XXIV REUNIÓN BIENAL DE QUÍMICA ORGÁNICA

Real Sociedad Española de Química

Donostia-San Sebastián, 11-13 de julio de 2012
Palacio de Congresos y Auditorio Kursaal

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EDICIONES PREVIAS

Edición	Año	Lugar	Fechas
I	1966	Santa María de Huerta (Soria)	30/marzo-2/abril
II	1968	Monasterio de Piedra (Zaragoza)	
III	1970	Peñíscola (Alicante)	
IV	1872	El Escorial (Madrid)	
V	1974	Jaca (Huesca)	
VI	1976	La Manga del Mar Menor (Murcia)	
VII	1977	La Espluga de Francoli (Tarragona)	
VIII	1979	Ronda (Málaga)	abril
IX	1981	La Toja (Pontevedra)	abril
X	1983	Cáceres	septiembre
XI	1985	Valladolid	septiembre
XII	1987	Córdoba	septiembre
XIII	1991	Sitges (Barcelona)	abril
XIV	1993	Palma de Mallorca	abril
XV	1995	Perlora (Asturias)	4-6/abril
XVI	1997	Ciudad Real	1-3/abril
XVII	1998	Logroño	24-26/junio
XVIII	2000	A Coruña	11-13/abril
XIX	2002	Carmona (Sevilla)	11-14/junio
XX	2004	Zaragoza	9-12/junio
XXI	2006	Valladolid	18-20/septiembre
XXII	2008	Tarragona	25-28/julio
XXIII	2010	Murcia	16-18/junio

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1967-1972	Ignacio Ribas Marqués
1972-1976	Rafael Pérez Álvarez-Ossorio
1976-1981	Francisco Fariña Pérez
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24 Reunión Bienal de Química Orgánica

Donostia- San Sebastián, 11-13 de julio de 2012, Palacio de Congresos Kursaal

		Sala A	Sala B	Sala C	Sala D
MIÉRCOLES	10:00 - 15:00	Recogida de documentación			
	15:00 - 15:20	Ceremonia de apertura			
		Mod: J Bosch			
	15:20 - 16:20	**CP-1 Phil Baran**			
	16:20 - 16:45	Pausa café			
		Mod: J C Carretero	Mod: V S Martín	Mod: J Vilarrasa	
	16:45 - 17:15 17:15 - 17:45	**CI-1 Raquel P. Herrera** (Premio Lilly) **CI-2 Ana B. Cuenca**			
	17:45 - 19:30	**CO 1-7**	**CO 8-14**	**CO 15-21**	
	20:30	Cocktail de bienvenida (Palacio Miramar)			

JUEVES		Mod: J M Saá			
	9:00 - 10:00	**CP-2 Magnus Rueping**			
	10:00 - 10:30 10:30 - 11:00	**CI-3 Fernando López** **CI-4 Carlos Valdés**			
	11:00 - 11:30	Pausa café			
		Mod: M A Sierra	Mod: J M González	Mod: E Lete	Mod: J R Granja
	11:30 - 12:45	**CO 22-26**	**CO 27-31**	**CO 32-36**	**CO 37-41**
	12:45 - 13:30	**Flash 1-7**	**Flash 8-14**	**Flash 15-21**	**Flash 22-28**
	13:30 - 15:00	Almuerzo			

		Sala A	Sala B	Sala C	Sala D
JUEVES		Mod: J Jiménez-Barbero			
	15:00 - 16:00	**CP-3 Nazario Martín**			
	16:00 - 16:30	**CI-5 Paolo Melchiorre**			
	16:30 - 16:45	Entrega de premios G-QO			
	16:45 - 17:15	Pausa café			
		Mod: J M Lassaletta	Mod: R Pleixats	Mod: A Ballesteros	Mod: F J Fañanás
	17:15 - 17:45	**CI-6 Ana Castaño**			
	17:45 - 18:15	**CO 42-43**	**CO 44-45**	**CO 46-47**	**CO 48-49**
	18:15 - 19:30	**Flash 29-39**	**Flash 40-50**	**Flash 51-61**	**Flash 62-72**
	19:30	Reunión del Grupo de QO			

VIERNES		Mod: M Yus		
	9:00 - 10:00	**CP-4 Herbert Mayr**		
	10:00 - 10:30 10:30 - 11:00	**CI-7 Mercedes Amat** **CI-8 José J. Fernández**		
	11:00 - 11:30	Pausa café		
		Mod: E Domínguez	Mod: R Fernández	Mod: R Ortuño
	11:30 - 12:00 12:00 - 12:30	**CI-9 Silvia Ortega** **CI-10 Luis A. Sarandeses**		
	12:30 - 13:30	**Flash 73-81**	**Flash 82-90**	**Flash 91-99**
	13:30 - 15:00	Almuerzo		
		Mod: C Nájera		
	15:00 - 16:00	**CP-5 Mattew Gaunt**		
	16:00 - 16:30 16:30 - 17:00	**CI-11 Ezequiel Pérez** **CI-12 Teresa Sierra**		
	17:00 - 17:30	Pausa café		
		Mod: A Vallribera	Mod: J M Aizpurua	Mod: J Bonjoch
	17:30 - 18:40	**Flash 100-109**	**Flash 110-119**	**Flash 120-129**
	18:40 - 19:00	**Clausura**		
	21:30	Cena de clausura (Restaurante Bekoerrota, BUS)		

CONFERENCIAS PLENARIAS

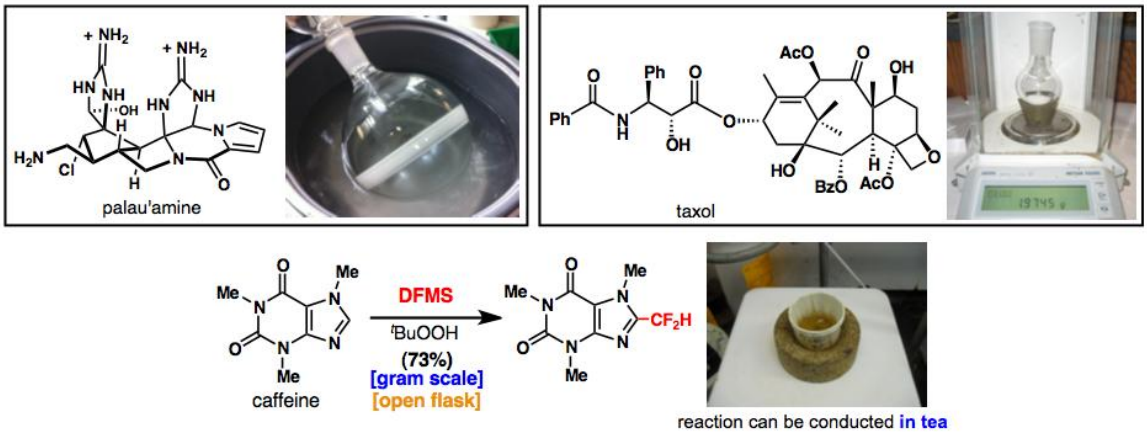
CP-1

Studies in Natural Product Synthesis

Phil S. Baran

Department of Chemistry and Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037
e-mail: pbaran@scripps.edu

