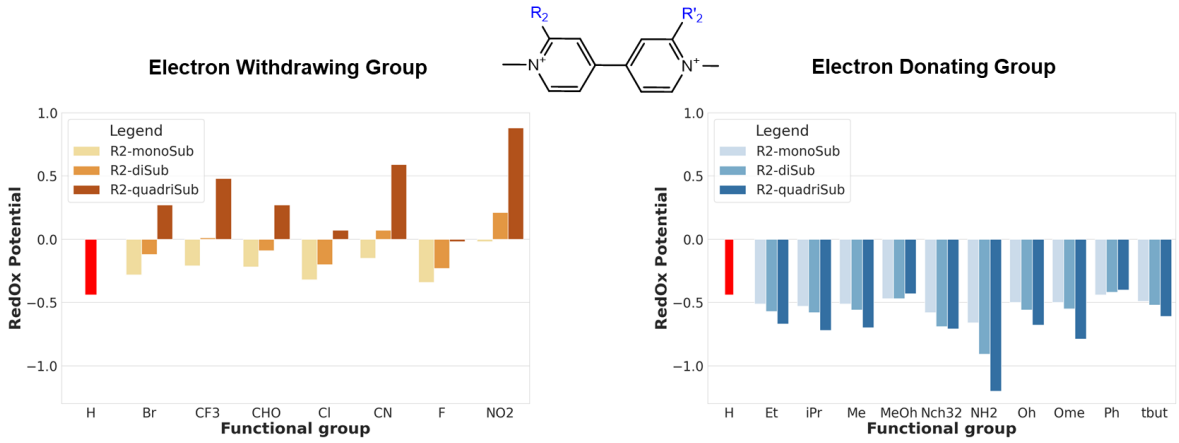


Figure 1. Computed Redox Potential (in Volts, vs NHE) plots of Methyl-Viologen(MV) Derivatives functionalized in the R2-position with EWGs (left part) and EDGs (right part).

The first observation is the electronic effect of the functional group. The more electron-donating, the higher the potential, while the opposite effect is observed with EWG. The second observation is the number of substituents, as the number increase the effect of the functional groups increase.

References:

[1] (a) Sánchez-Díez, E; et al. Journal of Power Sources, 2021, 481, 228804. (b) Xie, H., Cao, Y., Liu, W., Wan, C., & Guo, J., Energy & Environmental Science, 2013, 6(3), 932-937.
[2] L. Striepe, T. Baumgartner, Chem. Eur. J. 2017, 23, 16924.
[3] (a) de la Cruz, C.; Molina, A.; Patil, N.; Ventosa, E.; Marcilla, R.; Mavrandonakis, A, Sustainable Energy Fuels, 2020, 4, 5513-5521, (b) de la Cruz, C.; Sanz, R.; Suárez, A.; Ventosa, E.; Marcilla, R; Mavrandonakis, A.; ChemSusChem, 2023, 16, e202201984

Reducing the symmetry of cofacial porphyrin nanocages

B. Torres Calvo, [a] A. de Juan[a]

[a] *Nanostructured Molecular Systems and Materials Group, Departamento de Química Orgánica, Universidad Autónoma de Madrid, 28049, Madrid, Spain*
e-mail: beatriz.torresc@estudiante.uam.es

Keywords: *self-assembly, metalloporphyrin cages, supramolecular receptors*

Nature represents a shining model of inspiration on how to deal with energy, waste and raw material source issues, where optimally organized molecules transform solar energy into chemical energy. Porphyrins are responsible for executing many of the essential life processes, such as: electron transfer (cytochrome), oxygen transport/storage (hemoglobin), and enzymatic transformations (peroxidases).[1] In the last few years, there has been a rising interest in building preorganized structures (molecular cages) based on porphyrin units, endowed with well-defined nanocavities for catalysis, molecular recognition, as well as for purification applications.[2] These nanocages can be formed by covalent bonds, metal-ligand and supramolecular interactions.
This project aims to develop novel molecular cages based on two cofacially arranged porphyrins, each of them bearing a different metal, thus reducing the symmetry of the cage. The synthesis of these molecular hosts relies on the coupling of the two metallomacrocycles through linkers that employ two different covalent bonds: an irreversible connection, such as the amide bond, and a reversible (i.e. dynamic) bond, like the imine (Figure 1). In the future, further work will focus on exploiting these heterometallic cages for the selective recognition of non-symmetric guests.

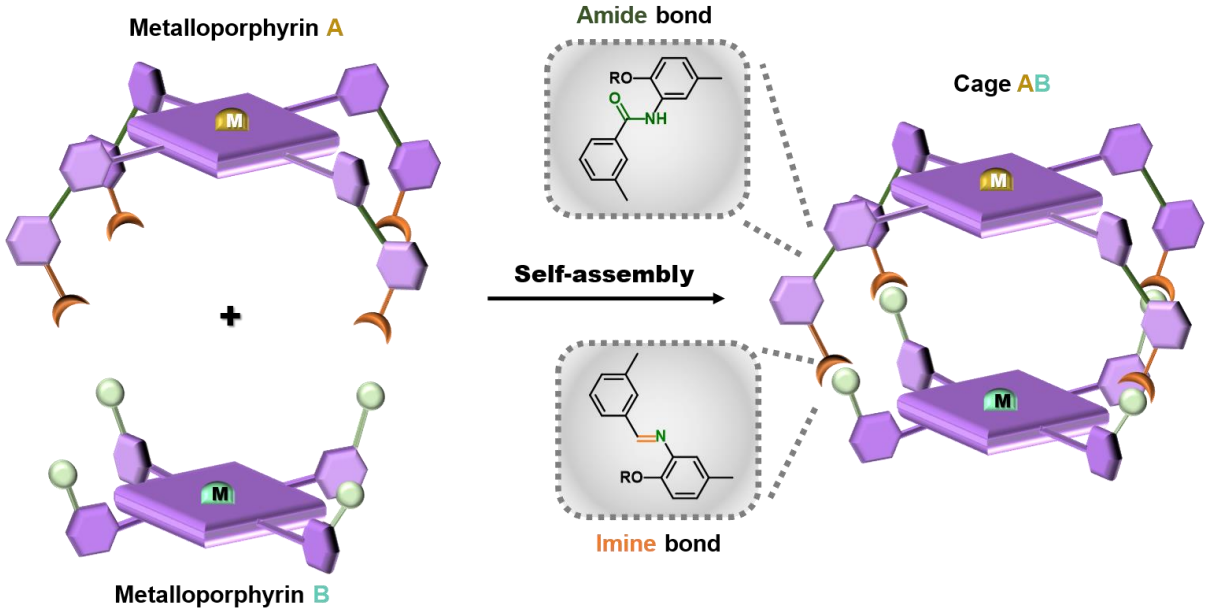


Figure 1. Self-assembly scheme of two different metalloporphyrins into cages attached by amide and imine bonds.

References:

[1] (a) Feng, L.; Wang, K. Y; Zhou, H. C. *Trends Chem.* **2020**, 2, (6), 555-568. (b) Kadish, K. M.; Smith, K. M.; Guilard, R., *The Porphyrin Handbook*; Academic Press: San Diego, 2000.
[2] (a) Shoji, Y.; Tashiro, K.; Aida, T. *J. Am. Chem. Soc.*, **2010**, *132*, 5928-5929. (b) Zheng, Y. R. et al, *J. Am. Chem. Soc.*, **2010**, *132*, 16873-16882. (c) Katagiri, H.; Tanaka, Y.; Furusho, Y. Yashima, E. *Angew. Chem.*, **2007**, *46*, 2435-2439.

Self-assembled Nanotubes based on Amidinium-Carboxylate Interactions in Water

M. Vos Gracia,[a] F. Aparicio,[a,b]

[a]*Nanostructured Molecular Systems and Materials Group, Departamento de Química Orgánica, Universidad Autónoma de Madrid, 28049 Madrid, Spain.*

[b] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain.*

e-mail: miriam.vos@estudiante.uam.es

Keywords: *supramolecular nanotubes, amidinium-carboxylate interactions, non-covalent dimer.*

Assembled tubular systems have multiple functions and applications,[1,2] like in the formation of transmembrane ion channels by aquaporin, a protein that selectively transports water. Taking inspiration from these systems, our project aims to form water-soluble self-assembled tubular systems using supramolecular interactions.[3,4] Two π-conjugated semicircular systems with two amidinium and two carboxylate functional groups at the ends will be synthesized and characterized (Figure 1). The synthetic route has been designed considering two main synthetic phenylene-ethynylene fragments: *core* and *arms*. These fragments can be coupled by Pd-catalyzed Sonogashira reactions between terminal alkynes and haloarenes leading the final semicircular monomers. In a very convergent approach, protected carboxylic acid as ester can be used as a common precursor for the synthesis of carboxylate and amidinium final compounds. The cyclic dimers designed would show high complementarity due to the formation of amidinium-carboxylate salt bridges and could be stacked by π-π interactions to form self-assembled nanotubes.

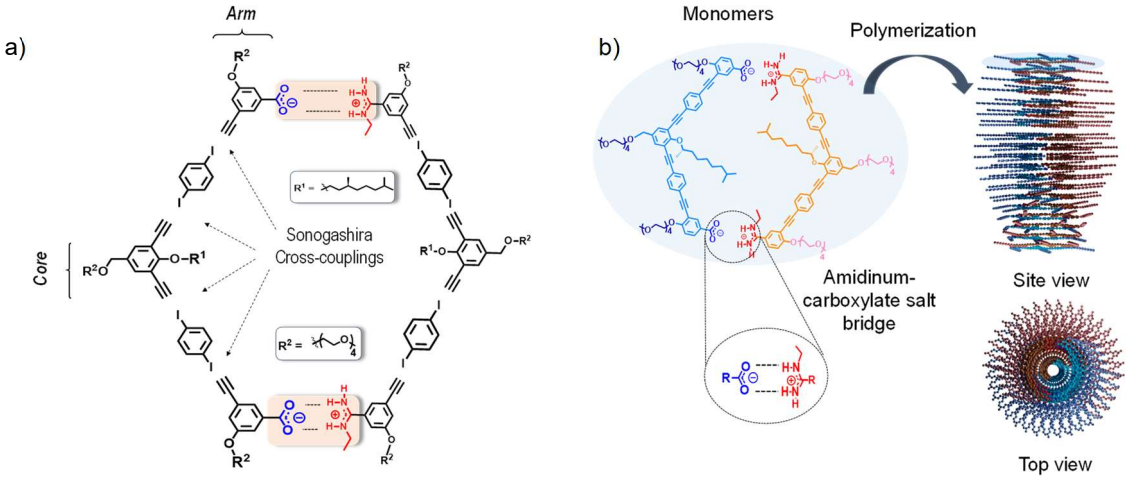


Figure 1. a) Structural fragments and monomer synthesis, b) Dimer originated by the self-assembly of the monomers and subsequent stacking to form the nanotube.

References:

[1] Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri., M. R. *Angew. Chem. Int. Ed.* **2001**, *40*, 988-1011.

[2] Chamorro, P.; Aparicio. F. *Chem. Commun.* **2021**, *57*, 12712-12724.

[3] Chamorro, P.; Aparicio, F.; Chamorro, R.; Bilbao, N.; Casado, S.; Gonzalez-Rodriguez, D. *Org. Chem. Front*. **2021**, *8*, 686-696

[4] Aparicio, F.; Chamorro, P.; Casado, S.; Gonzalez-Rodriguez, D. *Angew. Chem. Int. Ed.* **2020**, *59*, 17091-17096.

Unleashing the power of photocatalysis: synthesis of cyclopropanes and functionalization of silyl enol ethers through carbenes in organic synthesis

Carlos Bernabeu Rodríguez, José Alemán.

Organic Chemistry Department, Módulo 2, Universidad Autónoma de Madrid, 28049 Madrid, Spain.
e-mail: cabern03@ucm.es

***Keywords**: photocatalysis, carbenes, visible light.*

Carbenes play a crucial role in organic chemistry as intermediates, enabling a wide range of chemical reactions. Metal-catalyzed carbene transfer reactions have made significant advancements in recent years, but there is a growing preference for more sustainable approaches. Photolysis of diazocompounds has emerged as an effective strategy for carbene formation without the need for metal catalysts, offering an alternative to traditional metal-catalyzed methods.[1,2] Notably, the use of photocatalysts, particularly ruthenium and iridium complexes, has garnered significant attention due to their ability to facilitate diverse synthetic mechanisms.[3]

Within this context, our current research focuses on investigating the reactions between silyl enol ethers and photogenerated carbenes. Initially, I explored the photochemical reactions between silyl enol ethers and diazocompounds (R= Ar, Figure 1A), where visible light irradiation induced carbene formation. This process led to the generation of cyclopropanes through a [2+1] cycloaddition reaction. Remarkably, this method eliminates the need for solvents and photocatalysts, achieving a sustainable approach while delivering favorable yields (Figure 1A). Furthermore, I have studied on the reaction between silyl enol ethers and diazocompounds (R= EWG) using photocatalysts (Figure 1B). This investigation has led to the successful realization of an alkane insertion reaction into an olefin, resulting in the creation of fascinating synthetic substrates. Through this innovative approach, we will obtain substrates that enable beta-functionalization of a carbonyl group.

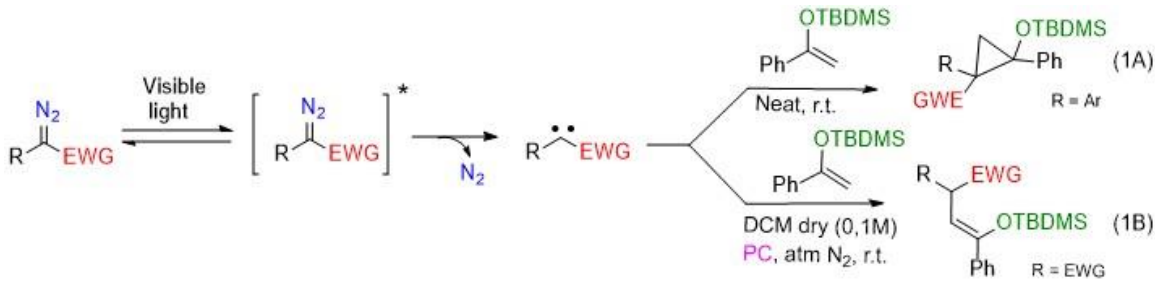


Figure 1. Divergent reactivity from photo generated carbenes and its reactivity with double bonds.

References:

[1] Yang, Z.; Stivanin, M. L.; Jurberg I. D.; Koenings, R.M. *Chem. Soc. Rev*. **2020**, *49*, 6833.
[2] Jana, S.; Li, F.; Empel, C.; Verspeek, D.; Aseeva, P.; Koenigs, R. M. *Chem. Eur. J.* **2020**, *26*, 2586.
[3] Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. *Org. Process Res. Dev*. **2016**, *20*, 1156.

Pre-stability study of the active principle of a generic antidiabetic drug

M. Carrasco Alcaide, M. del Olmo García, J. Gómez Tomás.
Formulation development R&D, FAMAR Health Care Services, Av. Leganés 62, 28923 Alcorcón, Spain.
e-mail: mcarra24@ucm.es

Keywords: *Pre-stability, antidiabetic, tablet.*

FAMARs generic antidiabetic drug is based on a Reference Listed Drug (RDL), which is presented as a concentrated powder containing the antidiabetic active principle (Compound A), indicated to improve glycemic control in adult patients with type 2 diabetes mellitus. Each tablet of the RDL contains 50 mg of Compound A and different excipients, such as anhydrous lactose, microcrystalline cellulose and sodium starch.
Compound A is a potent and selective inhibitor of DPP-4, a member of the incretin (pancreatic islet) enhancer group. Its administration produces a rapid and complete inhibition of DPP-4 activity, resulting in increased postprandial and fasting endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). When the hormone levels are increased, Compound A enhances beta-cell glucose sensitivity, promoting glucose-dependent insulin secretion.
Obtaining an optimal pharmaceutical formula that guarantees that our generic drug will produce the desired therapeutic effects in the established time, requires an in-depth study of the active ingredient. For this purpose, among many other experiments, we will carry out a pre-stability study of different batches of tablets, the results of which will lead us to create and subsequently choose the definitive pharmaceutical form to finalize the galenic development.[1]
Pre-stability can be defined as the ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life. During these studies, products are stored under aggressive conditions (heat and humidity) in order to force their degradation and to evaluate their stability at shorter times, at longer times and at accelerated conditions.[2]

References:

[1] Vila, J.; Jose, L. *Aspectos Fundamentales de Los Sistemas Farmacéuticos y Operaciones Básicas*, 1st ed.; Tecnología Farmacéutica, Vol. 1; Síntesis S.A., 2001.
[2] CPMP/ICH. ICH Topic Q 1 *A Stability Testing Guidelines : Stability Testing of New Drug Substances and Products*. *European Medicines Agency* 1998, No. January.

Influence of the spacer length in the supramolecular polymerization of PDI derivatives

L. Espejo Martín, L. López-Gandul, F. García, L. Sánchez Martín.

Grupo de Moléculas Anfifílicas y Polímeros Supramoleculares
Departamento de Química Orgánica, Facultad de CC. Químicas, Universidad Complutense de Madrid.
luespejo@ucm.es

Keywords: *Perylene diimides, supramolecular polymers, hysteresis.*

Supramolecular polymers are complex polymeric structures formed by reversible, non-covalent interactions between monomeric units. Perylene diimides (PDIs) are important organic molecules with diverse applications, including organic photovoltaics and biomedicine.[1,2] In the past years, our research group has synthesized multiple *N*-annulated PDIs with different spacer lengths in order to study the influence of these in their self-assembly features.[3] *N*-annulated PDIs exhibit strong non-covalent interactions, such as π-π stacking due to their aromatic core which enable their self-assembly into well-defined supramolecular polymers. This project presents the synthesis of *N*-annulated PDI-**1** with a 4-methylene spacer (Fig. 1a) as well as the study of its supramolecular behaviour. The formation of the supramolecular interactions was studied by variable concentration ^{1}H-NMR experiments. The supramolecular polymerization mechanism was investigated through variable-temperature UV-Vis spectroscopy experiments in methylcyclohexane (MCH) (Fig 1b). Monitoring the absorbance at 602 nm as a function of temperature revealed the characteristic profile of a cooperative mechanism (Fig 1c). Notably, there is a significant shift in the elongation temperature between the heating and cooling curves (Fig 1d). This is typical of systems with kinetically controlled species during the aggregation process and is particularly novel for structures lacking hydrogen bonds in supramolecular arrays. This behaviour has not been reported before for the 2-methylene spacer congener,[4] and opens a new line of research among these growingly interesting moieties.

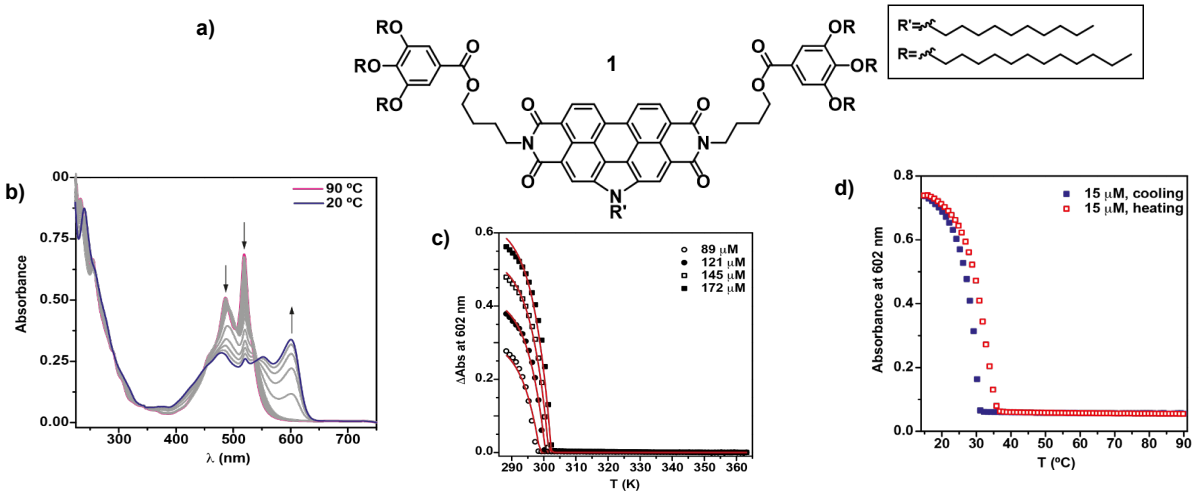


Figure 1. a) *N*-annulated PDI-1; b) UV-Vis experiments at different temperatures (MCH, 100μm); c) Cooling curves at 602 nm in MCH; d) Hysteresis plot.