This talk will focus on advances in heterocyclic chemistry made as a consequence of preparing palau'amine on a gram-scale. The advantages of harnessing innate reactivity and embracing the logic of C–H functionalization will be demonstrated in this context. A direct consequence of aiming for a practical synthesis of palau'amine was the invention of exceptionally practical reactions with broad utility for the largest body of practicing organic chemists: those in the pharmaceutical industry.



CP-2

Chiral Counterion Pair Catalysis: From Concepts to Applications

Magnus Rueping

Institute of Organic Chemistry, RWTH Aachen, Landoltweg 1, 52074 Aachen, E-mail: Magnus.Rueping@RWTH-Aachen.de

The development and application of metal-free catalysts has become an important topic in organic synthesis and catalysis. Recently, chiral Brønsted acids and Lewis bases have been shown to be vital alternatives to metal catalysts and examples of highly enantioselective transformations have been reported. These reactions, similar to several enzymatic processes, proceed through ion-pair and hydrogen-bond activation or through intermediary formed covalent bonds. In this presentation our introduction to enantioselective Brønsted acid and Lewis base catalysis will be shown and new and valuable transformations based on chiral ion pair concept and activation will be highlighted; including the development of enantioselective reductions, new cascade and domino reactions, asymmetric carbonyl activations as well as the concept of co-operative metal and Brønsted acid catalysis. Additionally, efforts to delineate the general requirements for performing asymmetric Brønsted acid and Lewis base catalysis as well as the applicability of these catalytic processes to the synthesis of heterocycles and natural products will be outlined.

Supramolecular Chemistry of Carbon Nanostructures: Concave-convex Interactions

Nazario Martín
Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, E-28040 Madrid, Spain. e-mail: nazmar@quim.ucm.es. http://www.ucm.es/info/fullerene. IMDEA-Nanociencia, Campus de Cantoblanco, E-28049 Madrid, Spain

The readily available electron donor exTTF molecule has proved their effciency for the design of unprecedented receptors for fullerenes and other carbon nanoforms. In this regard, custom-made tweezers and, particularly, macrocyclic receptors for fullerenes are proving a valuable alternative to achieve the affinity and selectivity required to meet goals such as the selective extraction of higher fullerenes, their chiral resolution or the self-assembly of functional molecular materials.
In this presentation some of the important breakthroughs based on electroactive TTF-type derivatives as supramolecular receptors for fullerenes and carbon nanotubes (CNTs) will be highlighted. Bowl and belt-shaped fullerene receptors based on this concave-convex complementarity principle will be presented. Other related and more sofisticated supramolecular assemblies formed by macrocycles endowed with exTTF concave geometry and covex fullerene surfaces will be discussed.[1] This will open the question if the concave-convex interactions really exists.
The recognition motives can be also applied to carbon nanotubes with the aim of modifying their electronic properties,[2] as well as for the hierarchical organization of mesoscopic 3D helical fibers.[3]

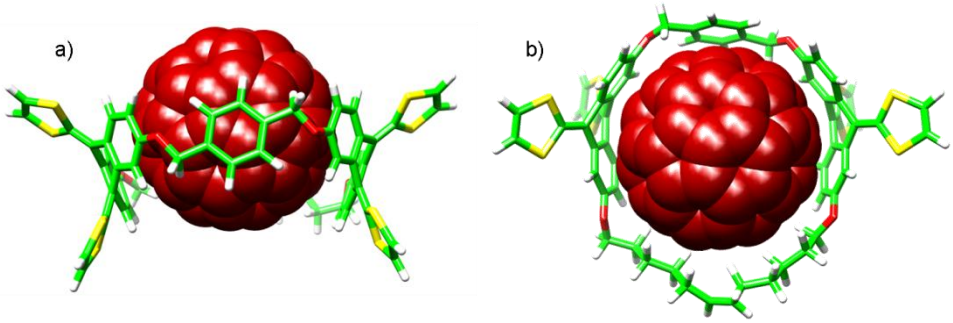


Figure. Side view (a) and top view (b) of the exTTFmacrocycle·C_{60} associate.

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a) Pérez, E. M.; Sánchez, L.; Fernández, G.; Martín, N. *J. Am. Chem. Soc*., **2006**, *128*, 7172. b) Pérez, E. M.; Martín, N. *Chem. Soc. Rev*., **2008**, *37*, 1512. c) Fernández, G.; Pérez, E. M.; Sánchez, L.; Martín, N. *Angew.Chem., Int. Ed*., **2008**, *47*, 1094. d) Isla, H.; Gallego, M.; Pérez, E. M.; Viruela, R.; Ortí, E.; Martín, N. *J. Am. Chem. Soc.*, **2010**, *132*, 1772. e) Huerta, E.; Isla, H.; Pérez, E. M.; Bo, C.; Martín, N.; de Mendoza, J. *J. Am. Chem. Soc*., **2010**, *132*¸ 5351. f) Grimm, B.; Santos, J.; Illescas, B. M.; Muñoz, A.; Guldi, D. M.; Martín, N. *J. Am. Chem. Soc*., **2010**, *132*, 17387. g) Canevet, D.; Gallego, M.; Isla, H.; de Juan, A.; Pérez, E. M.; Martín, N. *J. Am. Chem. Soc*., **2011**, *133*, 3184. h) Isla, H.; Grimm, B.; Pérez, E. M.; Torres, M. R.; Herranz, M. A.; Viruela, R.; Aragó, J.; Ortí, E.; Guldi, D. M.; Martín, N. *Chem. Sci*., **2012**, *3*, 498. i) For a recent review, see: Canevet, D.; Pérez, E. M.; Martín, N. *Angew. Chem. Int. Ed*. **2011**, *50*, 9248 – 9259.

[2] a) Herranz, M. A.; Ehli, C.; Campidelli, S.; Gutiérrez, M.; Hug, G. L.; Ohkubo, K.; Fukuzumi, S.; Prato, M.; Martín, N.; Guldi, D. M. *J. Am. Chem. Soc*., **2008**, *130*, 66. b) C. Romero.Nieto, R. García, M. A. Herranz, Ch. Ehli, M. Ruppert, A. Hirsch, D. M. Guldi, N. Martín, *J. Am. Chem. Soc*., **2012**, Article ASAP, DOI: 10.1021/ja211362z.

[3] a) López, J. L.; Atienza, C; Seitz, W.; Guldi, D. M.; Martín, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 9876 – 9880. b) López, J. L.; Atienza, C.; Insuasty, A.; López-Andarias, J.; Romero-Nieto, C.; Guldi, D. M.; Martín, *N. Angew. Chem. Int. Ed*. **2012**, *51*, 3857 –3861.

CP-4

Mythology in Organic Chemistry: A Kinetic Analysis

Herbert Mayr

Department Chemie der Ludwig-Maximilians-Universität München
Butenandtstr. 5-13, 81377 München, Germany, Herbert.Mayr@cup.uni-muenchen.de

Several concepts in organic chemistry persist, though their inconsistency has repeatedly been demonstrated in the past. This lecture will report on recent developments in the author's laboratory on three different topics

1) **Reactivity selectivity principle:**[1] In activation-controlled reactions, selectivity may decrease, increase, or remain constant as reactivity increases. Only when the diffusion limit is approached, is an increase of reactivity generally associated with a decrease of selectivity.

2) **Kornblum's rule and Salem-Klopman concept of charge and orbital controlled reactions:**[2] The ambident reactivities of the prototype nucleophiles, thiocyanate, cyanide, nitrite, cyanate, nitronate, phenylsulfinate, amide, and pyridone anions, cannot be described by these rules. Changes from kinetic to thermodynamic control, and from activation to diffusion limited reactivity has to be considered when interpreting ambident reactivities. A novel approach to ambident reactivity based on Marcus theory will be presented.

3) **α-Effect:** According to IUPAC,[3] *the α-effect describes a positive deviation of an α-nucleophile (a nucleophile bearing an unshared pair of electrons on an atom adjacent to the nucleophilic site) from a Brønsted-type plot of lg k vs. pKa constructed for a series of related normal nucleophiles. More generally, it is the influence of the atom bearing a lone pair of electrons on the reactivity at the adjacent site.* Systematic kinetic investigations of the nucleophilic reactivities of a series of hydrazines in various solvents do not give evidence for unusual reactivities, i. e., reactivities which differ from those of ordinary alkylamines.[4] The concept of the α-effect should, therefore, be revised.

(1) H. Mayr, A. R. Ofial, *Angew. Chem. Int. Ed. Engl.* **2006**, 45, 1844-1854.
(2) H. Mayr, M. Breugst, A. R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 6470-6505.
(3) P. Müller, Glossary of Terms used in Physical Organic Chemistry, *Pure Appl. Chem*. **1994**, *66*, 1077-1184.
(4) T. A. Nigst, J. Ammer, H. Mayr, *Angew. Chem. Int. Ed.* **2012**, *51*, 1353-1356.

CP-5

New Catalytic Strategies for Chemical Synthesis

Matthew Gaunt

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2, 1EW, United Kingdom

e-mail: mjg32@cam.ac.uk

CONFERENCIAS INVITADAS

A Decade of Asymmetric Organocatalysis

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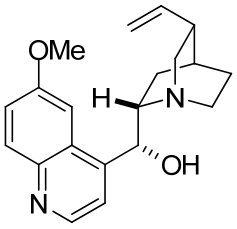
[a] *Laboratorio de Síntesis Asimétrica, Departamento de Química Orgánica. Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza.*
[b] *ARAID, Fundación Aragón I+D, E-50004 Zaragoza.*
e-mail: raquelph@unizar.es

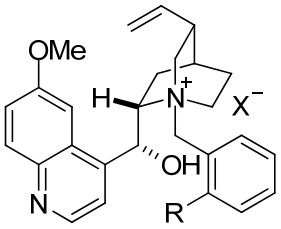
Great achievements have been reached in the last twelve years in the field of *Asymmetric Organocatalysis*. This new discipline has appeared as a useful alternative strategy between those previously and more broadly explored, the metal and enzymatic catalysis. Among the diverse kind of catalysts discovered in this discipline, those concerning cinchona alkaloids (**1**),[1] phase-transfer catalysts (**2**),[2] chiral secondary amines (**3**)[3] or thiourea catalysts (**4**)[4] have experimented an incredible development. In this context, we have successfully contributed to the progress of this area studying different catalytic reactions by mean of some of these appealing catalysts.

In this talk I would like to show our more relevant results in each one of these subareas of research through a wonderful journey along this amazing field. Different catalytic reactions will be highlighted and our last results concerning a new organocatalytic aza-Michael addition methodology will be disclosed.[5]



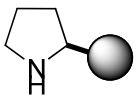
1

Hydrophosphonylation



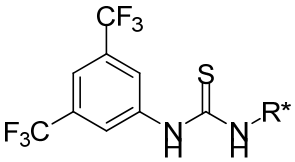
2

Mannich-type reaction
Aza-Henry reaction
Strecker reaction



3

Dienamine catalysis



4

Michael additions
Friedel-Crafts-type
aza-Michael addition

1. Song, C. E. (Ed.) *Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis*, Wiley-VCH: Weinheim, **2009**.
2. Maruoka, K. (Ed.) *Asymmetric Phase Transfer Catalysis*, Wiley-VCH: Weinheim, **2008**.
3. Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178-2189.
4. Pihko, P. M. (Ed.) *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH: Weinheim, **2009**.
5. Alcaine, A.; Marqués-López, E.; Herrera, R. P. *Submitted manuscript*.

CI-2

Some Gold-Catalyzed Little Secrets

Ana B. Cuenca-González
Departamento de Química Orgánica Universidad de Valencia, 46100 Burjassot, Valencia, Spain
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Expansion of homogeneous gold catalysis keeps occurring and unanticipated new transformations are being discovered every other day.[1] Coupled to such growth, the notion that small variations, on either the catalyst system or substrates, happen to promote different *modus operandi* for gold-catalyzed reactions is also playing a role in the comprehension of these processes.[2] Some nice examples about the great potential that derives from the ability that some gold-complexes have to influence the outcome of the catalyzed reaction *brought to light* examples that open the door to more rationally designed catalysis.[3] How to unmask the factors responsible for such catalysts control?