References:

[1] Würthner, F.; Nowak-Król, A. *Org. Chem. Front.* **2019**, *6*, 1272.
[2] Rajasekar, M.; Lavanya, M. *RSC Adv.* **2022**, *12*, 15925.
[3] Greciano, E. E.; Calbo, J.; Ortí, E.; Sánchez, L. *Angew. Chem. Int. Ed.* **2020**, *59*, 17517.
[4] Greciano, E. E.; Calbo, J.; Ortí, E.; Sánchez, L. *Angew. Chem. Int. Ed.* DOI: 10.1002/anie.202005837

Pharmacokinetic characterization of the antidiuretic drug AD01

J. F. Ferreira Alves,[a] M. J. Fernández.[a]

[a]*Famar Health Care Services*
e-mail: joanafer@ucm.es

Keywords: *solubility, dissolution profiles.*

AD01 is a peptide drug that treats kidney diseases such as diabetes insipidus and nocturnal enuresis and its chemical structure is similar to the structure of the hormone arginine vasopressin (ADH), as shown in **Figure 1**.[1,2] The objective of this work is to determine one of the fundamental pharmacokinetic parameters of the drug AD01, which is the solubility through dissolution profiles.

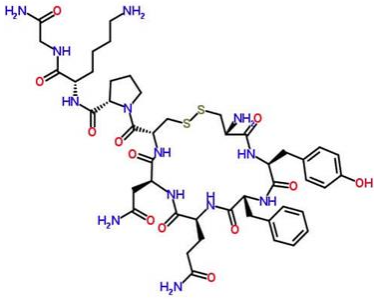


Figure 1. Chemical structure of the hormone arginine vasopressin (ADH).

To determine the solubility of the drug AD01 in the body, dissolution profiles are carried out at different times, between 0 and 30 minutes in a Sotax equipment and analysed by HPLC with a UV detector.[3]

Table 1. Results of dissolution profiles of the antidiuretic drug AD01 in a time point 3 months of a stability study.[1]

Dissolution Profiles		
Samples	**Presentation form 1 (30 tablets)**	**Presentation form 2 (100 tablets)**
Time (minutes)	**AD01 dissolved (%)**	**AD01 dissolved (%)**
5	45 ± 19	46 ± 12
10	89 ± 4	91 ± 4
15	98 ± 1	99 ± 2
30	100 ± 1	100 ± 2

[1]The average of six duplicates of the dissolution of two types of packaging of the drug AD01 at different times between 0 and 30 minutes are shown.

The results shown in **Table 1** indicate AD01, in a time point 3 months of a stability study, is 100% dissolved after 30 minutes in both presentation forms. It is concluded the dissolution results are satisfactory, the dissolution behave of AD01 is the same in both presentation forms and preserves this pharmacokinetic parameter, being compared with AD01 from factory.

References:

[1] Dabrowski, E.; Kadakia, R.; Zimmerman, D. *Best Pract. Res. Clin. Endocrinol. Metab.* **2016**, *30*, 317.
[2] Torok, B.; Fazekas, C. L.; Szabo, A.; Zelena, D. *Int. J. Mol. Sci.* **2021**, *22*, 9415.
[3] Liu, P.; De Wulf, O.; Laru, J.; Heikkila, T.; van Veen, B.; Kiesvaara, J.; Hirvonen, J.; Peltonen, L.; Laaksonen, T. *AAPS PharmSciTech*. **2013**, *14*, 748.

Synthesis of polyaromatic hydrocarbons (PAHs) containing the carbazole skeleton

S. Gallardo López, C. Aragoncillo, J.M. Alonso

Grupo de Química de Sistemas Insaturados y Heterociclos Bioactivos, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040, Madrid
e-mail: sagall03@ucm.es

Keywords: *alkyne, carbazole, metathesis*

The carbazole nucleus is an aromatic heterocyclic motif found in many biologically active compounds.[1] In addition, in the last three decades, carbazole derivates have gained a lot of attention in the field of organic optoelectronics, specifically in OLEDs (Organic Light Emitting Diodes) and OPVs (Organic Photovoltaics).[2]
In this context, our research group is working on the preparation of new carbazole-based helicene compounds exhibiting interesting photophysical properties.[3] The aim of this work is the preparation of novel cata-condensed (bis)carbazole derivates with extended conjugation through a reaction sequence including organometallic coupling reactions, halogen-migration processes and carbonyl-alkyne metathesis (Figure 1).

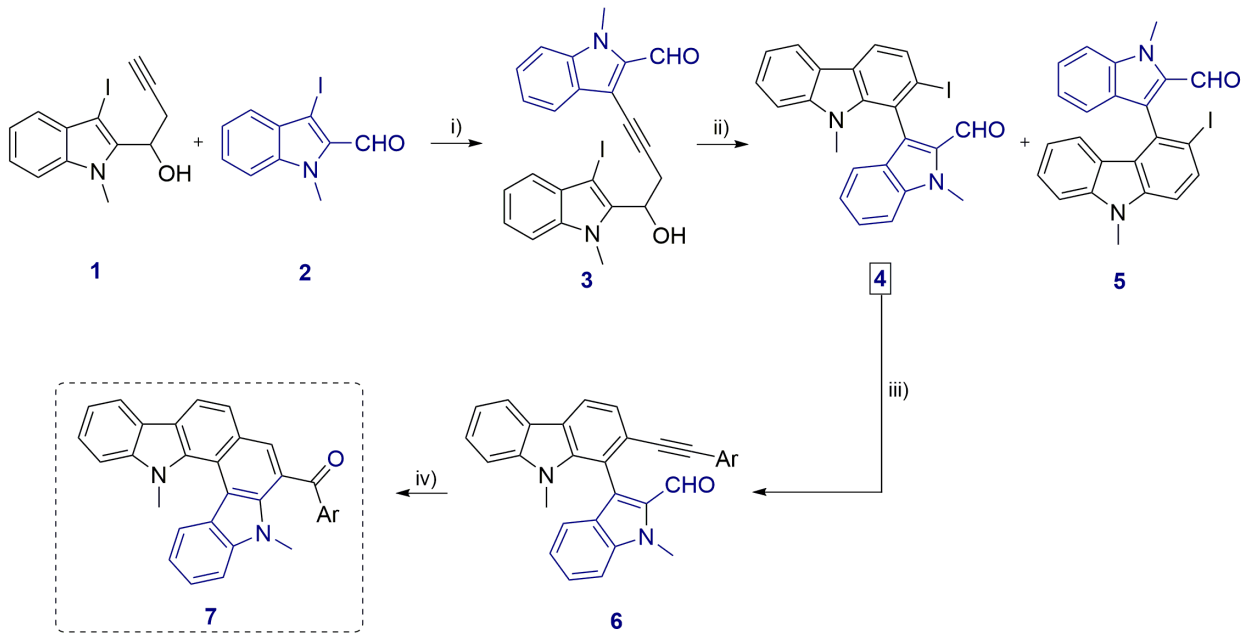


Figure 1. Synthetic route for the preparation of new carbazole-based PAHs. i) Sonogashira coupling, ii) Cyclization reaction with halogen migration, iii) Suzuki-Miyaura coupling, iv) Carbonyl-Alkyne Metathesis.

References:
[1] (a) Głuszyńska, A. *Eur. J. Med. Chem.* **2015**, *94*, 405. (b) Kasim, S.; Al-Dabbagh, B.; Mustafa, Y. *Eurasian Chem. Commun.* **2022**, *4*, 495.
[2] (a) Krucaite, G.; Grigalevicius, S. *Synth. Met.* **2019**, *247*, 90. (b) Konidena, R. K.; Thomas, K. R. J.; Park, J.W. *ChemPhotoChem.* **2022**, *6*, DOI: 10.1002/cptc.202200059.
[3] Alcaide, B.; Almendros, P.; Aragoncillo, C.; Busto, E.; López-Calixto, C. G.; Liras, M.; de la Peña O'Shea, V. A.; García-Sánchez, A.; Stone, H. V. *Chem. Eur. J.* **2018**, *24*, 7620.

Synthesis of chemical probes for the identification of therapeutic targets of cannabinoid ligands

P. García-López,[a] V. Muñoz-Canales,[a] O. Palomares,[b] B. Benhamú,[a] M. Martín-Fontecha.[a]

[a]*Medicinal Chemistry Laboratory, Dept. Organic Chemistry;* [b]*Vaccines and Dendritic Cells Lab, Dept. Biochemistry and Molecular Biology, Faculty of Chemical Science, Universidad Complutense de Madrid, E-28040, Madrid.*
e-mail: patrga15@ucm.es

Keywords: *WIN55,212-2, chemical probes, target identification*

The synthetic cannabinoid ligand WIN55,212-2 (WIN) is receiving a growing attention due to its recently reported immunomodulatory capacity.[1] Beyond cannabinoid receptors, the therapeutic targets of WIN are currently unknown, and their identification could open new avenues for the development of novel vaccines for the prevention of allergy and other immune-mediated diseases. The development of chemical probes is a research topic of great interest as it allows the association of specific proteins with the observed therapeutic effects.

In this context, the main objective of this project is the synthesis of the designed chemical probes **1-4** (Figure 1) that contain the WIN scaffold functionalized with a small photocrosslinking moiety such as diazirine and a terminal alkyne. Both tags are linked to the naphthalene or piperazine subunit. The WIN-based probes will be subsequently used in a chemical proteomic platform previously set up in our group,[2] for profiling WIN-binding proteins in biological systems. The incubation of the probe with the desired proteome, followed by UV irradiation and click chemistry reaction with the adequate reporter (biotin or fluorophore bearing an azide group) enables the visualization and enrichment of probe-labeled proteins. This approach will allow the identification of new therapeutic targets for the development of effective pharmacological treatments of immune-related diseases.

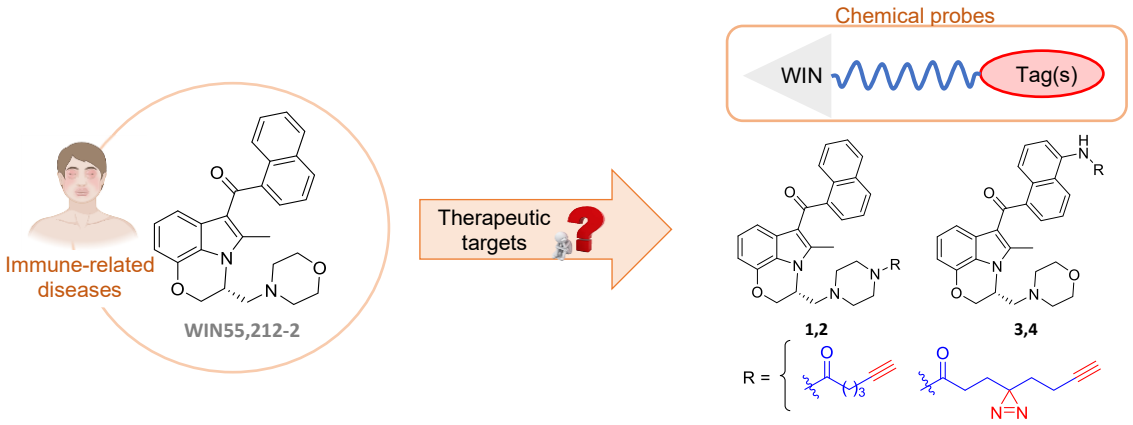


Figure 1. WIN-based chemical probes for target identification.

References:

[1] (a) Angelina, A.; Pérez-Diego, M.; Maldonado, A.; Rückert, B.; Akdis, M.; Martín-Fontecha, M.; Akdis, C. A.; Palomares, O. *Allergy* **2022**, *77*, 1029. (b) Angelina, A.; Pérez-Diego, M.; López-Abente, J.; Rückert, B.; Nombela, I.; Akdis, M.; Martín-Fontecha, M.; Akdis, C.; Palomares, O. *Mucosal Immunol*. **2022**, *15*, 96.

[2] (a) Gamo, A. M.; González-Vera, J. A.; Rueda-Zubiaurre, A.; Alonso, D.; Vázquez-Villa, H.; Martín-Couce, L.; Palomares, Ó.; López, J. A.; Martín-Fontecha, M.; Benhamú, B.; López-Rodríguez, M. L.; Ortega-Gutiérrez, S. *Chem. Eur. J.* **2016**, *22*, 1313. (b) Martín-Fontecha, M.; Angelina, A.; Rückert, B.; Rueda-Zubiaurre, A.; Martín-Cruz, L.; Van de Veen, W.; Akdis, M.; Ortega-Gutiérrez, S.; López-Rodríguez, M. L.; Akdis, C. A.; Palomares, O. *Bioconjugate Chem.* **2018**, *29*, 382.

Advanced applications of carbon dots in the ecological transition

D. González-Pinardo,[a] L. Rodríguez-Pérez,[a] M. A. Herranz,[a] N. Martín.[a,b]

[a]*Organic Molecular Materials Group, Organic Chemistry Department, Faculty of Chemical Sciences Universidad Complutense de Madrid, Avda. Complutense s/n 28040, Madrid, Spain,*
[b]*IMDEA-Nanoscience, C/ Faraday 9, Campus de Cantoblanco, 28049, Madrid, Spain.*
e-mail: dagonz21@ucm.es

Keywords: *carbon dot, chirality, catalysis*

In recent decades, the unsustainable consumption of the Earth's natural resources and increase in pollution has raised alarm bells in society, leading to the search of more ecological alternatives in multiple fields, especially in the chemical sciences and chemical industry.
Following this concept, in this communication we present the preparation and use of carbon dots, quasi-spherical nanoparticles that excel, due to their low toxicity and environmentally friendly synthesis,[1] as recyclable chiral catalysts for the reduction of aromatic ketones.
In order to achieve this goal, in a first instance, we have applied a bottom-up strategy to prepare carbon dots using urea and citric acid as precursors under hydrothermal conditions and, secondly, we have synthesized enantiomerically pure 1,1′-bi-2-naphthol (**BINOL**) derivatives, a commonly used chiral molecule in catalytic reactions.[2,3] Finally, the design and synthesis of the carbon dot-based catalysts (**Figure 1**) was done *via* covalent bonding of the carbon nanoparticles with the racemic or enantiomerically pure derivatives. The initial trials on the catalytic reduction of aromatic ketones by these carbon dot-BINOL conjugates will be discussed in the symposium.

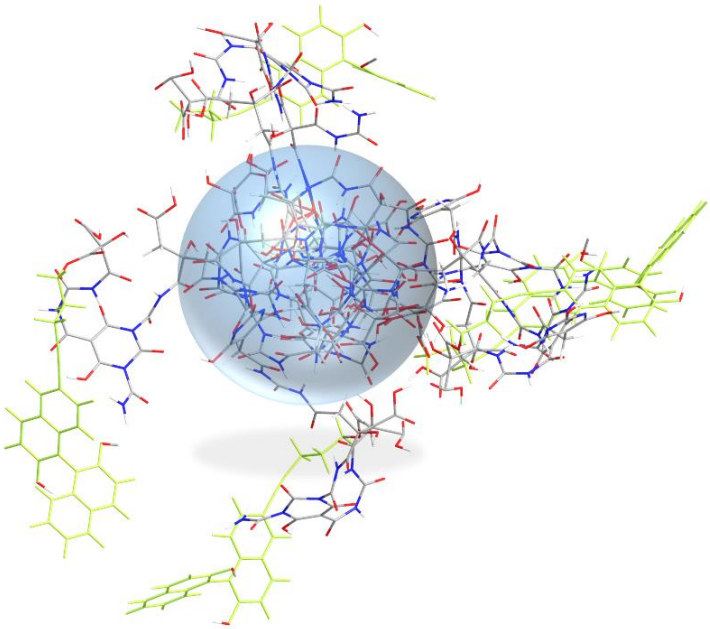


Figure 1. Schematic representation of the carbon dot catalyst synthetized, with the active BINOL (S) moieties around the nanoparticle as outlined before.

References:

[1] (a) Chahal, S.; Macairan, J.-R.; Yousefi, N.; Tufenkji, N.; Naccache, R. *RSC Adv.* **2021**, *11*, 25354. (b) Wang, B.; Waterhouse, G. I. N.; Siyu, L. *Trends Chem.* **2023**, *5*, 76.
[2] Wang, X.; Guo. J.; Qie, F.; Yan. Y. *J. Mater. Sci*. **2019**, *54*, 6908.
[3] Schiffers, R.; Kagan, H. B. *Synlett*, **1997**, 1175.

Deoxygenative arylation of alcohols by metallaphotoredox methodology

R. Hortigón Ortega,[a] J. A. Rincón Cabezudo,[b] P. García Losada.[b]

[a]*Universidad Complutense de Madrid,* [b]*Eli Lilly and Company.*
e-mail: richorti@ucm.es

Keywords: *metallaphotoredox, catalysis, flow chemistry*

Among the different metallaphotoredox processes developed during the last decade, several of the most synthetically appealing feature the use of strongly oxidizing excited iridium (III) complexes that permit the oxidation of diverse species through single electron transfer (SET) processes. This work focuses on deoxygenative sp^2-sp^3 coupling between an alkyl alcohol and an aryl bromide, where the oxidation of an alcohol-NHC adduct generates an alkyl radical that is trapped by a nickel species and in turn couples with the aryl halide.[1]
A set of standardised reactions were carried out in which different alcohols were tested with the same aryl bromide, and different aryl bromides were tested with the same alcohol following the general reaction scheme shown in Figure 1. The same oxazolium salt was employed to form the alcohol-NHC adduct in all cases.

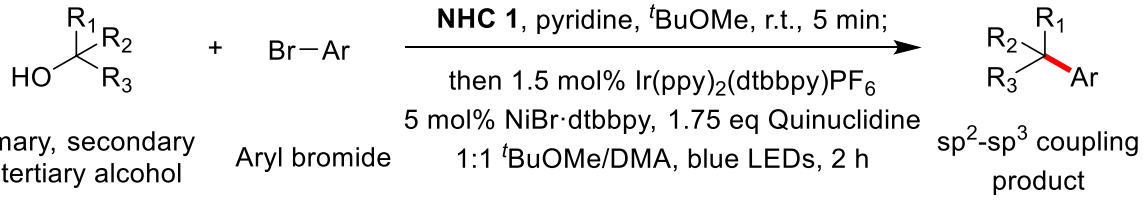


Figure 1. General reaction for the deoxygenative arylation of alcohols.

To study couplings between alcohols and aryl halides with different stereoelectronic properties, more diverse examples were studied. Even some species that were not expected to give good results based on literature descriptions turned out to give good results, such as the product **3be** (Fig. 2). An example of aryl chloride was also studied in order to compare with aryl bromides (**2a** vs **2b**). The aryl bromide showed better results than the chloride with higher conversion ratios.