We present here our discreet[4] contribution to this area through a series of transformations dealing with the gold-catalyzed nucleophilic addition to alkynes and our attempts to understand how these processes operate.

. (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev*. **2008**, *37*, 1766-1775. (b) Corma, A.; Leyva-Pérez, A.; Sabater, María J. *Chem. Rev*. **2011**, *111*, 1657-1712. (c) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev*. **2012**, *41*, 2448-2462 and references cited herein.

2. (a) Gorin, D. J.; Sherry, B. D.; Toste, D. F. *Chem. Rev.* **2008**, *108*, 3351-3378. (b) Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc*. **2012**, *134*, 5697-5705.

3. (a) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030. (b) Alcarazo, M.; Stork, T.; Anoop, A., Thiel, W.; Fürstner, A. *Angew. Chem.* **2010**, *122*, 2596–2600; *Angew. Chem. Int. Ed.* **2010**, *46*, 2542–2546. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed*. **2010**, *49*, 5232-5241.

4. (a) Cuenca, A. B.; Montserrat, S.; Hossain, K. M.; Mancha, G.; Lledós, A.; Medio-Simón, M.; Ujaque, G.; Asensio, G. *Org. Lett*. **2009**, *11*, 4906-4909. (b) Gimeno, A.; Medio-Simón, M.; Ramírez de Arellano, C.; Asensio, G.; Cuenca, A. B. *Org. Lett*. **2010**, *12*, 1900-1903.

Gold(I)-catalyzed cycloadditions of allenes

Isaac Alonso,[1] Hélio Faustino,[1] Javier Francos,[1] Paloma Bernal, José L. Mascareñas[1] and Fernando López[2]

[1]*Departamento de Química Orgánica y Centro Singular de Investigación en Química Biológica y Materiales Moleculares. Unidad Asociada al CSIC. Universidad de Santiago de Compostela.*

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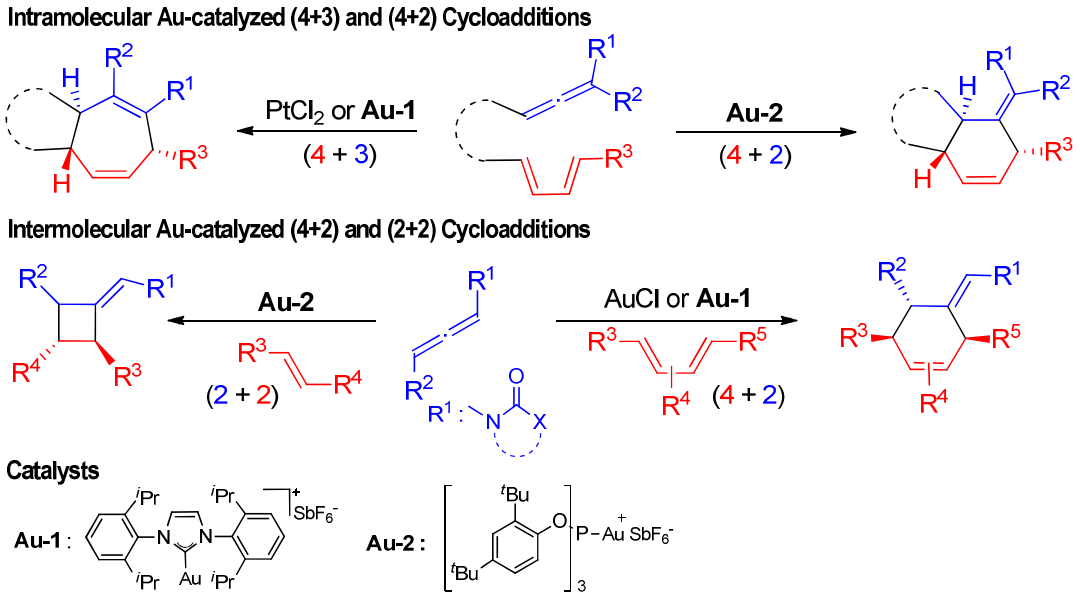
In recent years, platinum and, particularly, gold complexes have emerged as excellent catalysts for promoting novel types of cycloaddition reactions, usually involving non-activated carbon-carbon unsaturated systems.[1]

In this context, we demonstrated the possibility of using allenes as three- or two-carbon atom components in intramolecular Au-catalyzed (4 + 3) and (4 + 2) cycloadditions with dienes, allowing the access to synthetically relevant bicyclic systems incorporating six or seven-membered rings.[2] Herein, we will briefly summarized our results on this field and we will present our more recent results on the development of intermolecular variants of these and other Au-catalyzed cycloadditions of allenes, such as a new (2 + 2) annulation between allenamides and alkenes.[3] Finally, mechanistic details and recent results on the development of highly enantioselective versions of some of these cycloadditions will also be presented.[4]



[1] For a review, see: López, F.; Mascareñas, J. L. *Beilstein J. Org. Chem.* **2011**, 7, 1075

[2] (a) Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2008**, *47,* 951. (b) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem. Eur. J.* **2009**, 15, 3336. (c) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020.

[3] (a) Faustino, H.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Sci.* **2011**, 2, 633. (b) Faustino, H.; Bernal, P.; Castedo, L.; López, F.; Mascareñas, J. L. *Adv. Synth. Catal.* (*in press*).

[4] Alonso, I.; Faustino, H.; López, F.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11496.

Unconventional Transformations of Carbonyl Compounds through Sulfonylhydrazones

Carlos Valdés
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Julian Clavería 8. Oviedo 33006. Spain
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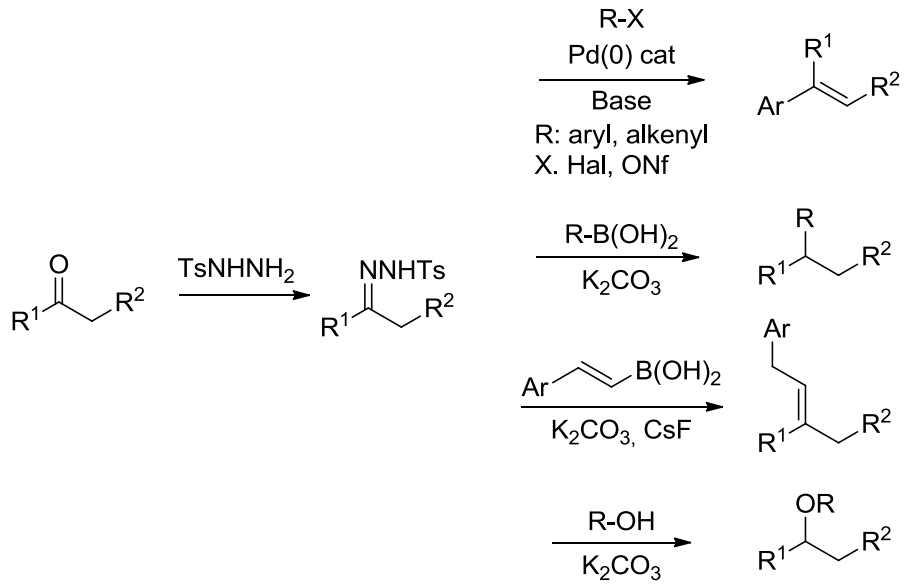
In our research group, we have recently discovered a new type of Pd-catalyzed cross-coupling reaction between aryl halides and tosylhydrazones that gives rise to polysubstituted alkenes. This transformation features wide scope and since the tosylhydrazones can be readily prepared from carbonyl compounds represents a new way to manipulate this important functional group.[1]

These results have triggered a renovated interest in the chemistry of tosylhydrazones by several groups. In particular, we have employed these reagents in different versions of the Pd-catalyzed cross-coupling, including cascade processes. Moreover, we have also uncovered new metal-free C-C and C-heteroatom bond forming reactions.[2] This presentation will cover the more recent contributions of our group in this area.



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About the Asymmetric Functionalisation of Carbonyls after the Advent of Cinchona-based Primary Amine Catalysis

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Asymmetric aminocatalysis[1] has greatly expanded the chemist's ability to stereoselectively functionalise unmodified carbonyl compounds. Recent advances in cinchona-based primary amine catalysis have provided new synthetic opportunities and conceptual perspectives for successfully attacking major challenges in carbonyl compound chemistry, which traditional approaches have not been able to address.[2]

In particular, 9-amino(9-deoxy)epi cinchona alkaloids, primary amines easily derived from natural sources, have enabled the stereoselective functionalisation of a variety of sterically hindered carbonyl compounds, which cannot be functionalised using secondary amines and which are often elusive substrates for metal-based approaches too. Their advent has greatly expanded the synthetic potential of aminocatalysis (Figure 1).

Here, some recent contributions from our laboratories are presented.[3]

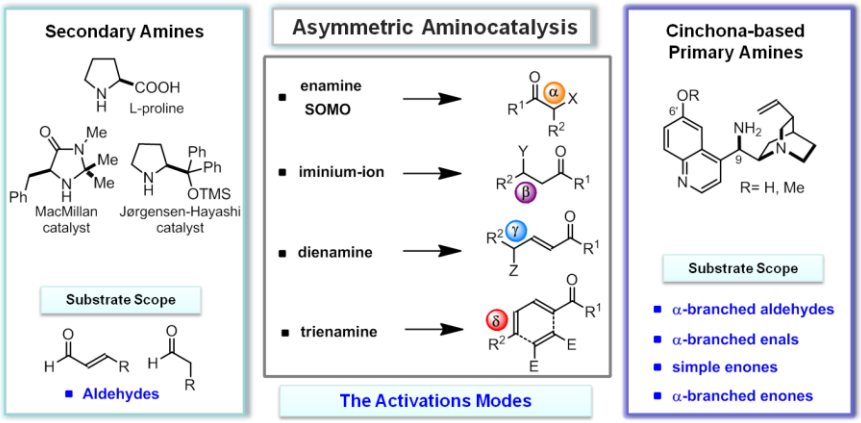

Figure 1. The state-of-the-art of asymmetric aminocatalysis

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CI-6

The Lilly Open Innovation Drug Discovery Program

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The Lilly Open Innovation Drug Discovery (OIDD) program was launched in August 2011 to engage investigators worldwide in the identification of novel compounds that have potential to be developed into drug candidates for key areas of disease of interest to Lilly. OIDD has been embraced by the scientific community, both scientists and technology transfer professionals alike. To date, more than 250 academic institutions and small biotech companies around the globe have become affiliated with the program and thousands of compound samples have been evaluated in both phenotypic and target-based screening modules. In addition, the OIDD panel includes a neglected disease screening module (Tuberculosis).
This presentation will describe the scientific foundation behind OIDD, the business model and a general discussion of Lilly's early discovery process focusing on some recent examples of completed and ongoing collaborations.

Towards the Enantioselective Synthesis of Madangamine Alkaloids

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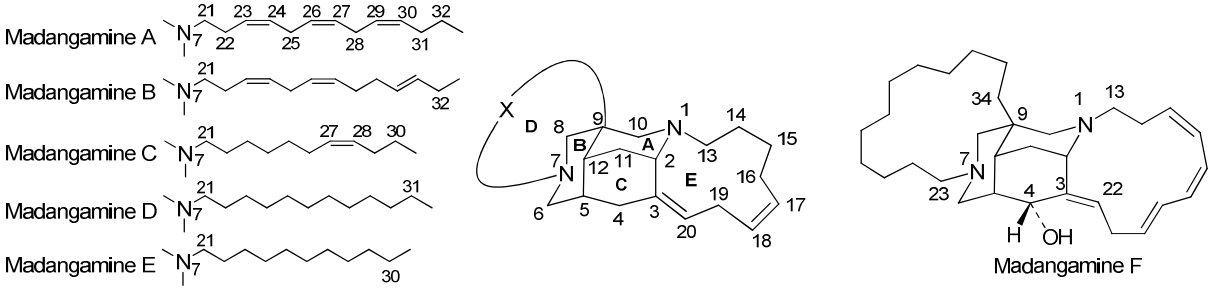
Madangamine A is a cytotoxic alkaloid isolated in 1994 by Andersen and co-workers[1] from the marine sponge *Xestospongia ingens* collected off Madang, Papua New Guinea. Its high cytotoxic activity against different tumor cell lines has drawn attention to these sponges, leading to the isolation of four analogs named madangamines B-E.[2] More recently, madangamine F, also showing cytotoxic activity, has been isolated from the marine sponge *Pachychalina alcaloidifera*.[3] Structurally, the madangamines possess a diazatricyclic nucleus (rings A-C) and two carbon bridges connecting N-1 with C-3 and N-7 with C-9. Madangamines A-F differ in the length, position, and degree of unsaturation of the carbon chain between N-7 and C-9 (D ring), whereas madangamine F bears an additional hydroxy group at C-4 and a longer chain between N-1 and C-3 (E ring). Although some polycyclic alkaloids from marine sponges, such as the manzamines, have received considerable attention from a synthetic standpoint in the last years, the total synthesis of alkaloids of the madangamine group has not been reported.