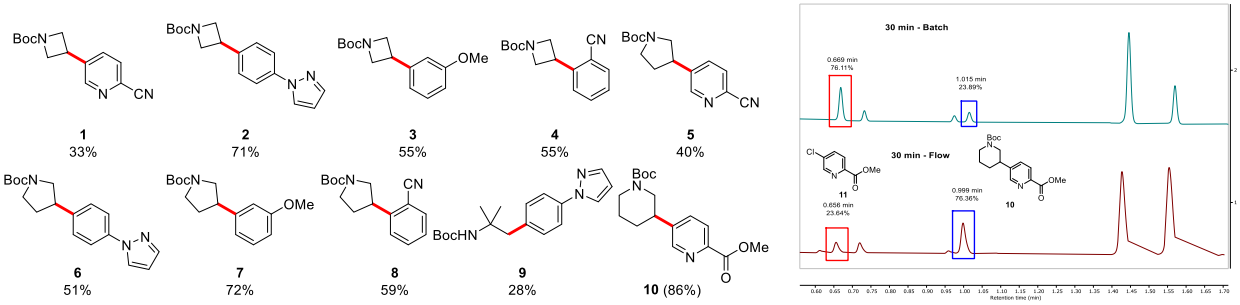


Figure 2. Some products obtained by deoxygenative arylation of alcohols (left) and a batch/flow comparison of the same reaction (right).

An attempt was also made to transfer this reaction from batch to flow chemistry. Improved conversion was obtained for the coupling between 11 and 1-Boc-3-hydroxypiperidine to yield product 10 after 30 min of reaction in the flow reactor compared to the same time in batch (Cl:10-1:3 (flow) vs 3:1 (batch)).

References:

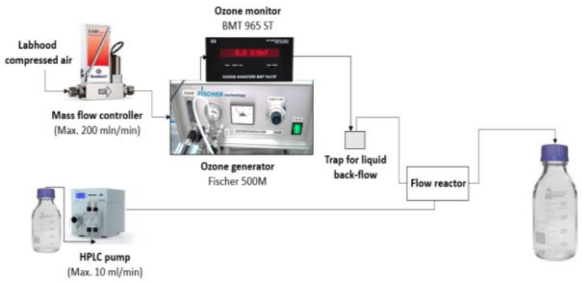
[1] Dong, Z.; MacMillan, D.W.C. *Nature* **2021**, *598*, 451.

Development and application of microscale organic synthesis platforms using continuous flow gas-liquid mixtures

G. A. Hrehoret,[a] P. García Losada,[b] G. R. Cumming.[b]

[a]*Universidad Complutense de Madrid, Facultad de Ciencias Químicas, Departamento de Orgánica,* [b]*Eli Lilly & Co*
e-mail: ghrehore@ucm.es

Keywords: *Ozonolysis, Flow, Selectivity.*

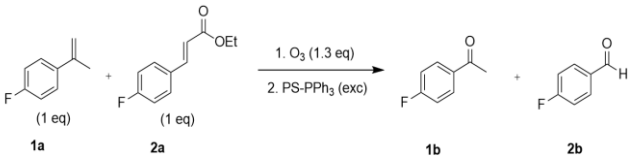


Ozonolysis is a very powerful technique with wide application and inherent atom efficiency.[1a] While the reaction is appealing for industrial application,[1b] very low temperatures are typically used, and risks are associated with unstable ozonide intermediates. Flow chemistry can address both issues due to improved mixing and lower in-process volumes.[1c]

Figure 1. Flow reactor prototype.

Lilly has developed a prototype flow ozonolysis system (Figure 1). The work reported here covers the use of this system in selective reaction of carbon-carbon multiple bonds.

Selectivity between electronically differentiated alkenes:



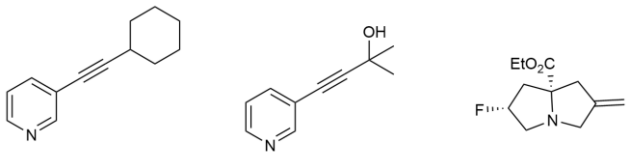
To study selectivity, the reaction was first carried out with a mixture of two substrates, demonstrating selectivity for the more electron rich. Substrates containing multiple oxidizable groups were then prepared and studied under similar conditions.

Figure 2. Conversion was of 100% for 1a and 35% for 1b**.**

Alkyne ozonolysis in flow:

Alkyne ozonolysis is a less widely studied reaction that can give rise to diketones or carboxylic acids.[2] Diketones are of special interest due to heterocycle synthesis, common motifs in medicinal chemistry. To study alkyne ozonolysis, 4 electronically different substrates were synthesized. Conversion is expected to be lower in electron deficient alkynes.

Ozonolysis of nitrogenated substrates:



Nitrogenated compounds are also common in medicinal chemistry, so three more substrates have been tested with varying results, further described in the poster.

Figure 3. Substrate scope.

References:

[1] (a) Fisher, T.J.; Dussault, P.H. *Tetrahedron* **2017**, *73*, 4233. (b) Van Ornum, S.G., Champeau, R.M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990. (c) Gemoets, H.P.L. *Chem. Soc. Rev.*, **2016**, *45*, 83.
[2] Alterman, J.L.; Vang, X.D; Stroud, M.R; Halverson, L.J; Kraus, G.A. *Org. Lett.* **2020,** *22*, 7424.

Synthesis and characterization of new BODIPYs with absorption/emission on the red region for Phototheragnosis.

N. Izquierdo Cachazo,[a] G. Durán-Sampedro,[a] A. Prieto-Castañeda,[a] A. R. Agarrabeitia,[a] M. J. Ortiz.[a]

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

Keywords: *Fused BODIPY-Dimers, Photodynamic therapy, Phototheragnosis.*

In the last decades, the development of organic fluorophores, in particular, boron dipyrromethenes (4-bora-3a,4a-diaza-*s*-indacenes, BODIPYs), has been an emerging area due to their excellent properties such as high chemical and physical stability, high fluorescence emission, high molar absorption coefficients, good solubility in organic solvents and versatile synthesis.[1] In addition, their structure can be easily modified, which allows them to modulate their photophysical properties.[1] All this has led to its application in different areas, such as bioimaging[2] or photodynamic therapy (PDT).[3] Recent interest in developing dyes with absorption/emission in the near-infrared region (NIR), mainly within the biological window (650-900 nm), has led to BODIPY derivatives with extended π-conjugation, for example, the fusion of additional aromatic units to the core of the fluorophore.[4] Numerous systems of this type are proposed as potential photosensitisers for biomedical applications, such as in PDT or fluorescent markers for *in vivo* imaging.[3] The combination of PDT with diagnostic imaging results in phototheragnosis,[5] in which a single agent performs the function of fluorescence labelling for diagnostics and cytotoxicity based on reactive oxygen species (ROS) generation for PDT.

Moreover, in recent years, it has been observed that organic fluorophores containing sulphur or selenium atoms are of great importance in the fields of medicinal chemistry and materials due to their potential pharmacological properties.[6]

In this work, the synthesis and characterization of new S/Se-fused BODIPY dimers has been carried out. The resulting dimers have been differentially functionalized to improve their photophysical properties and to design possible theragnostic agents.

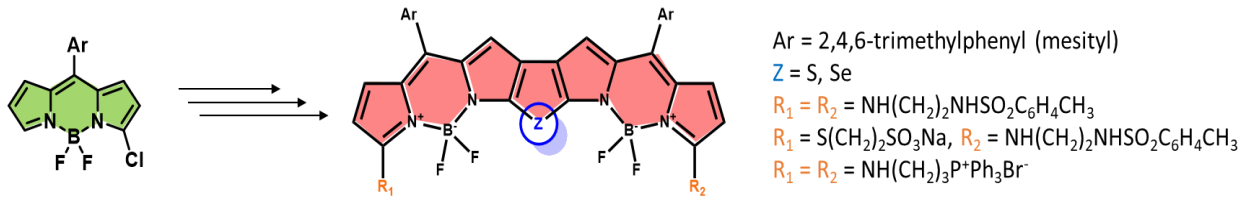


Figure 1. Synthesis of fused BODIPY dimers.

References:

[1] Boens, N.; Verbelen, B.; Ortiz, M. J.; Jiao, L.; Dehaen, W. *Coord. Chem. Rev*. **2019**, *399*, 213024.
[2] Kolemen, S.; Akkaya, E. U. *Coord. Chem. Rev*. **2018**, *354*, 121
[3] Zhang, W.; Ahmed, A.; Cong, H.; Wang, S.; Shen, Y.; Yu, B. *Dyes Pigm*. **2021**, *185*, 108937.
[4] Shukla, V. K.; Chakraborty, G.; Ray, A. K.; Nagaiyan, S. *Dyes Pigm*. **2023**, *215*, 111245.
[5] Mao, Z.; Kim, J. H.; Lee, J.; Xiong, H.; Zhang, F.; Kim, J. S. *Coord. Chem. Rev*. **2023**, *476*, 214908.
[6] (a) Kim, Y.; Jun, T.; Mulay, S. V.; Manjare, S. T.; Kwak, J.; Leed, Y.; Churchill, D. G. *Dalton Trans*. **2017**, *46*, 4111.
(b) Mahajan, A.; Singh, A. P.; Yadav, R. K.; Singh, A. P. *Mater. Today Procc.* **2022**, *52*, 321

New designs of BODIPY-based dyes with CPL emission

P. Izquierdo Cazorla, B. Lora Maroto, F. Moreno Jiménez.

Dpto. de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria s/n, 28040, Madrid, Spain.
e-mail: pizqui02@ucm.es

Keywords: *CPL, BODIPYs, ICT*

The interest of circularly polarized luminescence (CPL) lies in the higher resolution provided by CP light when compared to linear- or non-polarized lights, which enables the development of smarter photonic tools.[1,2] However, it is difficult to develop CPL emitters that gather high fluorescence efficiency, high degree of CPL and accessible synthesis in the same system. Among all the CPL emitters, those based on simple organic molecules (CPL-SOMs) have special interest because they show high brightness and tunable properties, together with the advantages derived from their organic nature.[2] However, the level of the CPL emission from these systems is still low, and therefore, investigation in CPL-SOMs is a sought-after field in photonics.
Helicity has demonstrated to be a feature that enhances CPL emission.[2] In this regard, de la Moya´s group has previously reported a synthetically accessible and conformationally flexible CPL-SOM: a bis(BODIPY) based on chiral ethane-1,2-diamine (**1**, Figure 1a) that adopts a helical conformation in solution.[3] Previous studies in the group suggest that this molecule experiences an intramolecular charge transfer (ICT) upon excitation between the two identical BODIPY chromophores, which influences the CPL emission and is an interesting phenomenon to explore. We aim to study this phenomenon on other BODIPYs having more than two BODIPY units. Therefore, in this work we are synthesizing and studying the chiroptical behaviour of new tetra(BODIPY)s based on **1** with an enantiopure tetramine or tetraol as the spacer (**2**, Figure 1b).

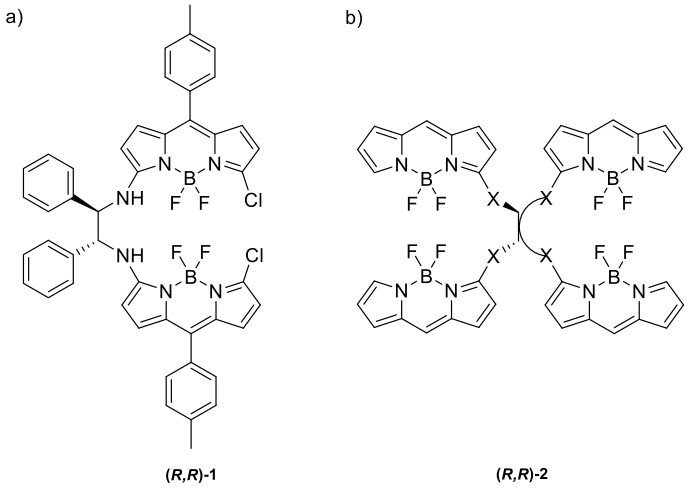


Figure 1. (a) Bis(BODIPY)-based CPL emitter developed in de la Moya´s group; (b) Tetra(BODIPY) design that is being studied in this project.

References:

[1] J. P. Riehl, F. S. Richardson, *Chem. Rev.* **1986**, *86*, 1.
[2] C. Ray, E. M. Sánchez-Carnerero, F. Moreno, B. L. Maroto, A. R. Agarrabeitia, M. J. Ortiz, Í. López-Arbeloa, J. Bañuelos, K. D. Cohovi, J. L. Lunkley, G. Muller, S. de la Moya, *Chem. Eur. J.* **2016**, *22*, 8805.
[3] E. M. Sánchez-Carnerero, F. Moreno, B. L. Maroto, A. R. Agarrabeitia, J. Bañuelos, T. Arbeloa, I. López-Arbeloa, M. J. Ortiz, S. de la Moya, *Chem. Commun*, **2013**, 49, 11641.

Synthesis of new oxindole derivatives with anti-inflammatory activity for respiratory viral infections

S. Jutglar Rigau, [a] A. García Csákÿ, [a] S. Roscales García. [a]

[a]*Pluridisciplinar Institute, Complutense University of Madrid, Paseo Juan XXIII 1, 28040, Madrid, Spain.*
e-mail: sjutglar@ucm.es

Keywords: *oxindole, inflammation, TGF-β/ALK5 inhibitors*

Inflammation is a homeostatic response of the organism to different endogenous or exogenous aggressions, which appear in response to persistent infections, autoimmune diseases, metabolic and degenerative diseases, atherosclerosis and cancer. [1]

Steroidal and non-steroidal anti-inflammatories are some of the most widely used analgesics to reduce inflammation, but their generalised use is limited by their significant side effects and their effects on the body's metabolism.

New approaches to overcome inflammation include the use of immunoselective anti-inflammatories, such as TNF-α inhibitors, for the treatment of autoimmune and inflammatory diseases for instance rheumatoid arthritis; histone deacetylase (HDAC) inhibitors, which treat Friedreich's ataxia, an inherited disease that damages the nervous system; and inhibition of transforming growth factor-beta (TGF-β) receptors, such as ALK5, to treat fibrosis, the growth of cells, helping to prevent the development of tumour growth processes, and decreasing inflammation.[2]

Therefore, the main objective of this research is the synthesis of new derivatives of N-(3-(hetarylidene)-2-oxoindolin-5-yl)-3-(piperidin-1-yl)propanamides (**Figure 1**) as TGF-β/ALK5 inhibitors, with the potential to decrease the inflammatory response caused by respiratory viral infections.[3]

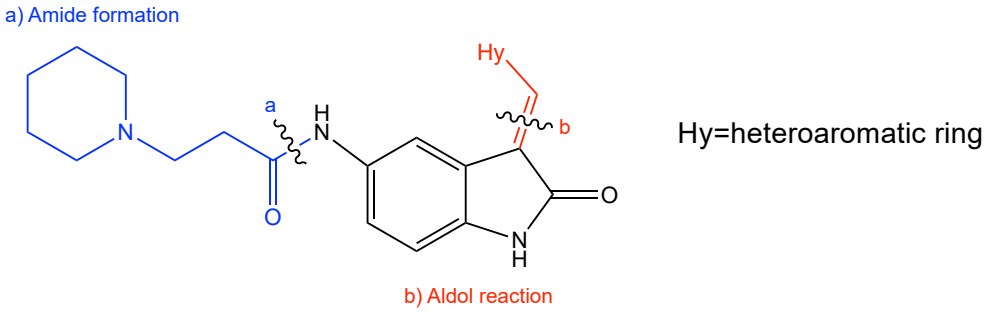


Figure 1. General structure of the oxindole derivatives to be synthesized.

References:

[1] Divins, M. *Farmacia Profesional*, **2014**, *28*, 18.

[2] Ling, L.E, Lee, W.C. *Curr. Pharm. Biotechnol.* **2011**, *12*, 2190.

[3] Sánchez-Sancho, F.; del Pozo, C.; Csáky, A. G.; Marcilla, A.; del Pozo, J.; Oliver, E.; Ibáñez, B.; Roscales, S.; Cumella, J. M.; Baquero, M. G.; Sánchez, C. M. Derivados de imidazo[1,2-*a*]piridina con actividad antiinflamatoria. Patente en proceso de solicitud (Marzo 2023, OTRI, UV).

Nanomaterials in catalytic processes

F. Martín Garrido, A. Guerrero,[a] M.J. Mancheño Real,[b] J. Osío Barcina.[b]

[a]*Physical Chemistry Department. Faculty of Chemical Sciences, Universidad Complutense de Madrid, Avda. Complutense s/n 28040, Madrid, Spain.*
[b]*Organic Chemistry Department. Faculty of Chemical Sciences, Universidad Complutense de Madrid, Avda. Complutense s/n 28040, Madrid, Spain.*
e-mail: femart10@ucm.es

Keywords: *Catalysis, nanorods, core-shell colloids, Covalent Organic Framework (COF)*

Catalytic chemical reactions are ubiquitous and play critical roles in everyday life. For decades, chemists have increased the rate of chemical reactions using different type of catalysts. Nevertheless, for most current industrial catalytic processes, the catalysts still require high temperatures and/or pressures to operate efficiently.[1] Core–shell nanocrystals with noble metals,[2] as cores and catalytic metals as shells, have recently opened a new avenue to catalyst design due to their enhanced and tunable catalytic properties. However, the use of colloidal inorganic nanocrystals (NCs) as dispersible particles is limited by their stability in organic solvents that hampers their potential applications. Therefore, hybrid materials are proposed to overcome this limitation. Au@Pd core–shell nanocrystals are primary choices as NCs catalysts due to lattice matching and perfect combination of optical properties with strong catalytic functions,[3] that depend on their synthetically tunable sizes and compositions. Thus, the objective of this project is to synthesize and evaluate the catalytic activity of Au@Pd core–shell nanorods as colloids and interfaced with other nanomaterials (Covalent Organic Frameworks) in important catalytic processes as for instance, the catalytic acetoxylation of alkenes.[4]

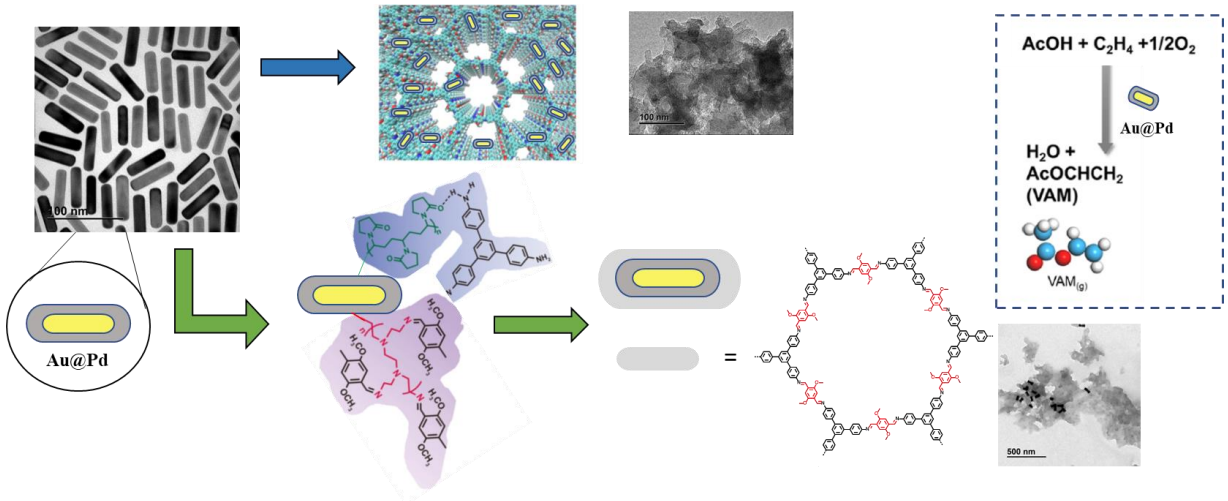


Figure 1. Au@Pd nanoparticles hybrid materials in catalytic processes

References:

[1] Dong, Y; Hu, C.; Xiong, H; Long, R.; Xiong, Y. *ACS Catalysis* .**2023**, *13*, 6730
[2] Peña Rodríguez, O.; Díaz-Nuñez, P.; González-Rubio, G; *et al*. *Sci Rep*. **2020**, *10*, 5921
[3] Chen, L; Wang, W.; Tian, J.; *et al. Nat Commun*. **2021**, *12*, 4556
[4] Nakaya, Y; Hayashida, E. J. Am. Chem. Soc. **2023**, *145*, 2985

Synthesis, optimization and characterization of multivalent carbohydrate systems and study of their applications in Dengue virus infection

A. Martín López,[a] P. Ramírez-López,[a] M. J. Hernáiz. [a]

[a]*Department of Chemistry in Pharmaceutical Science, Faculty of Pharmacy, Universidad Complutense de Madrid, 28040 Madrid, Spain.*
e-mail: ainhma06@ucm.es

Keywords: *D-glucuronic acid, click chemistry*

Carbohydrates are biomolecules involved in numerous functions, including pathological processes, through carbohydrate-protein interactions, which are involved in infectious processes where the etiological agent is bacterial or viral.[1] Specifically, D-glucuronic acid (GlcA) is a monosaccharide with a crucial role in Dengue virus recognition because it is an essential monosaccharide in the structure of the flavivirus receptor.[2] In this sense, the binding of multiple copies of GlcA to the same platform has proven to be a successful tool in the preparation of organic structures that have a high binding affinity for this viral protein, thus inhibiting the infectivity of Dengue virus.