Alkaloids of the madangamine group



The construction of the diazatricyclic core of madangamines from chiral bicyclic lactams[4] as well as our studies on the elaboration of the macrocyclic D and E rings en route to these alkaloids will be described.[5]

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CI-8

Studies on polyketides from dinoflagellates

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During the last years our research group has been focused on the chemical study of dinoflagellates as an important source of bioactive compounds. Some toxic species of these microalgae are responsible of the "Harmful Algal Blooms" (HABs) also known as red tides. HABs are great interests for their environmental impact and involve potential risk for public health by entering toxins into the food chain by contaminated mollusc and, in some cases, through marine aerosols or by direct contact with the toxic metabolite in the sea.[1]

On the other hand, these toxins have very complex structures and their structural elucidation has became a challenge within the natural products research area and showed an extraordinary value to study intracellular processes.[2] The genus *Prorocentrum* is recognized as co-responsible for the toxic syndrome Diarrethic Shellfish Poisoning (DSP). This genus has been described as producer of many secondary metabolites with remarkable structural diversity, including linear polycyclic compounds, macrolide[3] and polyhydroxy compounds of high molecular weight.[4] As a result of our search for new bioactive products in artificial cultures, this communication describes structural and biosynthetic studies of metabolites isolated from cultures of *Prorocentrum belizeanum*

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Chemical Probes for the Study of G Protein-Coupled Receptors

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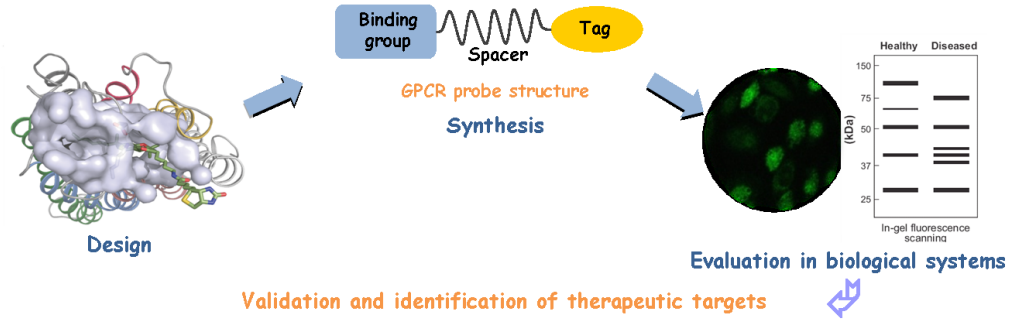
Functional proteomics has emerged as a powerful chemical strategy to characterize enzyme function directly in native biological systems on a global scale.[1] Development of probes to cover other fractions of the proteome currently constitutes an important challenge. To date, no probes have been developed for the study of G protein-coupled receptors (GPCRs), which constitute almost the 50% of the druggable genome.[2] We have started a project aimed at the development of a set of chemical probes bearing different tags that enable visualization, isolation, enrichment and/or identification of GPCRs.

We have focused our initial efforts on serotonin and cannabinoid receptors, due to their clinical significance and our previous experience.[3] Our strategy encompasses the design of the chemical probes using homology models of the corresponding GPCR in complex with the selected scaffolds, the synthesis of the designed probes, and the evaluation of their potential in biological systems of increasing complexity.

Here, we will show our latest results focused on the serotonin 5-HT_{1A} and 5-HT_6 receptors,[4] as well as in CB_1 and CB_2 cannabinoid receptors.[5] Up to this moment, we have introduced different labelling moieties including fluorophores, biotin, benzophenone and terminal alkynes. Some of the synthesized probes display high affinity for the target receptors and have been used for their direct visualization in cell systems. In addition, probes which combine benzophenone and biotin or a fluorophore in the same molecule are being evaluated for covalent binding and affinity pull-down of target protein(s). These strategies should contribute to optimize the therapeutic exploitation of known or new members of the GPCR superfamily by providing valuable information about their location or level of expression.



Acknowledgements: This work has been supported by grants from Ministerio de Economía y Competitividad (MINECO, SAF2010-22198-C02) and Comunidad de Madrid (CM, S2010/BMD-2353). Authors are grateful to MINECO and European Social Fund for Juan de la Cierva (J.A.G.-V.) and Ramon y Cajal (S.O.-G.) grants, and to CM and to UCM for predoctoral grants to A.G. and A.R., respectively.

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CI-10

Avances en la Química de los Organometálicos de Indio: desde Nuevas Reacciones hasta Materiales Moleculares

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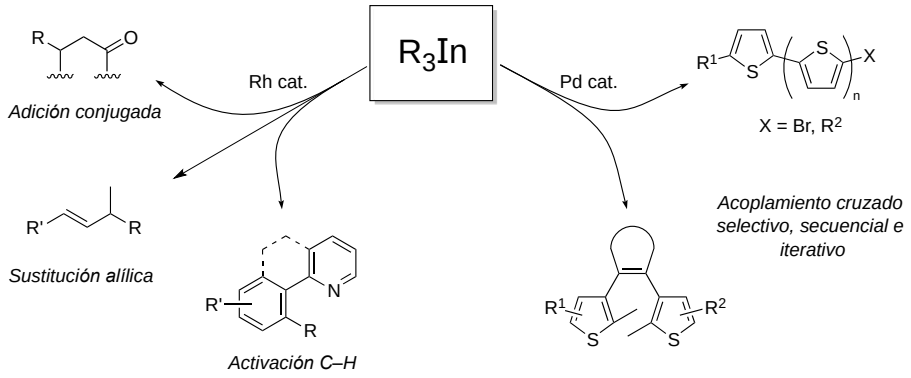
A lo largo de los últimos años, los compuestos organometálicos de indio(III) se han mostrado como reactivos útiles en reacciones orgánicas fundamentales, revelándose como una eficaz alternativa a otros organometálicos. Generalmente, la reactividad de los organoíndicos está asociada a la utilización de metales de transición como catalizadores, siendo la transmetalación la etapa clave del proceso. En este sentido, hemos desarrollado nuevas reacciones de los organoíndicos catalizadas por metales de transición (Pd, Ni, Cu). En esta comunicación se describen nuevas aplicaciones de estos organometálicos en dos vertientes: el desarrollo de nuevos procesos bajo catálisis por complejos de rodio y la aplicación de las reacciones de acoplamiento cruzado catalizadas por paladio en la síntesis de nuevos compuestos de interés.[1]



Los organometálicos de indio(III) reaccionan bajo catálisis de Rh(I) con cetonas α,β-insaturadas para dar los productos de adición conjugada, con halogenuros alílicos proporcionando regioselectivamente compuestos de α-sustitución, y con 2-arilpiridinas y derivados conduciendo a los productos de activación C–H y acoplamiento cruzado.