In this report, we present an efficient and sustainable methodology using, click chemistry, (Figure 2) which is a 1,3-dipolar cycloaddition between alkynes and azides catalyzed by Cu(I) (CuAAC) for the functionalization of polyalkyne aromatic scaffolds (Figure 1) with GlcA to obtain corresponding glycostructure as new platforms for multivalent D-glucuronic acid multivalent presentation of D-glucuronic acid. Subsequently, studies will be carried out to determine the magnitude of the force of interaction strength between the glycostructures obtained in this project and Dengue virus envelope protein. Technique such surface plasmon resonance (SPR) will be used in this research. This is essential in developing therapeutic systems that rely on high affinity and selective binding to function. Thus, the factors that influence the binding processes will be analysed.

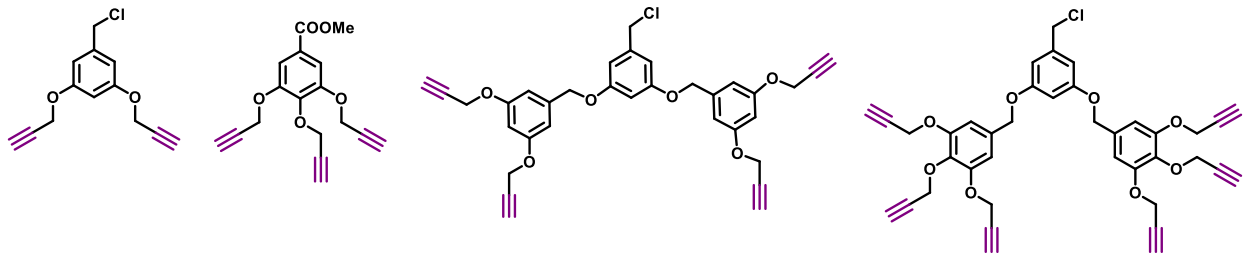


Figure 1. Alkyne-based scaffolds.

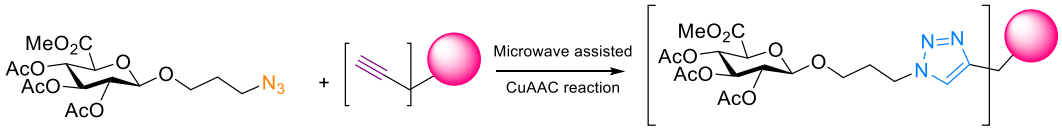


Figure 2. Functionalization of polyalkynyl aromatic scaffolds with D-glucuronic acid.

References:

[1] P. Hoyos, A. Perona, O. Juanes, A. Rumbero, M. J. Hernáiz, *Chem. Eur. J.* **2021**, *27*, 7593.

[2] C. García-Oliva, A. H. Cabanillas, A. Perona, P. Hoyos, A. Rumbero, M. J. Hernáiz. *Chem. Eur. J.* **2020**, *26*, 1588.

Study of degradation and stability of rifampicin in pharmaceutical formulation

M. Martínez Fernández, C. Linares López, C. Díaz Medina.

Analytical development R&D, FAMAR Health Care Service, Av. Leganes 62, 28923 Alcorcon, Spain.
e-mail: miguma12@ucm.es

Keywords: Rifampicin, impurities.

The degradation and stability of pharmaceutical compounds play a critical role in ensuring their efficacy and safety. This chemistry project focuses on investigating the degradation pathways and stability profile of rifampicin, a widely used antibiotic, in different pharmaceutical formulations.

Experimental methods, such as high-performance liquid chromatography (HPLC) and spectroscopic techniques, will be employed to monitor the degradation of rifampicin over time under different stress conditions, including temperature, acid-base treatment, and light exposure.

Furthermore, the influence of formulation factors, such as pH, excipients, and packaging materials, on the stability of rifampicin will be investigated. The project aims to determine the optimal conditions for storage and formulation to minimize degradation and extend the shelf life of rifampicin-based pharmaceutical products.[1]

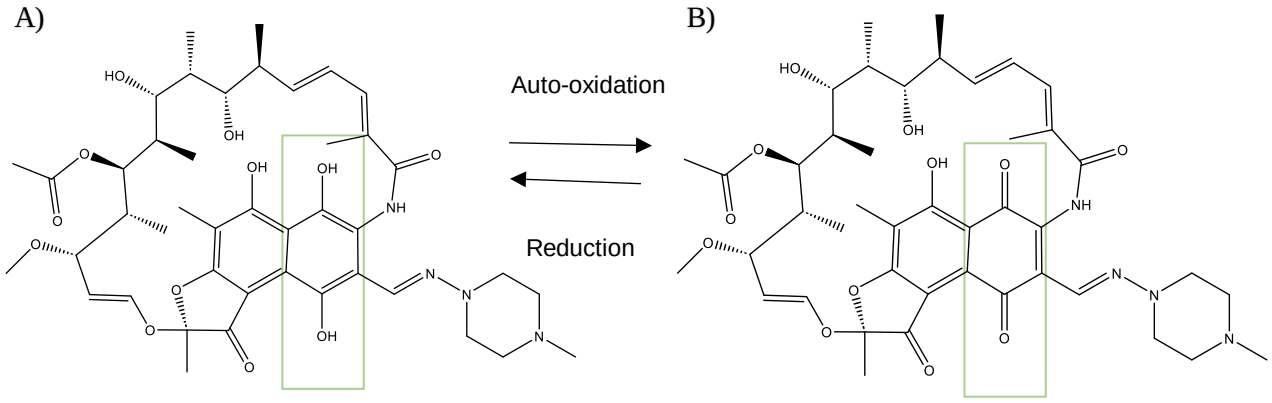


Figure 1: A) Rifampicin structure. B) Rifampicin quinone (degradation product).[2,3]

References:

[1] Página web de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) http://www.aemps.gob.es/

[2] British Pharmacopeia **2023**,1497.

[3] E. Calleri; E. De Lorenzi; S. Furlanetto; G. Massolini; G. Caccialanza. *J. Pharm. Biomed. Anal.* **2002**, *29*, 1089.

New compounds for the treatment of neurodegenerative diseases

A. Martínez-Rodríguez,[a] M. Toledano-Pinedo,[a] M.M. Rodríguez-Fernández,[b] J.L. Marco-Contelles. [a]

[a]*Laboratory of Medicinal Chemistry, IQOG-CSIC, Madrid, Spain.*
[b]*Organic Chemistry Department, Autonomous University, Madrid, Spain.*
e-mail: aritzmar@ucm.es

Keywords: *Alzheimer's disease, Contilisant, Contilistat.*

Alzheimer's disease (AD) is a complex and multifactorial neurodegenerative disease that affects a large part of the adult population. The origin of AD is still unknown, and although there are treatments that improve the conditions and quality of life of patients, AD does not have an effective cure. AD is a progressive and irreversible neurological disorder that occurs in the central nervous system, mainly in the hippocampus and cortex, areas of the forebrain related to memory and higher cognitive functions.[1] For this reason, during the last decades work has been done on the study of new agents based on the concept of multitarget compounds.[2]
Contilisant (Figure 1) is a multipotent molecule, identified in our research group, with important properties for the treatment of Alzheimer's disease. It is a permeable, antioxidant and neuroprotective agent, with a high affinity for histamine 3 receptor (H3R) and sigma 1 (S1R) as well as a potent inhibitor of monoamine oxidase (MAO A and B) and cholinesterase (ChE) enzymes, which cause the serotonin, norepinephrine and dopamine deficit present in people with this disease.[3]

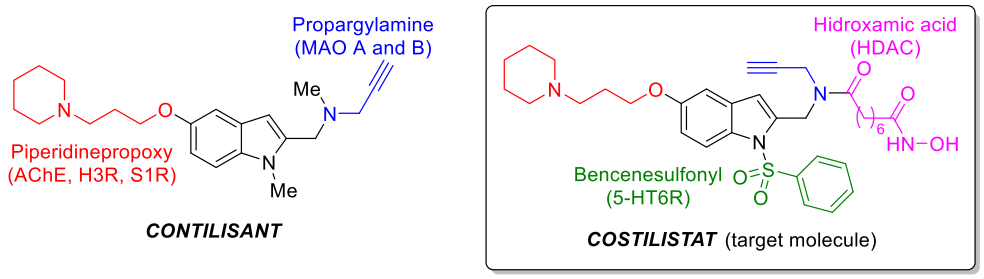


Figure 1. ***Contilisant*** and ***Contilistat*** chemical structures.

In order to improve its pharmacological properties, a new compound that we have called ***Contilistat*** (Figure 1) has been designed bearing new pharmacophore groups (GPs), such as hidroxamic acid for the inhibition of histone deacetylase (HDAC) enzymes, and bencenesulfonyl motif for the modulation of serotonine 6 receptor (5-HT6R),[4] adding positive and superior biological effects. The main goal is the synthesis and bio-evaluation of a new ligand analogue of ***Contilisant*** for a more effective AD therapy.

References:

[1] a) Knopman, D.S., Amieva, H., Petersen, R.C. et al. *Nat. Rev. Dis. Primers*. **2021**, *7*, 33. b) Breijyeh Z, Karaman R. *Molecules*. **2020**, *25*, 5789.
[2] P. Zhang, S. Xu, Z. Zhu, J. Xu. *Eur. J. Med. Chem*. **2019**,*176*, 228.
[3] Bautista-Aguilera, Ó. M.; Budni, J.; Mina, F.; Medeiros, E. B.; Deuther-Conrad, W.; Entrena, J. M.; Moraleda, I.; Iriepa, I.; López-Muñoz, F.; Marco-Contelles, J. *J. Med. Chem*. **2018**, *61*, 6937.
[4] (a) Melesina, J.; Simoben, C. V.; Praetorius, L.; Bülbül, E. F.; Robaa, D.; Sippl, W. *ChemMedChem* **2021**, *16*, 1336. (b) Karila, D.; Freret, T.; Bouet, V.; Boulouard, M.; Dallemagne, P.; Rochais, C. *J. Med. Chem*. **2015**, *58*, 7901.

A straightforward entry to methylene benzocyclobutanes

E. Millán Miquel,[a] C. Corral,[a] I. Colomer.[a]

[a]*Instituto de Química Orgánica General (IQOG-CSIC), Juan de la Cierva 3, 28006, Madrid, Spain.*
e-mail: eumillan@ucm.es

Keywords: *Benzocyclobutanes, Hydroarylation, Heck reaction*

Methylene benzocyclobutanes (BCBs) are a group of bicyclic molecules in which a cyclobutene moiety is fused to a benzene ring. BCB is an interesting scaffold in organic chemistry, found in numerous bioactive compounds, for instance ivabradine is a well-known drug to treat heart disease (Figure 1, left),[1] but also with potential applications in material chemistry, for example via *o*-quinodimethane, an intermediate generated by thermal electrocyclic ring-opening (Figure 1, left).[2] However, it is hard to access BCBs, typically using C-H activation,[3a,3b] [2+2] cycloaddition,[3c] photocatalytic process[3d] and Suzuki-Miyaura cross coupling.[3e] The limited number of methods to synthesize BCBs makes very attractive to develop new methodologies.

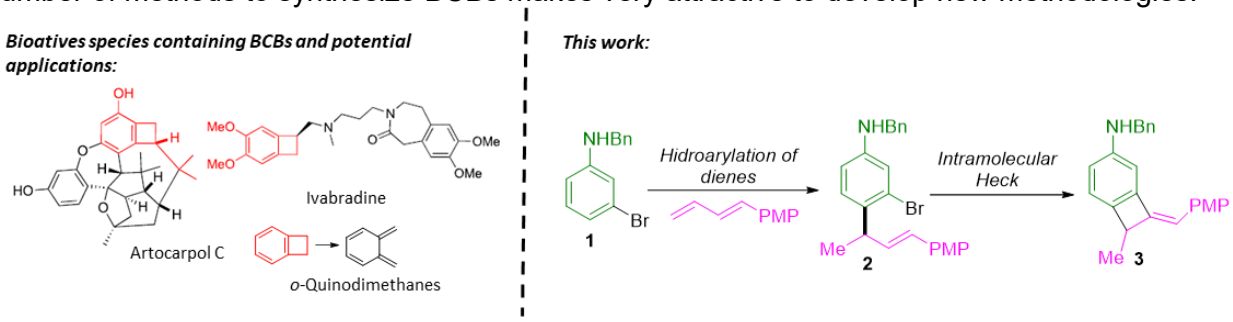


Figure 1. BCBs containing bioactive molecules (left) and proposed synthesis of BCBs via selective hydroarylation of dienes followed by a Heck reaction (right).

Based on our extensive experience in the functionalization of anilines **1** using HFIP,[4] we envisioned the possibility to access intermediates **2** (Figure 1, right), that could engage in a transition metal-catalyzed carbocyclization, to afford BCB **3**.

Herein, we report the first general method to access methylene benzocyclobutanes **3** in an efficient and robust manner using simple starting materials, that entails a chemo- and regioselective hydroarylation of conjugated dienes, followed by an unprecedented regioselective intramolecular Heck reaction (Figure 1, right).

References:

[1] a) Tsotinis, A., Afroudakis, P. A., Garratt, P. J., Bocianowska-Zbrog, A., Sugden, D. *ChemMedChem*. **2014**, *9,* 2238. b) McLean, T. H., Parrish, J. C., Braden, M. R., Marona-Lewicka, D., Gallardo-Godoy, A., Nichols D. E. *J. Med. Chem.* **2006**, *49*, 5794.

[2] a) Harth E., Van Horn, B., Lee, V.Y, Germack, D. S., Gonzales, C. P., Miller, R. D., and Hawker, C. J. *J. Am. Chem. Soc*. **2002**, *124*, 8653–8660. b) Segura, J. L., Martín, N. *Chem. Rev.* **1999**, *99*, 3199. c) Li, Q., Chen, L., Gadinski, M. R., Zhang, S., Zhang, G., Li, H. U., Iagodkine, E., Haque, A., Chen, L., Jackson, T. N., Wang, Q. *Nature* **2015,** *523,* 576.

[3] a) Fujii, T., Gallarati, S., Corminboeuf, C., Wang, Q., Zhu, J. *J. Am. Chem. Soc.* **2022**, *144*, 8920. b) Yang, J., Lin, Y., Sheng, T., Hu, L., Cai, X., Yu, J. *Science.* **2023**, *380*, 639. c) Pugh, C., Baker, J.S., Storms, W.K. *Synlett.* **2014**, *25*, 148. d) Chen, D., Zhang, L., Yao, J., Zhou, H. *J. Org. Chem.* **2017**, *82*, 6202. e) Talbot, F. J. T., Zhang, S., Satpathi, B., Howell, G. P., Perry, G. J. P., Crisenza, G. E. M., Procter, D. J. *ACS Catal.* **2021**, *144*, 8920.

[4] a) Colomer, I. *ACS Catal.* **2020**, *10*, 6023-6029. b) Colomer, I., Chamberlain, A., Haughey, M. et al. *Nat. Rev. Chem.* **2017**, *1,* 0088.

Synthesis and study of a novel PBI derivative: the influence of the dipolar momentum in the formation of supramolecular polymers

A. Morón Blanco, L. López Gandul, L. Sánchez Martín.

Grupo de Moléculas Anfifílicas y Polímeros Supramoleculares, Departamento de Química Orgánica. Facultad de CC. Químicas.
e-mail: adrmoron@cum.es

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

Supramolecular polymerization constitutes a very active line of research in which a large variety of self-assembling units able to form functional supramolecular polymers have been investigated. Among these systems, perylene diimide 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 (NPBIs), where the lateral side chains and the central electro-donating pyrrol ring play a vital role in the self-assembly process.[2,3] The large aromatic surface of these molecules favors their aggregation into supramolecular polymers mainly by the π −stacking of the aromatic units. It has been reported that the presence of amides or esters in the peripheral chains strongly conditions the aggregation features of the monomers. Their importance is so high that depending on the presence of amide of ester functional groups, the species can self-assemble following different polymerization mechanisms and, thus, form structures with different morphologies.[4,5] In this project, the multistep synthesis of a new *N*-annulated PBI (**1**) and its self-assembling features are described to unravel the influence of the carbonyl groups in peripheral side chains in the aggregation process. A number of experiments have been carried out to decipher the supramolecular polymerization of **1.** Importantly, the supramolecular polymerization mechanism has been studied by means of variable-temperature UV-Vis experiments, using methylcyclohexane (MCH) as solvent (Fig. 1b). Unexpectedly, plotting the variation of the absorbance at λ = 518 nm versus temperature yields a sigmoidal curve, characteristic of an isodesmic polymerization mechanism (Fig. 1c).

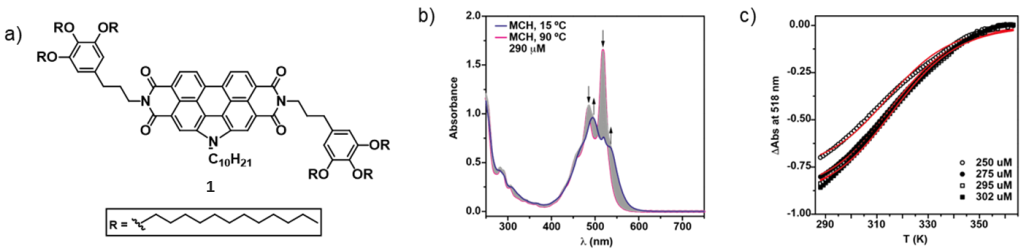


Figure 1. a) Structure of the *N*-annulated PBI. b) VT-UV-Vis spectra of the monomer. c) Fit for absorbance at 518 nm.

References:

[1] F. Würthner, C. R. Saha-Möller, B. Fimmel, S. Ogi, P. Leowanat, D. Schmidt *Chem. Rev.* **2016**, *116*, 962.
[2] (a) E. E. Greciano, B. Matarranz, L. Sánchez, Angew. Chem. Int. Ed. **2018**, 57, 4697. (b) E. E. Greciano, J. Calbo, E. Ortí, L. Sánchez, Angew. Chem. Int. Ed. **2020**, 59, 17517.
[3] E. E. Greciano, S. Alsina, G. Ghosh, G. Fernández, L. Sanchez, Small Methods, **2020**, 4, 1900715.
[4] C. Naranjo, S. Adalid, R. Gómez, L. Sánchez. *Angew. Chem. Int. Ed.* **2023**, 62, 1.
[5] M. Martínez, A. Doncel-Giménez, J. Cerdá, J. Calbo, R. Rodríguez, J. Aragó, J. Crassous, E. Ortí, L. Sánchez. *J. Am. Chem. Soc.* **2021**, 143, 13281.