Asimismo, los triorganoíndicos se han empleado en reacciones de acoplamiento cruzado selectivo, secuencial e iterativo, y se han aplicado en la síntesis de α,α'-oligotiofenos, unidades estructurales en materiales orgánicos con aplicaciones como dispositivos electrónicos, y de nuevos 1,2-ditieniletenos (DTEs) no simétricos, compuestos fotocromáticos que actúan como interruptores moleculares en base a una reacción de electrociclación 6π fotoquímica reversible.

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Dendrimeric structures for biomedical applications. Versatile design and photoswitchable dimension.

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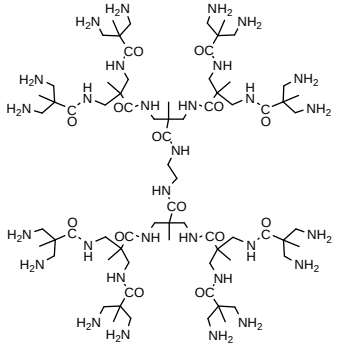
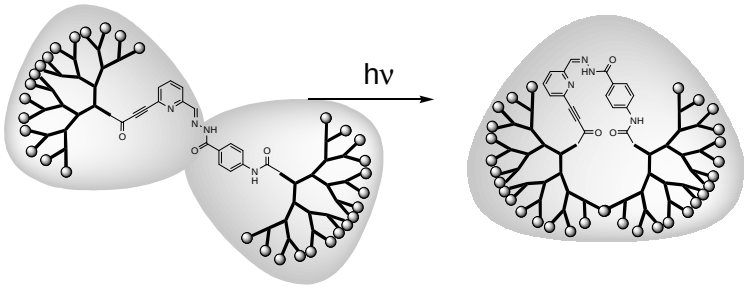
We present here the synthesis of a new class of Dendrimeric Systems (Dendrimers and Dendrons) and the study of their properties in molecular recognition processes involving the immune system.[1] These Dendrimers (***BAPAD***: ***B****is****A****minoalkyl****P****oly****A****mide****D****endrimers)*,[2] with peripheral amino groups and based on a skeletal amide bonds, will be prepared by iterative condensation of di(beta-amino)acids prepared by reduction of the corresponding azido or nitro compounds. Dendron-like systems will be prepared following the same methodology.

The versatility of these dendrimeric structures can be exploited by the dinitroderivative approach, according to the synthetic strategies that can be applied in the dendrimer construction.

We will present here how the properties of these Dendrimeric Systems can be implemented due to the development of Photo-Switchable articulating core. The 3D structure of Dendrimers will be photochemically controlled by *E/Z* photoisomerization of hydrazone type double bonds, switching the core of the Dendrimer. As well, we will design pyridyl-hydrazones based systems able to coordinate alkaline/alkaline earth cations to introduce a second control point in the articulation process of the Dendrimer.





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Functional Columnar Assemblies

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Many functional materials rely on a well-organized internal structure for their output properties, and this makes them suitable for a variety of applications. Indeed, the control of the macroscopic molecular arrangement is essential for certain properties to manifest or to be enhanced.

Our group has reported several examples of materials consisting of molecular building blocks encoded with functionality as well as with possibilities of self-organization. The final end is to create functional materials with well defined molecular architectures that enable structural- and order-dependent properties. A particular approach is to exploit mesogenic driving forces to generate functional architectures by the self-organization of molecules into columnar mesophases. Furthermore, these mesophases are often based on molecules that can self-aggregate in solvents to afford functional gel materials with defined columnar molecular arrangements along their fibers.

The work herein discussed will cover two types of functional columnar assemblies:

i) Chiroptical supramolecular switches consisting on H-bonded complexes derived from melamine and carboxylic acids that self-organize into well-defined columnar mesophases, the supramolecular chirality of which can be tuned in a reversible manner by illumination with circularly polarized light.[1,2]

ii) Luminescent materials based on mesogenic molecules derived from a rigid π-conjugated core, 1,6-diphenyl-3-hexen-1,5-diyne.[3] In bulk, the molecules self-organize into columnar mesophases that display luminescent as well as photoconducting properties. In solvents, the molecules give rise to fiber aggregates that can immobilize the solvent affording luminescent organogels with enhanced emission.[4]

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COMUNICACIONES ORALES

CO-1

Copper Nanoparticles in Multicomponent and Coupling Reactions

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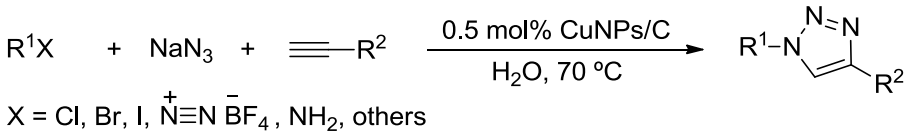
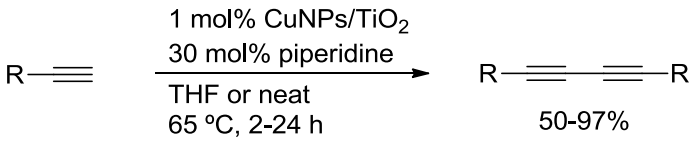
A versatile catalyst consisting of oxidised copper nanoparticles on activated carbon has been fully characterised and found to promote the multicomponent synthesis of 1,2,3-triazoles from organic halides, diazonium salts, aromatic amines, and epoxides in water (Scheme 1).[1]



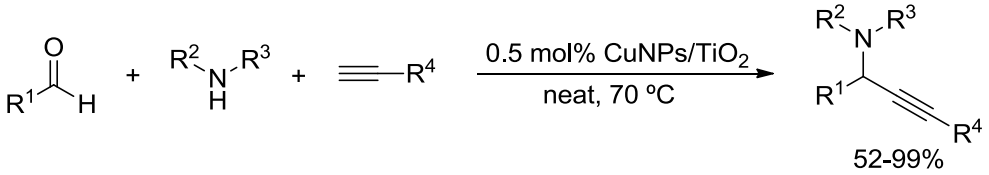
Scheme 1

When the copper nanoparticles are supported on titania, the oxidative homocoupling of terminal alkynes is effectively catalysed in the presence of piperidine as a base, in THF or under solvent-free conditions (Scheme 2).[2]



Scheme 2

The latter catalyst has also been shown to catalyse the multicomponent synthesis of propargylamines from aldehydes, amines, and alkynes (A^3 coupling) at 70 ºC under solvent-free conditions.[3]



Scheme 3

All the catalysts are easy to prepare, stable, reusable at a low copper loading, and exhibit higher catalytic activity than some commercially available copper sources. Some mechanistic aspects of these reactions have been undertaken which unveil the participation of copper(I) acetylides in a heterogeneous process.[4]

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[3] Unpublished results.
[4] Financial support: CTQ2011-24151, Consolider Ingenio 2010-CSD2007-00006, PROMETEO/2009/039.