Excipient compatibility study of compound A

M. Muñoz Herranz, M. del Olmo García, J. Gómez Tomás.
Formulation Development R&D, FAMAR HEALTH CARE SERVICES, Av. Leganés 62, 28923 Alcorcón, Spain.
e-mail: mmunoz19@ucm.es

Keywords: *anti-diabetic, compatibility, stability.*

Diabetes mellitus is a metabolic disease that has become a threat in recent decades as it generates complications such as cardiovascular and renal diseases, complications in pregnancy, etc. There are different types of diabetes mellitus, one of them is diabetes mellitus type 2 (DMT2) which appears due to insufficient insulin production by the pancreas or if the insulin produced does not work properly.[1] It can also appear if the body produces too much glucagon, which increases the production of sugar by the liver and raises blood sugar levels.
FAMAR HEALTH CARE SERVICES is developing a generic anti-diabetic drug for this disease. For this purpose, it is based on a Reference Listed Drug (RLD) containing an anti-biabetic Active Principle Ingredient (API) which we will call compound A, complying with the confidentiality agreement dictated by the company. This Active Ingredient improves the glycemic control of patients suffering from this disease. The administration of this API causes a significant and complete inhibition of DPP-4 activity. Consequently, compound A potentiates insulin secretion, inhibits glucagon release and reduces glucose production by the liver.
For the development of a quality drug, the selection of excipients is crucial in the final pharmaceutical formulation. Excipients and their concentration in the formulation are selected based on their functionality and compatibility with the API. [2] The main objective of this work is to carry out this compatibility study to select the most compatible excipients with Compound A. For this purpose, 20 binary mixtures are prepared. One of them contains only Compound A and the rest are composed of Compound A and a different excipient in each of them.
Then, the stability of the API and its interaction with the excipients must be evaluated. For this purpose, all mixtures are stored under accelerated conditions of 40°C/75%RH at times 0 and 1 month.[3] Once these times have passed, two analyses are performed under different chromatographic conditions on all the mixtures in order to know the known impurities of Compound A, those originated by the interaction with the different excipients in each of them and determined the degradation products, where it is determined if there is degradation of Compound A and if new impurities are generated.
Finally, some excipients are selected in order to subsequently develop different pharmaceutical formulations and, among them, choose the most stable one.

References:

[1] Bereda, G. *A Review of the Hybrid Description of Diabetes Mellitus*. BOHR International Journal of Current Research in Diabetes and Preventive Medicine 2022, (*2*), 35.
[2] Narang, A. S.; Rao, V. M.; Raghavan, K. S. *Excipient Compatibility. In Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice*; *Elsevier*, 2008; pp 125.
[3] CPMP/ICH. ICH Topic Q 1 *A Stability Testing Guidelines : Stability Testing of New Drug Substances and Products*. *European Medicines Agency* 1998, No. January.

Enantioselective synthesis of a potential inhibitor for SHP2 phosphatase by means of the addition of an enolate to a chiral sulfinyl imine

Pedro Muñoz Rodríguez, Víctor Laina Martín, Francisco Tato Moreno.

Synthelia Organics SL, C. de Torres Quevedo, 15, 28108, Alcobendas, Madrid.
email: pedmunoz@ucm.es

Keywords: *enantioselective synthesis, SHP2 inhibitor, oncogenesis*

The treatment for cancer is still nowadays one of most important research to be done in medical-chemistry laboratory. In this regard, the aim of this study is to synthetize an advanced intermediate of an inhibitor for SHP2 phosphatase, which is strongly related to cell proliferation, differentiation and survival, making it susceptible to be related to oncogenesis.[1]

The target molecule of this synthesis presents a stereogenic center in its structure. In addition, it has been demonstrated that one enantiomer is way more active than the other one,[1] thus, we are heading to a technical challenge to asymmetrically synthetize the desired enantiomer. Chiral inductors grant us with the capacity of perform asymmetric synthesis,[2] which is a very powerful way to synthetize compounds in an enantioselective manner. In this work, *tert*-butyl sulfinyl amides have been used for this purpose. This kind of chiral inductors have been already employed in some other works to generate stereocenters provided with amines[3,4] since they present a high efficiency and capability to attack ketones and aldehydes and cleave, giving the desired stereocenter.

There is a patented synthetic pathway in which the authors are reducing the sulfinyl imine to synthetize the desired product. However, the problem with this route is the low stereoselectivity.[1] In contrast, we envisioned an alternative route in which the sulfinyl imine would be attacked by an enolate (Figure 1). In this regard, this strategy would lead to the improvement of the stereoselectivity and the reduction of the number of steps and costs in a possible large-scale synthesis.

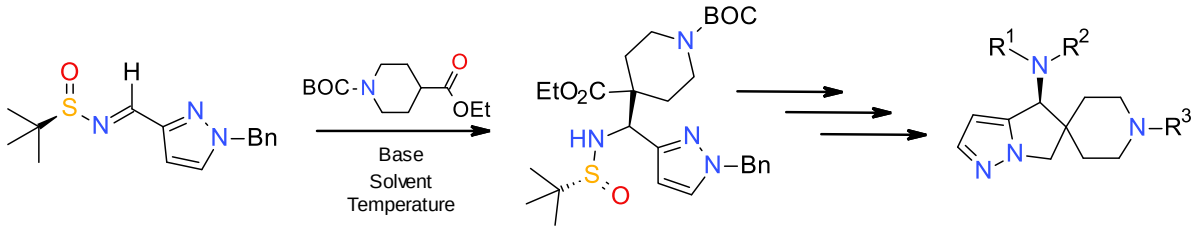


Figure 1. Key stereoselective step based on the nucleophilic addition of an enolate to a chiral sulfinyl imine.

References:

[1] World Patent. Di Fabio R.; Montalbetti C.; Petrocchi A.; Grillo A.; Randazzo P.; Rossetti I.; Ciammaichela A. (2022). *(S)-1-(5-((Pyridin-3-yl)thio)pyrazin-2-yl)-4'H,6'H-spiro[piperidine-4,5'-pyrrolo[1,2-b]pyrazol]-4'-amine derivatives and similar compounds as SHP2 inhibitors for the treatment of e.g. cancer.* WO2022/207924.

[2] Philip R. M.; Radhika S.; Saranya P. V.; Anilkumar G. *RSC Adv.* **2020**, *10*, 42441.

[3] Tang T. P.; Ellman J. A. *J. Org. Chem.* **2002**, *67*, 7819.

[4] Cogan D. A.; Ellman J. A *J. Am. Chem. Soc.* **1999**, *121*, 268.

Multivalent carbon nanoforms for targeted drugs development

C. Pravos-Gonzalo,[a] J. Cabrera-González,[a] B. M. Illescas.[a]

[a]*Organic Molecular Materials Group, Facultad de Ciencias Químicas, UCM, Avda. Complutense s/n, 28040 Madrid, Spain*.

e-mail: cpravos@ucm.es

Keywords: *Glycofullerenes, DC-SIGN and multivalency*

Glycofullerenes, which are fullerene-based structures bearing carbohydrate residues, have gained attention as potencial inhibitors of pathogen entry into cells. The unique properties of fullerenes, such as their nanoscale size, high stability, and versatile surface chemistry, make them promising candidates for biomedical applications. By modifying the number and nature of the attached carbohydrates residues, different strategies have been explored to enhance their inhibitory effects against pathogens.[1]

DC-SIGN is considered a universal receptor of pathogens and it selectively recognizes mannose and fucose residues. However, the interaction between these carbohydrates and the receptor is generally driven by weak supramolecular interactions. Various multivalent systems based on [60]fullerene have been designed to ensure a high affinity between glycofullerenes and DC-SIGN.[2,3]

In this project, the synthesis of a nanostructure has been tackled, in which 24 glycofullerenes will be covalently attached to a central C_{60} core. This will result in a glycomimetic with promising biological applications.

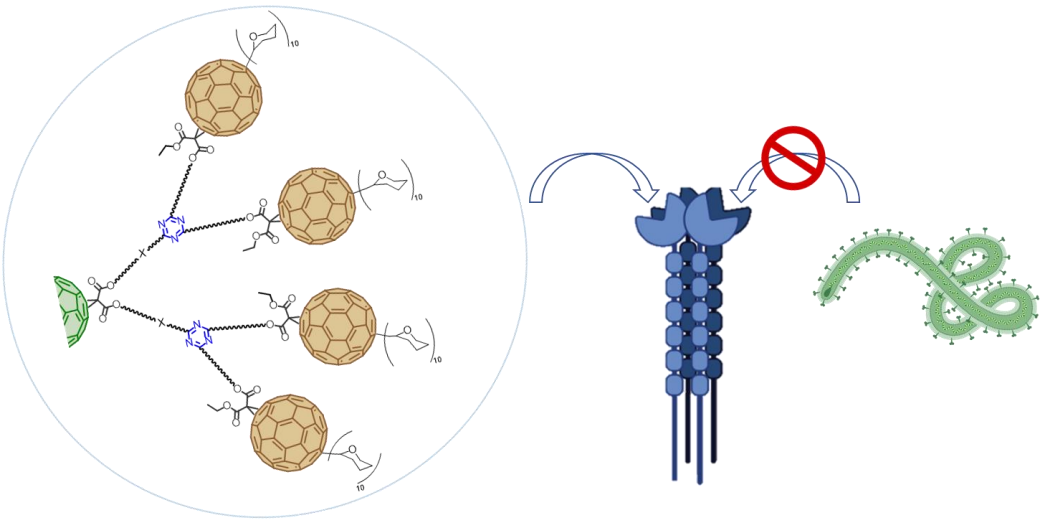


Figure 1. Blocking of the DC-SIGN receptor with a symmetrical hexaadduct of [60]fullerene and inhibition of certain viruses such as Ebola.

References:

[1] Nierengarten, I.; Nierengarten, J.-F. *Chem. Asian J.* **2014**, *9*, 1436.

[2] Ramos-Soriano, J.; Illescas, B. M.; Pérez-Sánchez, A.; Sánchez-Bento, R.; Lasala, F.; Rojo, J.; Delgado, R.; Martín, N. Int. J. Mol. Sci. **2022**, *23*, 5083.

[3] Ramos-Soriano, J.; Pérez-Sánchez, A.; Ramírez-Barroso, S.; Illescas, B. M.; Azmani, K.; Rodríguez-Fortea, A.; Poblet, J. M.; Hally, C.; Nonell, S.; García-Fresnadillo, D.; Rojo, J.; Martín, N. *Angew. Chem. Int. Ed.* **2021**, *60*, 16109.

Design and synthesis of molecular nanographenes for the study of their optical and electronic properties

I. Ramos Aranda,[a] J. M. Fernández García,[a] N. Martín León.[a,b]

[a] *Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040, Madrid, Spain.*
[b] *IMDEA-Nanoscience, C/ Faraday, 9. Ciudad Universitaria de Cantoblanco, 28049, Madrid, Spain.*
e-mail: igramo01@ucm.es

Keywords: *nanographenes, metallic polymers, molecular switch*

Nanographenes are structurally confined nanoscale graphene segments that show non-zero bandgaps that are mainly governed by their size and edge configurations. These molecules are being increasingly studied for this reason and potential applications in fields such as batteries, hydrogen storage materials and biomedicine.[1]

Nanographenes can be synthesized by two methods: top-down and bottom-up. The first is analogous to "cutting" the graphene sheet to obtain smaller parts, while the second starts from smaller precursors to reach the desired products. The main reason for using bottom-up classical organic synthesis is that it allows to uniformly control the distribution of sizes, obtaining defined molecules and thus modulating the properties of the final material.

In this work, five different nanographenes **2a**, **2b**, **3a**, **3b**, **4a** have been synthetized via Suzuki coupling on the precursors **1a** and **1b**, also prepared in a multigram scale. **2a** and **3a** can form dimers when complex with metals, while **2b** and **3b** would form linear metallic polymers. Finally, complexation of planar **4a** with metals could make it adopt a bilayer geometry,[2] the reversibility of this process would make **4a** act as a molecular nanographene switcher.[3]

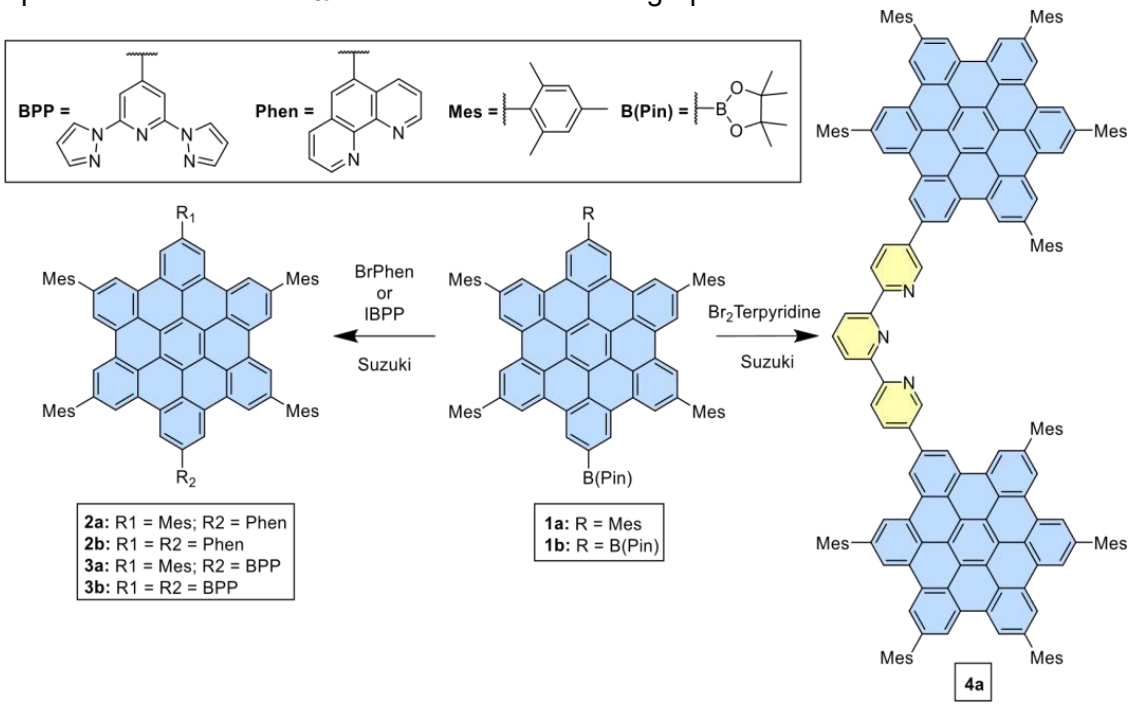


Figure 1. Molecular nanographenes synthetized in this work.

References:

[1] Narita, A.; Wang, X. Y.; Feng, X.; Müllen, K. *Chem. Soc. Rev.* **2015**, *44*, 6616.
[2] Evans, P. J.; Ouyang, J.; Favereau, L.; Crassous, J.; Fernández, I.; Perles, J.; Martín, N. *Angew. Chem. Int. Ed.* **2018**, *23*, 6774.
[3] Doistau, B.; Cantin, J.; Chamoreau, L.; Marvaud, V.; Hasenknopf, B.; Vives, G. *Chem. Commun.* **2015**, *51*,12916.

Synthesis of VEGFR2 (kinase) inhibitors as potential antitumor agents

P. I. Rubio Ramón,[a,b] C. Dardonville.[b]

[a]*Facultad de Ciencias Químicas. Universidad Complutense de Madrid,* [b]*Grupo de Antiparasitarios. Instituto de Química Médica. Consejo Superior de Investigaciones Científicas (IQM-CSIC).*
e-mail: pabloiru@ucm.es

Keywords: *kinase inhibitors, antitumor drugs*

Kinase inhibitors represent a diverse and powerful class of antineoplastic drugs. These agents possess the ability to selectively target protein kinases that undergo alterations in cancer cells, thereby contributing to their abnormal proliferation. Compound **1** is a type-II inhibitor of vascular endothelial growth factor receptor **2** (VEGFR2) that binds to the inactive form of VEGFR2 (Figure 1).[1]

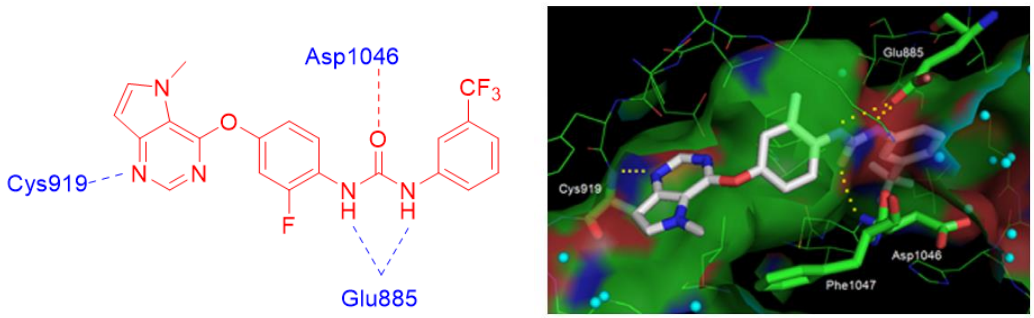


Figure 1. Chemical structure of compound 1 (left) and X-Ray co-crystal structure in complex with VEGFR2 (right).

Based on this compound in a screening performed our research group has identified the dichlorinated compound **2** as a micromolar range tyrosine kinase inhibitor (VEGFR2 and human EGFR).

The aim of this project is to synthesize a small library of tyrosine kinase inhibitors inspired from the structure of **2** and the prototype **1.** The target compounds are designed to increase hydrogen bond interactions in the hinge region of the active site (Cys 919).[2]

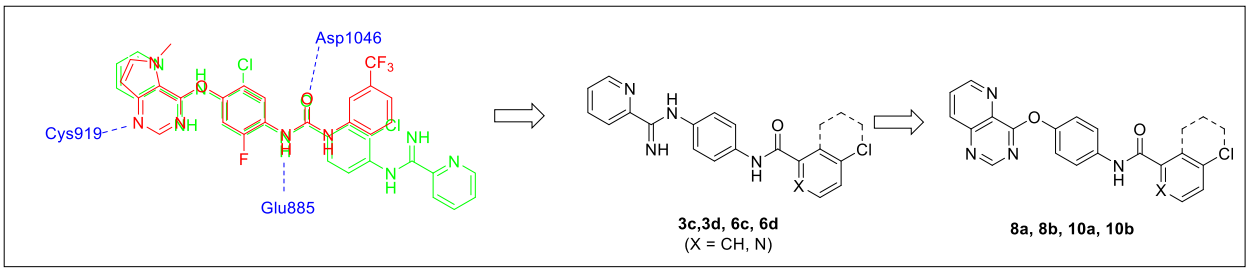


Figure 2. Overlapping of **1** and **2** structures and proposed scaffold modifications.

References:

[1] Oguro, Y.; Miyamoto, N.; Okada. *Bioorg. Med. Chem.* **2010**, *18*, 7260.

[2] Miyamoto, N.; Sakai, N.; Hirayama, T. *Bioorg. Med. Chem.* **2013**, *21*, 2333.

Synthesis of potential bioactive functionalized heterocycles

D. San Martín Loubet,[a] A. Luna Costales,[a] P. Almendros Requena.[b]

[a]*Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica Unidad Asociada al CSIC, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040-Madrid, Spain,* [b]*Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, IQOG-CSIC, Juan de la Cierva 3, 28006, Madrid, Spain.*

e-mail: dsanma01@ucm.es

Keywords: *allenes, carbazoles, palladium*

The allene functional group consists in two cumulated C–C double bonds. They show both high and unique reactivity and selectivity, having plenty of uses as synthetic precursors.[1] Moreover, carbazoles are a family of heterocyclic molecules that share unique properties, allowing them to have a lot of applications in some organic chemistry fields such as medicinal chemistry and material science.[2] In the last years, allenyl-indoles have been studied as precursors for the preparation of carbazole derivatives via a carbocyclization reaction under Au or Ag catalysis.[3] With this background, we decided to do further research in the carbocyclization process with an additional funtionalization. Herein, in this work we present a new synthetic methodology, based in a carbocyclization/functionalization tandem reaction, for the preparation of carbazole and dihydrocarbazole structures from allenyl-indoles and organic halides, under palladium catalysis (Figure 1). The reaction conditions were optimized using different solvents, palladium catalysts and temperatures in order to obtain the best yields. The scope of the reaction was studied using allenyl-indoles with electron-donating/electron-withdrawing substituents in different positions. It is worth noting that the carbocyclization process exhibits regioselectivity towards the 2,3,4-trisubstituted products instead of the 1,2,3-trisubstituted ones.

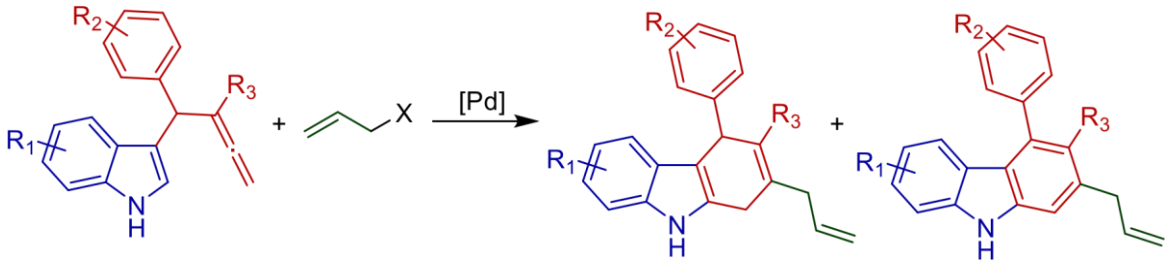


Figure 1. Pd catalyzed carbocyclization/coupling reaction of allenyl-indoles.

References:

[1] (a) Alonso, J. M.; Almendros, P. *Chem. Rev.* **2021**, *121*, 4193. (b) Mascareñas, J. L.; Varela, I.; López, F. *Acc. Chem. Res.* **2019**, *52*, 465. (c) Ye, J.; Ma, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 10809.

[2] (a) Caruso, A.; Ceramella, J.; Iacopetta, D.; Saturnino, C.; Mauro, M. V.; Bruno, R.; Aquaro, S.; Sinicropi, M. S. *Molecules* **2019**, *24*, 1912. (b) Ledwon, P. *Org. Electron*. **2019**, *75*, 105422.

[3] (a) Luna, A.; Herrera, F.; Higuera, S.; Murillo, A.; Fernández, I.; Almendros, P. *J. Catal*. **2020**, *389*, 432. (b) Guo, B.; Huang, X.; Fu, C.; Ma, S. *Chem. Eur. J.* **2016**, *22*, 18343.

Design, synthesis and study of luminescent supramolecular polymers

M. Sánchez Casillas, A. Schwalb Freire, R. Gómez Aspe.

Universidad Complutense de Madrid.

e-mail: marins28@ucm.es

Keywords: *supramolecular polymers, perylene bisimides.*

In the last two decades, perylene bisimide (PBI) based molecules have grown in relevance in the field of supramolecular chemistry. They consist of a rigid polycyclic aromatic structure substituted with two imide groups. Usually, the PBI abbreviation refers to the linear isomer, however, the Z-shaped isomer offers some interesting advantages: firstly, it possesses a twisted nature that prevents from close packing and improves its solubility, secondly, it has two additional derivatization sites with distinctive reactivities that allow for regiochemically controlled functionalization.[1]

In this project, the synthesis of the Z-shaped PBI shown in Figure 1, PBI-1, has been accomplished following a convergent synthetic route, with a similar methodology of that found in literature.[1,2] The aromatic core and the amide groups allow for the formation of supramolecular polymers through pi-stacking and hydrogen bond interactions, while the aliphatic peripheral units improve its solubility. Its also important to notice the ethylene bridge between the peripheral units and the PBI core, since this kind of spacers make the self-assembly process more complex.[3]

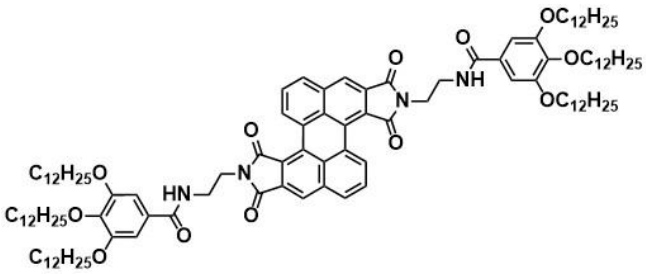


Figure 1. Chemical structure of PBI-1.

The self-assembly features of PBI-1 have been studied with different spectroscopic techniques: the ^{1}H-NMR and FTIR studies have shown that PBI-1 forms different metastable kinetic species through intramolecular hydrogen bonds. The UV-visible studies show that PBI-1 forms null-aggregates, since the aggregate is very similar spectroscopically to the monomer.[4] Its polymerization mechanism could not be clarified, as the plot of the absorption versus the temperature didn't fit correctly, which seems to show a kinetic trapping may be occurring.

References:

[1] Billa, B.; Lin, C-H. *J. Chem.* **2021**,*86*, 9820.
[2] Greciano, E.E.; Sánchez, L. *Chem. Eur. J.* **2016**, *22*, 1.
[3] Greciano, E.E.; Alsina, S.; Ghosh, G.; Fernández, G.; Sánchez, L. *Small Methods*. **2020**, *4*, 1900715.
[4] Hestand, N.J.; Spano, F.C. *Chem. Phys*. **2015**, *143*, 244707.

Synthesis of novel imidazo[1,2-a]pyridine derivatives for application in new innovative therapies against inflammation

C. Sánchez García,[a] A. García Csákÿ,[a] S. Roscales García.[a]

[a] *Pluridisciplinar Institute, Complutense University of Madrid, Paseo Juan XXIII 1, 28040, Madrid, Spain.*
e-mail: clauds06@ucm.es

Keywords: *Inflammation, inhibitors of ALK5, imidazo[1,2-a]pyridines*

Inflammation is a protective response of the body in which vascularized tissues transport defense cells and protective molecules to sites of infection or cellular injury. This response is essential to eliminate aggressors and their consequences.[1]

New approaches to treating inflammation focus on developing innovative therapies that overcome the limitations and side effects of conventional anti-inflammatory drugs. In particular, the overexpression of transforming growth factor-beta (TGFβ) is linked to diseases like cancer, fibrosis, and inflammation. Therefore, targeted inhibition of TGFβ receptors, such as ALK5, has emerged as a potential therapeutic approach to modulate the inflammatory response.[2,3]

Our research group has identified several imidazo[1,2-*a*]pyridines as *in vivo* inhibitors of ALK5, with therapeutic potential for the treatment of macrophage-mediated inflammation and inflammation caused by respiratory viral infections.[4] The main focus of this research is the synthesis of new imidazo[1,2-*a*]pyridine derivatives to test their anti-inflammatory effect and increase our portfolio of therapeutically active compounds (Figure 1).

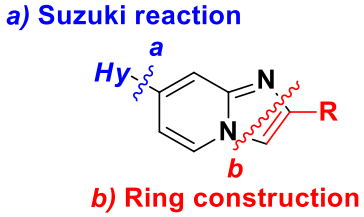


Figure 1. Synthesis of new imidazo[1,2-*a*]pyridines with potential anti-inflammatory effect.

References:

[1] Kumar, V.; Abbas, A. K.; Aster, J. C.; Perkins,; *Elsevier*, **2021**.

[2] Ling, L. E.; Lee, W. TGF-. *Curr. Pharm. Biotechnol*. **2011**, *12, 2190*.

[3] Tie, Y.; Tang, F.; Peng, D.; Zhang, Y.; Shi, H.. *Mol. Biomed*. **2022**, *3, 45*.

[4] Sánchez-Sancho, F.; del Pozo, C.; Csáky, A. G.; Marcilla, A.; del Pozo, J.; Oliver, E.; Ibáñez, B.; Roscales, S.; Cumella, J. M.; Baquero, M. G.; Sánchez, C. M. *Spanish Patent in application process, OTRI UV* **2023**.

Synthesis of new BODIPYs for photodynamic therapy and cellulose nanocrystals functionalization

A. Valverde,[a] J.L. Chiara,[b] E. Mann.[b]

[a]*Universidad Complutense de Madrid,* [b]*Instituto de Química Orgánica General (IQOG-CSIC), Madrid, Spain.*
e-mail: aleval06@ucm.es

Keywords: *BODIPY, photodynamic therapy, cellulose nanocrystals*

Photodynamic therapy (PDT) is nowadays a subject of extensive research in cancer treatment and microbiological infections. PDT relies on a molecule that acts as a photosensitizer, generating oxygen radical species and singlet oxygen, being both highly cytotoxic. Boron dipyrromethenes (BODIPYs) are a promising family of organic dyes that could be used for this purpose.[1] Recently, donor-acceptor dyads based on BODIPYs with electron donating aryl groups in the meso position have been described for efficient singlet oxygen generation.[2]
Cellulose nanocrystals (CNCs) are a fascinating class of nanomaterials with diverse biomedical applications. Their functionalization for the preparation of nanoparticle carriers represents a significant breakthrough in the field of drug targeting and delivery.[3]
The aim of this work is the design and synthesis of a new family of BODIPY-based single oxygen generators decorated with an alkyne group, and their subsequent anchoring to CNC functionalized with azide groups through a click-type reaction.

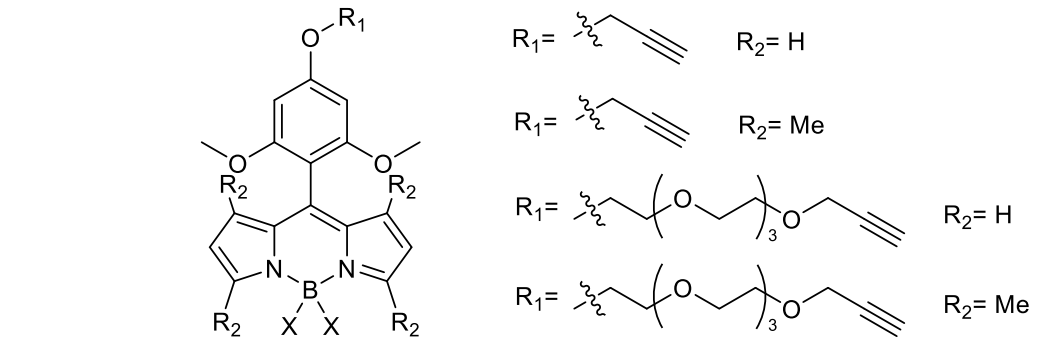


Figure 1. BODIPYs prepared in this work.

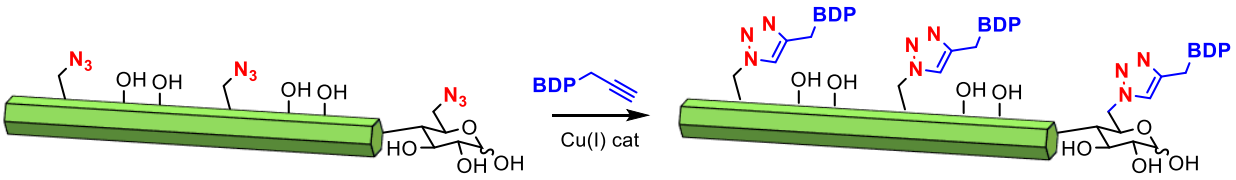


Figure 2. Cellulose nanocrystals functionalization via click reaction.

References:

[1] Prieto-Montero, R.; Prieto-Castañeda, A.; Sola-Llano, R.; Agarrabeitia, A. R.; García-Fresnadillo, D.; López-Arbeloa, I.; Villanueva, A.; Ortiz, M. J.; De la Moya, S.; Martínez-Martínez, V. *Photochem. Photobiol.* **2020**, *96*, 458.
[2] Buglak, A. A.; Charisiadis, A.; Sheehan, A.; Kingsbury, C. J.; Senge, M. O.; Filatov, M. A. *Chem. Eur. J.* **2021**, *27*, 9934.
[3] Mali, P.; Sherje, A. P. *Carbohydr. Polym.* **2022**, *275*, 118668.

Towards new ligands based in [2,2]paracyclophane for organometallic catalysis

Manuel Balboa, José L. Mascareñas, Fernando López

Center for Research in Biological Chemistry and Molecular Materials(CiQUS) and Department of Organic Chemistry, University of Santiago de Compostela(Spain)
e-mail: manuel.balboa.lopez@rai.usc.es

Keywords: *[2,2]paracyclophane, planar chirality, nitrogen fixation*

[2,2]paracyclophanes are molecules with an unusual tridimensional structure and very particular physicochemical properties. This combination makes these molecules excellent candidates to design new ligands for organometallic catalysis. In one hand, the parallel position of the two aromatic rings gives the possibility to modulate the electronic properties of the system in an unique way. On the other hand, the rigidity of it allows the asymmetric functionalization to obtain planar-chiral derivatives.[1]

Based in these two characteristics, in this project we explored two synthetic routes aimed to eventually prepared two new types of [2,2]paracyclophane-based ligands which could be applied to different research areas of interest in our group. In particular, we are very much interested in the development of new molybdenum catalysts that can promote the transformation of N_2 into NH_3 under ambient conditions,[2] as well as in the development of novel chiral gold complexes for Au(I)/Au(III) enantioselective catalysis.[3]

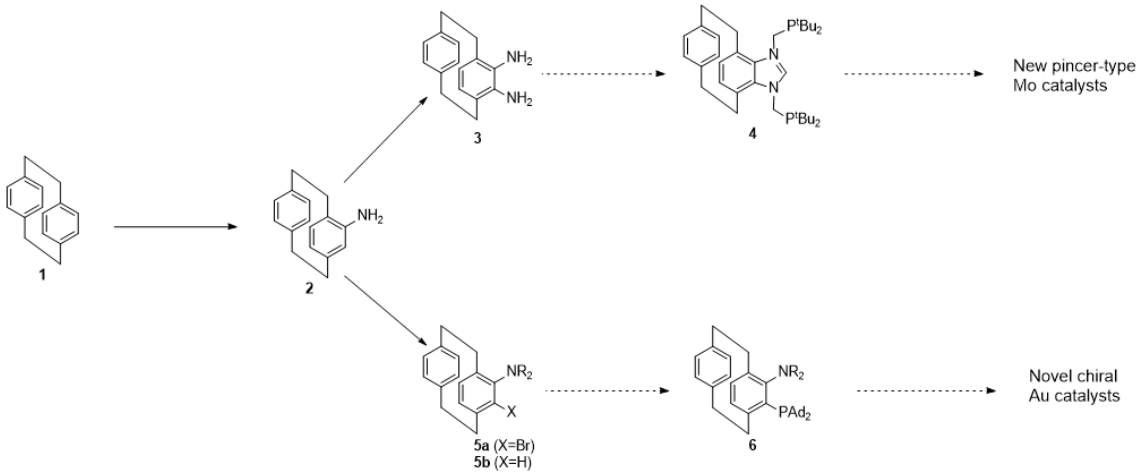


Figure 1. Designed routes for the synthesis of the ligands 4 and 6

In this context and considering the magnitude of this project, the aim of this Master's Thesis is to advance in the synthesis of the ligands **4** and **6** by obtaining the advanced precursors **3** and **5a/5b**. The work included the exploration of new reactions on paracyclophane systems and the optimization of the resulting routes, so that the synthesis of the ligands and their respective metal complexes can be obtained in the near future.

References:

[1] Hassan, Z.; Spuling, E.; Knoll, D. M.; Lahann, J.; Bräse, S. *Chem. Soc. Rev.* **2018**, *47*, 6947-6963.
[2] Ashida, Y.; Arashiba, K.; Nakajima, K.; Nishibayashi, Y. *Nature* **2019**, *568*, 536-540.
[3] Rocchigiani, L.; Bochmann, M. *Chem. Rev.* **2020**, *121*, 8364-8451.

Synthesis and structural studies of β-amino acid based foldamers

F. Bouzán Cumplido, J.C. Estévez Cabanas

CIQUS - Universidade de Santiago de Compostela

e-mail: fernan.bouzan@rai.usc.es

Keywords: *foldamers, β-amino acids, SPPS*

This project consists of the synthesis of cycloalkanic β-amino acid based foldamers and their structural studies. The synthetised foldamers are peptides formed by alternating residues of (*R,R*)-2-aminocyclohexanecarboxylic acid (*trans*-ACHC) and (*R,R*)-2-aminocyclopentanecarboxylic acid *(trans*-ACPC), as shown on figure 1. To achieve this, it is necessary to acquire both monomers, we do this by synthesizing *trans*-ACHC following and improving an efficient synthetic route to obtain this β-amino acid developed previously in our group. The trans-ACPC monomer is commercially available.

The final peptides are obtained through Solid Phase Peptide Synthesis (SPPS). It is therefore necessary to study how this compounds fold themselves with structural determination spectroscopic techniques such as NMR studies and Circular Dichroism (CD).

This work is motivated by a previous study of the group which presents how a similar peptide folds itself in different environments[1]. The understanding of how this type of compounds fold themselves is essential to the search of bioactive peptides. This could lead to a lot of different applications in different fields of study.

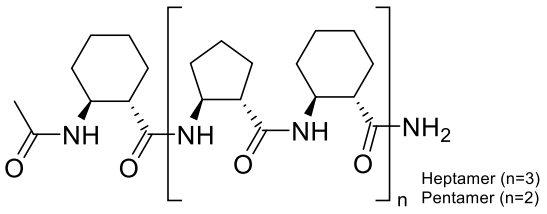


Figure 1. β-amino acid based peptides synthetized

References:

[1] Sussman, F., Sánchez-Pedregal, V. M., Estévez, J. C., Balo, R., Jiménez-Barbero, J., Ardá, A., Gimeno, A., Royo, M., Villaverde, M. C., & Estévez, R. J. (. Environmental Effects Determine the Structure of Potential β-Amino Acid Based Foldamers. *Chem. Eur. J.* **2018,** *24*, 10625-10629 https://doi.org/10.1002/chem.201801953

Determination of the dependance of the peptide coiled coil character upon pH and temperature

Daniel Crespo Veiga

[a]*Universidade de Santiago de Compostela,* [b]*Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares*

e-mail: daniel.crespo.veiga@rai.usc.es

Keywords: *(peptide, coiled coil, chromophore)*

We synthetized a polyglutamic based peptide by Solid Phase Peptide Synthesis (SPPS) and bound a chromophore group, named NBD, to the side chains of the residues of ornithine placed each 2 and 5 positions in the backbone, following the Knobs Into Holes (KIH) model, as displayed in figure 1. The hydrophobicity of the NBD groups will allow various peptide chains to interact with each other to create a coiled coil structure, which is formed by 2 or more alpha helix coupled to one another. We performed CD (Circular Dichroism) spectroscopy experiments to measure how the peptide goes from a random coil conformation, with all amino acid residues oriented aleatory, to a coiled coil conformation, and analyze how this transition depends upon the temperature and the pH. We learned that at lower pH, the peptide prefers to be in that coiled coil conformation, since the carboxyl groups of the side chains of the glutamic acid residues are not protonated and therefore there is no repulsion between them, which favours the interaction between peptide chains. The R factor (relation between absorbance at 222 and 208 nm observed in figure 2(a)) is an indicator of the conformation of the peptide; as R increases, the peptide goes from random coil to coiled coil structure (figure 2(b)). We also learned that at higher temperatures, the peptide loses its coiled coil structure as a result of denaturalization and adopts random coil conformation (figure 2(c)).

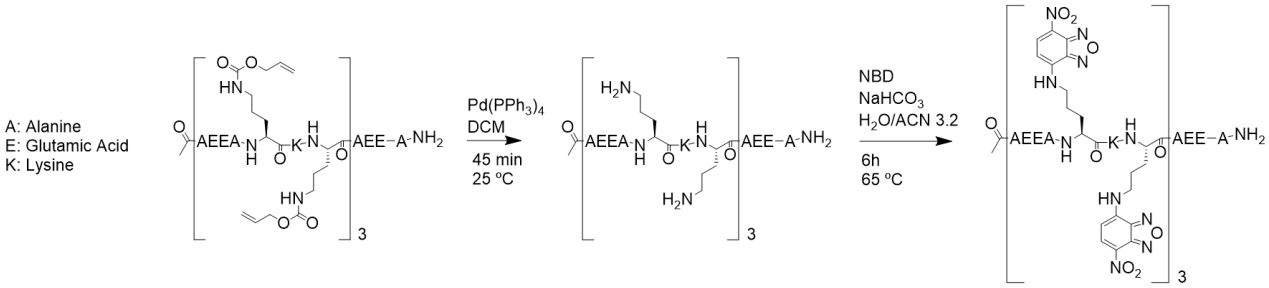


Figure 1. Scheme of the synthesis process of the peptide. First, we synthetize the peptide by SPPS and then we bond the NBD groups to the side chains of the residues of ornithine.

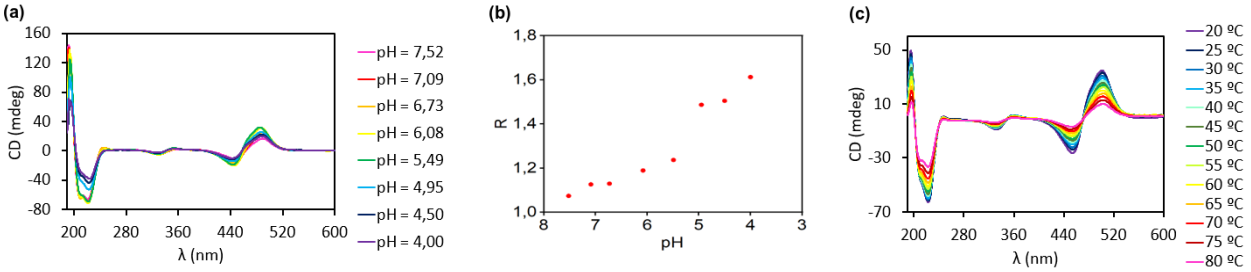


Figure 2. (a) CD spectrum at various pH. (b) R factor dependance on pH. (c) CD spectrum at various temperatures.

New Sustainable Routes to Azulenic PAHs

L. Lago Lorenzo, A. Suárez Lustres, J. A. Varela, C. Saá*

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Dpto. de Química Orgánica, USC, 15782 Santiago de Compostela
e-mail: laura.lago.lorenzo@rai.usc.es

Keywords: *Electrophilic carbocyclization, PAH's, azulene.*

Polycyclic aromatic hydrocarbons (PAHs) with no-benzenoid ring have always attracted the curiosity of chemists owing to their unique electronic, optical and structural features in comparison with their respective benzenoid counterparts.[1] Azulene, the structural isomer of naphthalene, is one of the most common non-alternant units which gives rise to curved nanographene systems with altered electronic and optical properties, making them ideal for the construction of semiconductors (Figure1). Consequently, in recent years it has become increasingly important to develop efficient and sustainable synthetic methods of non-benzenoid PAHs.

The aim of this work is to explore new sustainable routes to obtain azulenic PAHs by direct electrophilic carbocyclization on the seven-membered ring moiety (Scheme 1).

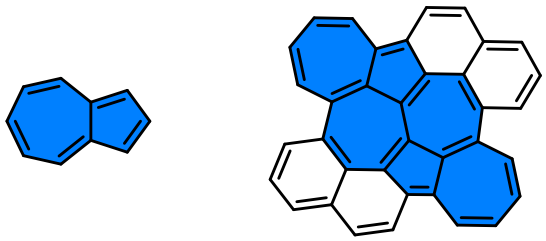
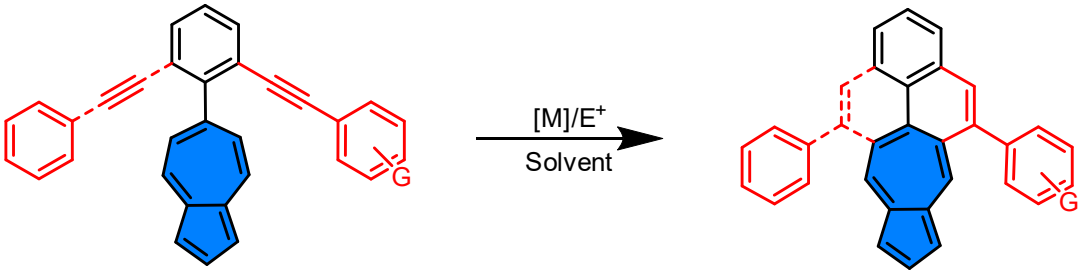


Figura 1. Azulene and azulenic PAHs.



Scheme 1. Mono and double cyclization of azulene derivatives.

References:

[1] (a) Zhang, X.-S.; Huang, Y.-Y.; Zhang, J.; Meng, W.; Peng, Q.; Kong, R.; Xiao, Z.; Liu, J.; Huang, M.; Yi, Y.; Chen, L.; Fan, Q.; Lin, G.; Liu, Z.; Zhang, G.; Jiang, L.; Zhang, D. *Angew. Chem. Int. Ed.* **2020**, *59, 3529*. (b) Medel, M. A.; Tapia, R.; Blanco, V.; Miguel, D.; Morcillo, S. P.; Campaña, A. G. *Angew. Chem., Int. Ed.* **2021**, *60, 6094.*

Metallo-Supramolecular Fibers from Chiral Phenylacetylene Monomers: Cation Induced Self-Assembly

H. Landín González, Emilio Quiñoá Cabana, Félix Freire Iribarne

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) USC

e-mail: helena.landin@rai.usc.es

Keywords: *Helical Polymers, Metallo-Supramolecular fibers, Phenylacetylene.*

A novel method has been discovered to obtain a previously unseen variety of metallo-supramolecular fibers. These fibers are formed by combining a phenylacetylene monomer with with different silver salts. The resulting complex undergoes self-assembly rapidly, and by adjusting the ratios of the monomer to silver(I), it becomes possible to control the fiber morphology, ranging from individual fibers to three-dimensional networks. Additionally, by manipulating the amount of cosolvent added, the helical assemblies can be transformed from solutions into gels.

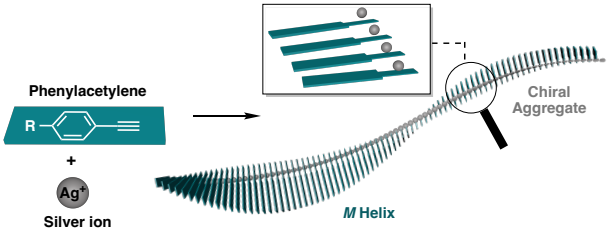


Figure 1. Spontaneous aggregation of PA-Ag(I)-PA complex.

References:

[1] J. Matern, Z. Fernández, N. Bäumer, G. Fernandez, *Angew. Chem. Int. Ed.*, **2022**, *61*, e202203783.
[2] L. Brunsveld, B. J. B. Folmer, E. W. Meijer, R. P. Sijbesma, *Chem. Rev.*, **2001**, *101*, 4071-4098.

Synthesis of peptides based on α, β-amino acids for ice recrystallization inhibition

D. Mateo del Río, A. Jiménez Vázquez, Ramón J. Estévez Cabanas, J.C. Estévez Cabanas

University of Santiago de Compostela, CIQUS
e-mail: daniel.mateo@rai.usc.es

Keywords: *Amino acids, peptides, ice recrystallization inhibition (IRI)*

The activity of ice recrystallization inhibition (IRI) is a promising line of research. By impeding the growth of ice crystals, it is possible to increase the preservation of both organisms and materials at low temperatures, improving current methods that have an efficiency of 40 per cent.

To achieve this, this study proposes the synthesis of artificial peptides capable of mimicking the activity of antifreeze proteins. The first proposed peptide (**D**) is a decamer composed of three different amino acids: **A** (*L*-leucine), **B** (hydrophobic branch amino acid), **C** (hydrophilic branch amino acid), with the sequence: **ABACABACAB**.

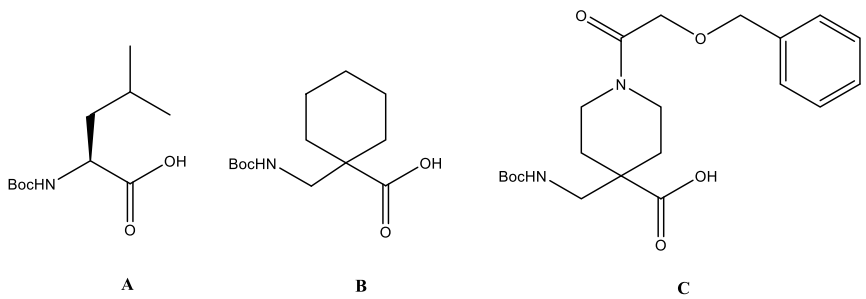


Figure 1. Amino acids deployed for the synthesis of the peptide.

Peptide **D**, with the amino acids sequence **ABACABACAB**, synthesized from its amino acid constituents using solid phase synthesis with the resin MBHA, is supposed to be structured to form a helix. In this helical structure, the hydrophilic branches are oriented outward on the same side, conferring amphiphilicity to the peptide, a property that enhances its IRI activity. In this study, it has been necessary to synthesize and optimize the route of non-commercial precursor amino acids, namely **B** and **C**, with a focus on the latter.

^{1}H and ^{11}B NMR study of the interactions between Wulff-type boronic acids and 1,2-diols for their application as fluorescence sensors

A. Maza Barón, L. García Abuín, E. Fernández Megía*

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, España.
e-mail: alvaro.maza@rai.usc.es

Keywords: *boronic acids, catechol, fluorescence sensor*

Boronic acids have a wide array of biomedical applications, such as fluorescence sensors for saccharide sensing. This application stems from their ability to bind to 1,2- and 1,3-diols, which allows the formation of boronic esters with molecules like saccharides, glycoproteins, or dopamine. Among boronic acids, Wulff-type boronic acids have revealed suitable for the formation of boronic esters in aqueous media. [1] The possibility of a dative bond between the nitrogen and boron atoms and a lower pK_a for the amine result in the formation of boronates at neutral pH. However, the precise structure of boronic esters is still a matter of recent debate. [2] Indeed, more studies are still required to ascertain the structural changes and equilibria these molecules may undergo when subjected to a diverse range of conditions, [3] like the pH in solution.

Pursuing this goal, our research group has carried out a series of dynamic structural studies of a Wulff-type boronic acid combining both ^{1}H and ^{11}B NMR. The information given by the combined use of both nuclei in NMR has proven to be a great asset, helping us deepen our understanding of the chemical properties of this molecule in solution along with the interactions with catechol as a model 1,2-diol. [2] Next, several fluorescence studies have been performed using an anthracene fluorescence sensor derivative, [4] to examine how fluorescence intensity is affected upon boronate ester formation and how this variation can be explained based on the knowledge gained by NMR experiments.

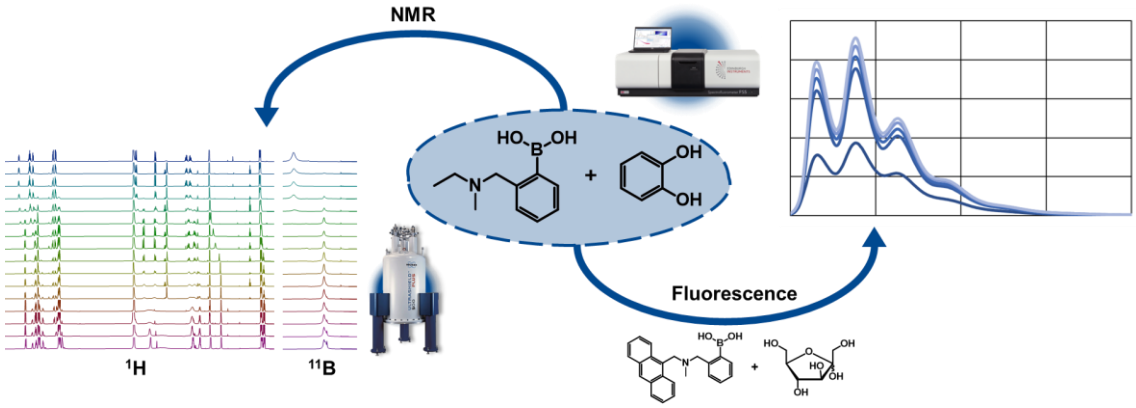


Figure 1. Schematic of the NMR and fluorescence study of the interactions between boronic acids and 1,2-diols.

References:

[1] Brooks, W. L. A.; Sumerlin, B. S. *Chem. Rev*. **2016**, 116, 1375-1397.
[3] Zhu, L.; Shabbir, S. H.; Gray, M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *J. Am. Chem. Soc.* **2006**, 128, 1222-1232.
[2] Valenzuela, S. A.; Howard, J. R.; Park, H. M.; Darbha, S.; Anslyn, E. V. *J. Org. Chem*. **2022**, 87, 15071−15076.
[4] Sun, X.; Chapin, B. M.; Metola, P.; Collins, B.; Wang, B.; James, T. D.; Anslyn, E. V. *Nat. Chem*. **2019**, 11, 768-778

Development of new molecular vehicles based on Deep Eutectic Solvents for poly-ion delivery

M. Nó Gómez, A. Sánchez Fernández, J. Montenegro García

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: miguel.no@rai.usc.es

Keywords: *Deep Eutectic Solvent, membrane transport, Chemical Biology.*

Deep Eutectic Solvents (DESs) are anhydrous mixtures of an organic salt with a neutral hydrogen bond donor, characterised by a depression in the melting point compared to their pure components. A range of intermolecular interactions, such as electrostatic, Van der Waals, and hydrogen bonding, dictate the DES properties, leading to the possibility of tunning the characteristics of the solvent through changes in its precursors.[1] In their application in Chemical Biology, DESs are thought to be a possible tool for the stabilisation and membrane transport of biomolecular cargoes, as some precedents have been reported.[2] However, little is known about the mechanistic aspects of these phenomena.

The aim of this work is to set fundamental knowledge about the use of DESs as new molecular vehicles for the solubilisation and selective transport of model peptides across lipid barriers. For this purpose, several DESs with different hydrophobicity were formulated to investigate its role in the transport properties of the system. Short fluorescently labelled peptides were used as cargo models, where their properties were systematically designed to study the effect of charge distribution within the biomolecule. The resulting systems were characterised using UV-Vis and Fluorescent Spectroscopy. Our results revealed the ability of DESs to effectively solubilise the peptides in the absence and presence of water. Quenching in the UV-Vis spectra showed that charge neutralisation of the anionic peptides leads to fluorophore ionic aggregation in anhydrous DES. Furthermore, the mentioned aggregation in anhydrous DES is reversible when the DES-peptide system is reconstituted in aqueous buffer, leading to the formation of transient complexes. Finally, these transient complexes were object of internalisation assays in HeLa cells through confocal imaging. Altogether, this study shed some light on the cargo solvation and transport mechanism using DESs as vehicles, constituting a proof-of-concept for future delivery technologies using these synthetically accessible systems (Figure 1).

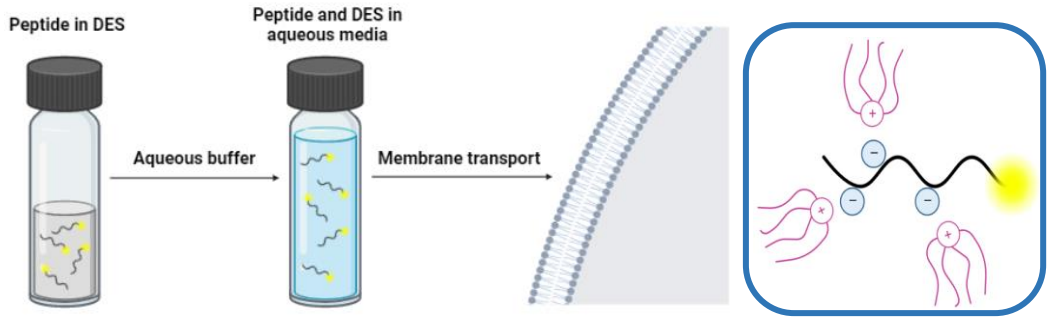


Figure 1. Proposed sequence of the use of DESs as transport agents (left) and dynamic complex formation (right).

References:

[1] (a) Smith, E.L.; Abbott, A.P.; Ryder, K.S. *Chem. Rev.* **2014**, 11060-11082. (b) Hansen, B.; Spittle, S.; Chen, B. *Chem. Rev.* **2021**, 1232-1285.

[2] (a) Sánchez-Fernández, A.; Basic, M.; Xiang, J. *J. Am. Chem. Soc.* **2022**, *144*, 23657-23667. (b) Angsantikul, P.; Peng, K.; Curreri, A.M. *Adv. Funct. Mater.* **2021**, 2002912.

New Sustainable Routes to PAHs Doped with Heteroatoms

D. Pernas Arias, S. Otero-Riesgo, J. A. Varela, C. Saá*

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Dpto. de Química Orgánica, USC, 15782 Santiago de Compostela
e-mail: daniel.pernas.arias@rai.usc.es

Keywords: *N-Doped PAH´s, C-H Activation, Ullazines*

Ullazines are relevant N-doped PAH´s containing 16 π-electrons in a planar structure, which have been employed in pioneer designs of dye-sensitized solar cells (Grätzel´s cells)(Figure 1).[1] Transition-metal catalyzed C-H bond activation has proven to be a powerful synthetic methodology to access to polycyclic aromatic hydrocarbons (PAH´s) from readily available starting materials.[2] Our group has developed a new sustainable synthetic route to aza-cyclopenta[c,d]phenalenes (Ullazines) by Rh(III)-catalyzed twofold C-H activation (double [4+2] oxidative annulation) of N-arylpyrroles with alkynes (Scheme 1).[3] We herein report a study of the scope and limitations of this metodology regarding the presence of different substituents on the arylalkynes and pyrrole ring.

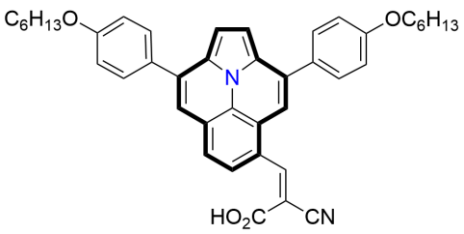
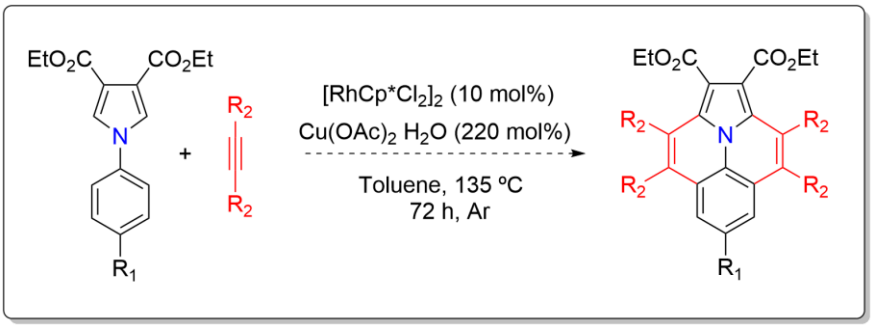


Figure 1. Ullazine-based organic photosensitizers.



Scheme 1. Rh(III)-catalyzed double [4+2] oxidative annulation of N-arylpyrroles with alkynes

References:

[1] Delcamp, J. H.; Yella, A.; Holcombe, T. W.; Nazeeruddin, M. K.; Grätzel, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 376-380.

[2] (a) Ghorai, D.; Choudhury, J. *ACS Catal*. **2015**, *5*, 2692-2696, (b) Davies, D. L.; Ellul, C. E.; Macgregor, S. A.; McMullin, C. L; Singh, K. J, *Am. Chem*. *Soc*. **2015**, *137*, 9659-9669. (c) Ge, Q,; Hu, Y.; Li, B.; Wang, B. *Org. Lett.* **2016**, *18*, 248-251. (d) Stępień, M., Gońka, E., Żyła, M., Sprutta, N. *Chem. Rev*. **2017**, *117*, 3479-3716.

[3] Villar, J. H.;Suárez, J.;Varela, J. A; Saá, C. *Org. Lett.* **2017**, *19*, 1702-1705.

Preparation of structurally complex triptycene derivatives by means of aryne cycloaddition reactions

N. Rey, J. Besteiro, L. M. Mateo, D. Pérez, E. Guitián and D. Peña

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela
e-mail: nicolas.rey@rai.usc.es

Keywords: *aryne, triptycene, cycloaddition*

Triptycene derivatives constitute a family of polycyclic aromatics hydrocarbons (PAHs) with unique three-dimensional geometries.[1] Thanks to their peculiar and sterically quite demanding structure, which resembles a three-bladed mill, these molecules are well soluble. Thanks to this combination of structural simplicity, steric demand and solubility, triptycenes find application in supramolecular chemistry and the development of molecular machines.[2]

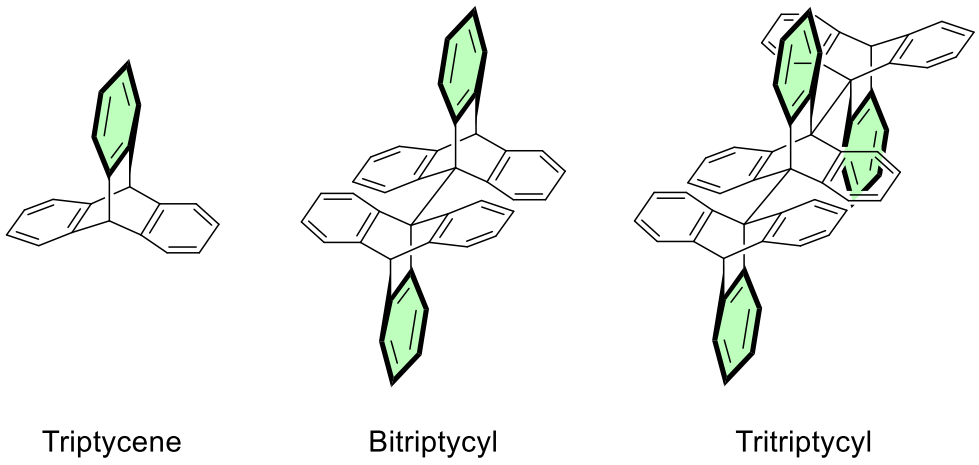


Figure 1. Chemical structure of triptycene and derivatives thereof

The work of our research group is focused on the development of synthetic methods for the preparation of PAHs and triptycenes through cycloaddition reactions between arynes and acenes.[3] This metodolgy, which is based on Kobayashi's aryne generation method,[4] has proven to be superior to previously described alternatives.[5] In fact, we were able to obtain triptycenes in clean reactions with excellent yields, and using relatively mild conditions. In this project we aim to extend this metodology in order to access strongly sterically hindered triptycene derivatives and explore the limits of aryne cycloadditions.

References:

[1] (a) Wozny, M.; Mames, A.; Ratajczyk, T., *Molecules* **2021**, *27,* 250. (b) Zhao, L.; Li, Z.; Wirth, T. *Chem. Lett.* **2010**, *39*, 658-667
[2] (a) Jiang, Y.; Chen, C. F., *Eur. J. Org. Chem.* **2011**, 6377-6403. (b) Chen, C. F.; Han, Y. *Acc. Chem. Res.* **2018**, *51*, 2093-2106
[3] Pérez, D.; Peña, D.; Guitián, E., *Eur. J. Org. Chem.* **2013**, 5981-6013
[4] Himeshima, Y.; Sonoda, T.; Kobayashi, H., *Chem. Lett*. **1983**, *12,* 1211-1214
[5] Koukotas, C.; Mehlman, S. P.; Schwartz, L. H., *J. Org. Chem.* **1966**, *31*, 1970-1971

Synthesis of peptide nanotubes with functionalized cavity for fullerene encapsulation

Sara Seoane Míguez, Juan R. Granja, Manuel Amorín.

Universidad de Santiago de Compostela (USC)
e-mail: sara.seoane.miguez@rai.usc.es

Keywords: *peptides, nanotubes, self-assembly*

Nanotubes are among the most pursued nanostructures due to their promising applications in various fields, such as in medicinal chemistry, drug transport, and catalysis among others. One of the most powerful strategies for its construction is through the stacking of flat-shaped cyclic peptide through hydrogen bonds. The main advantage of this method is that it allows easy and rigorous control of the internal diameter of the nanotube depending on the dimensions of the cyclic peptide [1]. Besides, peptides are very versatile and biocompatible building blocks [2]. The external properties of the nanotube can be modified depending on the selected natural amino acids. But for the modification of the internal properties, it is necessary to use unnatural amino acids, such as cyclic gamma- or delta-, field in which our group has been a pioneer. Thanks to the projection of methylene groups of these residues into the cavity, it is possible to obtain nanotubes with hydrophobic cavities and larger dimensions by providing rigidity to the cycle [3]. The aim of this project is synthesizing a nanotube equipped with a hydrophobic and wide cavity for the encapsulation of fullerene C60, which could have interesting electronic properties. To achieve this, a cyclic peptide consisting of 12 alternating alpha- and delta- residues will be synthesized, which be able to self-assembled depending on the pH of the medium through the interactions between the amide bonds and the amino acids side chains.

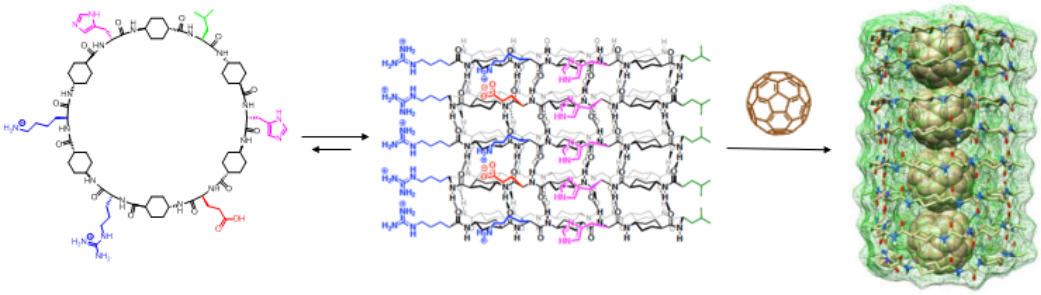


Figure 1. Self-assembly of the cyclopeptide synthesized with the alternate use of delta- and alpha- amino acids, capable of encapsulating C_{60} fullerene.

References:

[1] Rodríguez-Vázquez, N.; Amorín, M.; Granja, J. R. *Org. Biomol. Chem.*, **2017**,*15*, 4490-4505.
[2] González-Freire, E.; Novelli, F.; Pérez-Estévez, A.; Seoane, R.; Amorín M.; Granja, J. R., *Chem. Eur. J.* **2021**, *27*, 3029-3038.
[4] Lamas A.; Guerra, A; Amorín, M.; Granja, J. R., *Chem. Sci.,* **2018**, *9*, 8228.

Synthesis of triblock copolymers Aptamer – PEG – Aptamer

Juan Manuel Tapia Rodríguez, [a] Ramón Novoa Carballal, [b] Ramón Estévez Cavanas

[a] *Lincbiotech,* [b] *Universidade do Minho,* [c] *Universidade de Santiago de Compostela.*
e-mail: juanmanuel.tapia@rai.usc.es

Keywords: *Aptamer, PEG, copolymer*

Aptamers are short synthetic DNA or RNA sequences designed to interact specifically with a target molecule that can be rapidly selected in-vitro. The in vitro process, known as Systematic evolution of ligands by exponential enrichment (SELEX), applies to diverse molecules, from proteins to small organic compounds. This capability makes aptamers useful in similar applications to antibodies. Aptamers produce lower immunogenicity and can be synthesized relatively cheaply than antibodies. They are stable, even at room temperatures, and can be chemically modified to increase their resistance to nuclease-mediated degradation. Their manufacturing process can be scaled-up, and clinical-grade DNA is already on the market. Aptamers have been used as drugs as part of drug delivery systems to promote active targeting or identify a disease's molecular markers.[1] [2]

In biomedical applications, aptamers have been conjugated to PEG (e.g., PEG-Aptamer diblock copolymers, Aptamer-b-PEG-) have been prepared to enhance the stability and blood circulation time of aptamer drugs or as linkers between a hydrophobic core and aptamer targeting moieties of Drug delivery systems. [3]

Neither in the context of aptamers nor the context of DNA synthetic block copolymers, a triblock copolymer Aptamer-b-PEG-b-Aptamer has been prepared. Such structure can, for example, combine the capabilities of aptamer drugs, direct an aptamer drug to a specific receptor (the target of the second aptamer). The possibilities of such triblock copolymers in the biomedical field are vast. For this reason, this TFM will attempt to establish a simple, scalable, and efficient synthetic method to prepare Aptamer-b-PEG-b-Aptamer copolymers.

References:

[1] Zhou, J.; Rossi, J. J. Cell-Specific Aptamer-Mediated Targeted Drug Delivery. *Oligonucleotides*. February 1, 2011, pp 1–10. https://doi.org/10.1089/oli.2010.0264

[2] Keefe, A. D.; Pai, S.; Ellington, A. Aptamers as Therapeutics. *Nature Reviews Drug Discovery*. July 2010, pp 537–550. https://doi.org/10.1038/nrd3141.

[3] Jain, S.; Kaur, J.; Prasad, S.; Roy, I. Nucleic Acid Therapeutics: A Focus on the Development of Aptamers. *Expert Opinion on Drug Discovery*. Taylor and Francis Ltd. 2021, pp 255–274. https://doi.org/10.1080/17460441.2021.1829587

Building artificial metabolic networks by combination of enzymatic and metal catalysis

A. Vale Gómez,[a] A. Gutiérrez González,[a] M. Tomás Gamasa,[a] J.L. Mascareñas Cid.[a]

[a] *Departamento de Química Orgánica, Centro de Investigaciones en Química Biolóxica e Materiais Moleculares (CiQUS). Universidade de Santiago de Compostela, Rúa de Jenaro de la Fuente, Santiago de Compostela (Spain).*
e-mail: alejandra.vale@rai.usc.es

Keywords: *bioorthogonal, catalysis, tandem.*

The development of new bioorthogonal reactions is crucial in the fields of chemical biology and biomedicine. For instance, it is of utmost importance in the discovery of new treatments based on the *in situ* activation of prodrugs. [1] Various organometallic complexes have proven to be highly effective catalysts for new-to-nature reactions in biological settings, even within living cells. [2] Taking this into account, and the fact that natural enzymes are characterized by their substrate specificity, this project seeks to enhance the boundaries of bioorthogonal techniques through the design of a tandem reaction combining transition metal and native enzymatic catalysts in a concurrent and orthogonal manner. Tandem process shall be designed in such a way that the first catalytic transformation, carried out by the organometallic compound, will give rise to the substrate that will be susceptible to the second transformation, an enzyme-mediated process, which cannot take place until the previous one is completed (Figure 1.A).
In this ongoing project, we are developing a tandem reaction in biological media, from cellular lysates to living cells, in which a fluorophore is obtained (Figure 1.B). Furthermore, it is intended to be applied as a drug delivery system.

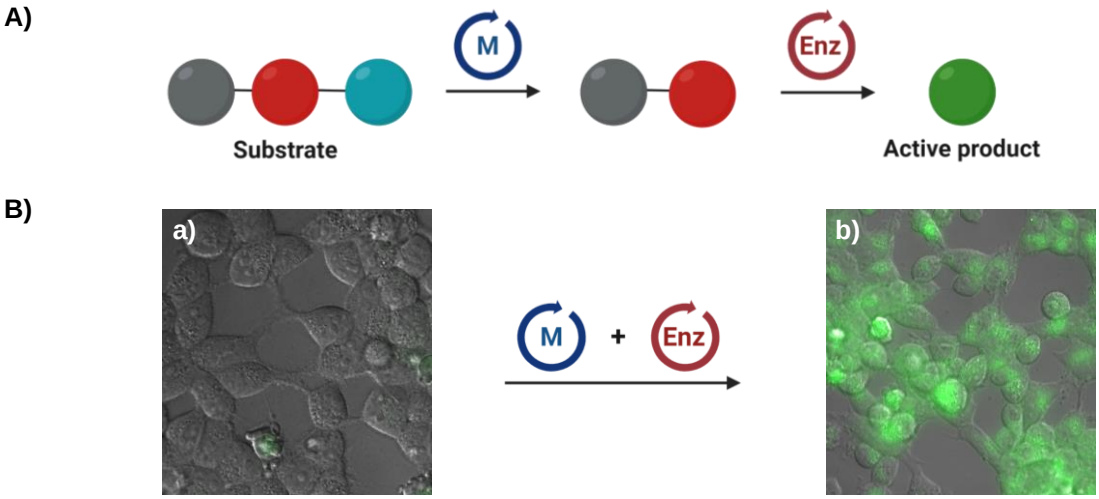


Figure 1. A) Schematic representation of a tandem process mediated by two consecutive types of catalysts. **B)** Fluorescence micrographies taken during *in cellulo* experiments of fluorophore uncaging in HEK293 cells: a) Cells incubated only with the substrate; b) Cells incubated with the substrate and the transition metal catalyst leading to the fluorescent product and demonstrating the success of the tandem process.

References:

[1] Matikonda, S. S.; Orsi, D. L.; Staudacher, V.; Jenkins, I. A.; Fiedler, F.; Chen, J.; Gamble, A. B. *Chem. Sci.* **2015**, 6, 1212-1218.

[2] a) Tomás-Gamasa, M.; Martínez-Calvo, M.; Couceiro, J. R.; Mascareñas, J. L. *Nat. Commun*. **2016**, 7, 12538; b) Vidal, C.; Tomás-Gamasa, M.; Gutiérrez, A.; Mascareñas, J. L. J. Am. Chem. Soc. **2019**, 141, 5125.

Advances on the metal-catalyzed C–C bond activation of [*N*]phenylenes and derivatives.

Juan Vázquez[a], Agustín Cobas[a] and Dolores Pérez[a]

[a]Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela
e-mail: juan.vazquez.viso@rai.usc.es

Keywords: *[N]phenylenes, C-C activation, polycyclic aromatic hydrocarbons*

[*N*]Phenylenes and their π-extended derivatives constitute a fascinating family of polycyclic conjugated hydrocarbons (PCHs) that combine the presence of benzene (aromatic) rings with cyclobutadiene (antiaromatic) rings, which gives them interesting electronic properties and a unique reactivity that has been little exploited to date. Among the most attractive reactions are those in which the opening of the cyclobutadienoid rings is promoted by activation of one of the C-C bonds by oxidative addition to a metal.[1] Examples of such processes have been described, allowing the reaction of the resulting transient metalacyclic intermediates with electron-rich alkynes to form new PAHs.[2] In this context, the objective of this project is twofold: on one hand, to explore this type of reactivity on different cyclobutadiene-containing PCHs (CBD-PCHs) recently synthesized in our group, including angular [3]phenylenes and CBD-oligoacenes; on the other hand, to evaluate the use of catalytic systems based on group 10 metals (Ni, Pd) that could be compatible with the use of electron-deficient alkynes or arynes[3], to be studied in a second phase of the master's thesis.

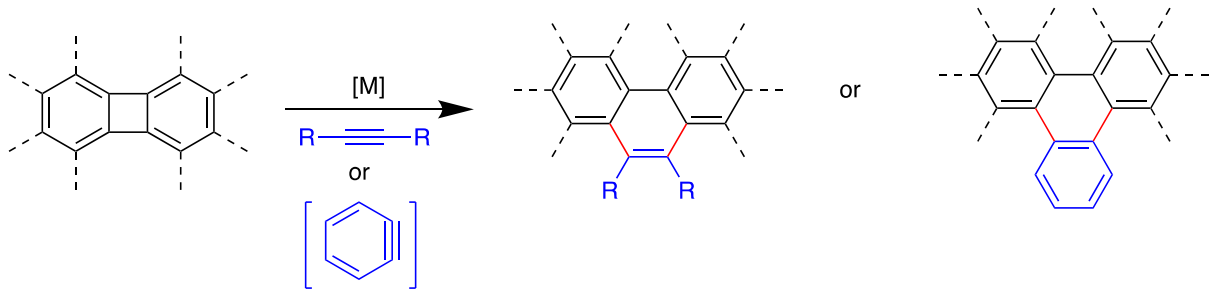


Figure 1. Study of the C-C activation of [*N*]phenylenes and derivatives.

References:

[1] C. Perthuisot. B. L. et al. *J. Mol. Catal. A*: Chem. **2002**, 189, 157-168

[2] X. Yin, K. Zheng, Z. Jin, M. Horst, Y. Xia *J. Am. Chem. Soc*. **2022**, 144, 1275-1274.

[3] F. García, D. Peña, D. Pérez, E. Guitián, Aryne Cycloadditions for the Synthesis of Functional Polyarenes, in Modern Aryne Chemistry, Wiley-VCH, **2021**, pp. 27-68.

Cu-catalyzed desymmetrization of *meso*-dibromocycloalkenes through borylative coupling with allenes

D. Rodríguez Pérez, M. Piñeiro Suárez, M. Fañanás Mastral

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Universidade de Santiago de Compostela, c/ Jenaro de la Fuente, 15782, Santiago de Compostela, España
e-mail: david.rodriguez.perez1@rai.usc.es

Keywords: *copper, catalysis, desymmetrization*

The desymmetrization of meso compounds is such a powerful synthetic strategy, enabling the formation of compounds with multiple stereocenters from simple symmetric precursors.[1]

During the past years, our research group has been working on the study of catalytic carboboration reactions using unsatured π-systems as pro-nucleophiles in borylative couplings.[2] These multicomponent Cu-catalyzed processes have the advantage of creating both C-C and C-B bonds in one step, allowing an efficient access to highly functionalized molecules. We have recently reported the first asymmetric copper-catalyzed allylboration of alkynes using allylic *gem*-dichlorides,[3] where a chiral 1,5-diene is formed after the regio- and stereoselective addition of a Cu-Bpin complex.

In this project we envisioned an application of this transformation in order to obtain homochiral multifunctional compounds through the catalytic desymmetrization of *meso*-dibromocycloalkenes employing allenes as starting materials (Figure 1).

Figure 1. Asymmetric catalytic allylboration of allenes

The main goal of this Master project is the search for an efficient catalytic system that allows carrying out the reaction with high levels of regio- and enantioselectivity, exploring different families of catalysts and reaction conditions. Preliminary results of this study are presented herein.

References:

[1] (a) Nájera, C., Foubelo, F., Sansano, J. M., Yus, M. *Tetrahedron* **2022** 106-107, 13629. (b) S. S. Goh, S. Guduguntla, T. Kikuchi, M. Lutz, E. Otten, M. Fujita, B.L. Feringa, *J. Am. Chem. Soc.* ***2018****, 140, 7052-7055*
[2] (a) E. Rivera-Chao, M. Fañanás-Mastral, *Angew. Chem. Int. Ed.* **2018**, 57, 9945–9949. (b) E. Rivera-Chao, M. Mitxelena, J. A. Varela, M. Fañanás-Mastral, *Angew. Chem. Int. Ed*. **2019**, 58, 18230-18234. (c) A. Chaves-Pouso, A. M. Álvarez-Constantino, M. Fañanás-Mastral, *Angew. Chem. Int. Ed.* **2022**, 61.
[3] M. Piñeiro-Suárez, A. M. Álvarez-Constantino, *ACS Catal.* **2023**, 13, 8, 5578-5583