CO-2

Well-Defined Copper(I) Catalysts for True Click Cycloaddition Reactions

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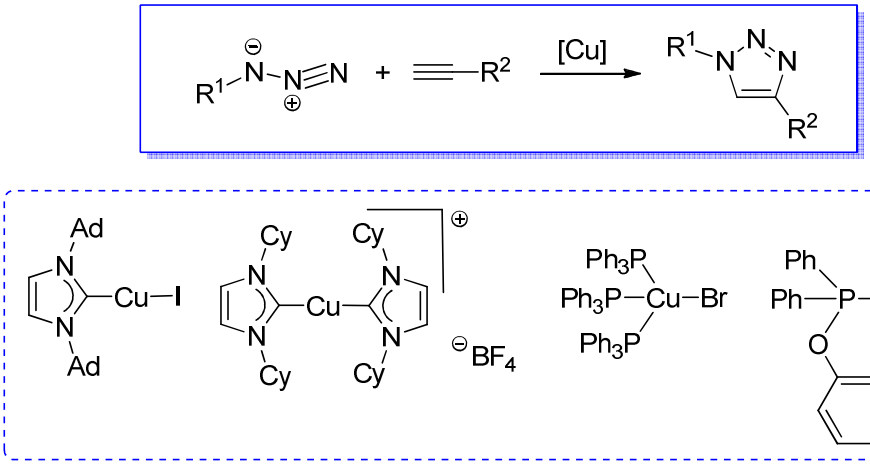
The copper(I)-catalysed selective formation of 1,4-disubstituted-1,2,3-triazoles is broadly considered as the most powerful Click reaction to date.[1] Despite its popularity, this cycloaddition process remains victim of its own success and only little efforts have been focused on developing efficient catalytic systems, preventing numerous applications from meeting the stringent Click criteria.

In this *Communication*, our contribution to the field will be discussed with a comparison of the catalysts developed so far bearing either N-heterocyclic carbene[2] or phosphorous ligands.[3]



Furthermore, our latest results for the more challenging reaction of azides and iodoalkynes will be presented, along with the first theoretical study on the reaction mechanism of this cycloaddition reaction.

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CO-3

C-H Insertion of Gold-Carbenes Generated from Cycloheptatrienes

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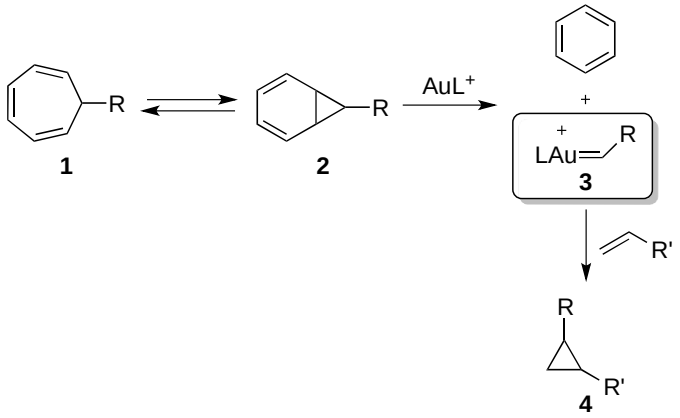
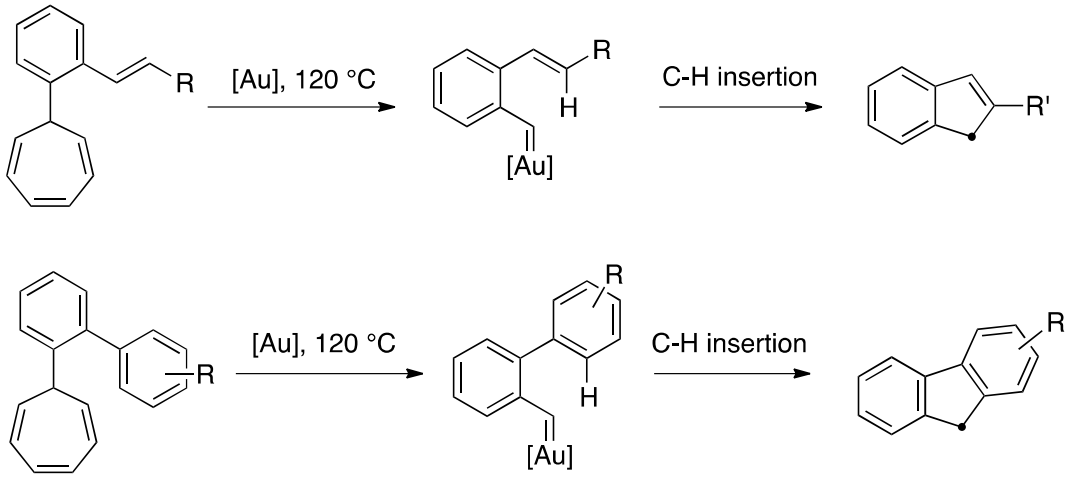
We have found that that 7-substituted 1,3,5-cycloheptatrienes **1** react with cationic Au(I) complexes through a retro-Buchner reaction to form gold(I) carbenes **3** that can be trapped with alkenes to form cyclopropanes **4**.[1]



Now we have found that gold(I) carbenes **3** undergo intramolecular sp^2 C-H insertion reactions to form indenes and fluorenes.



The scope and mechanism of this new C-H insertion reaction will be presented.

Acknowledgements. We thank the MICINN (CTQ2010-16088/BQU), the AGAUR (2009SGR47), and the ICIQ Foundation for financial support.

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A New Strategy for Catalytic Generation of Zinc Carbenes from Alkynes

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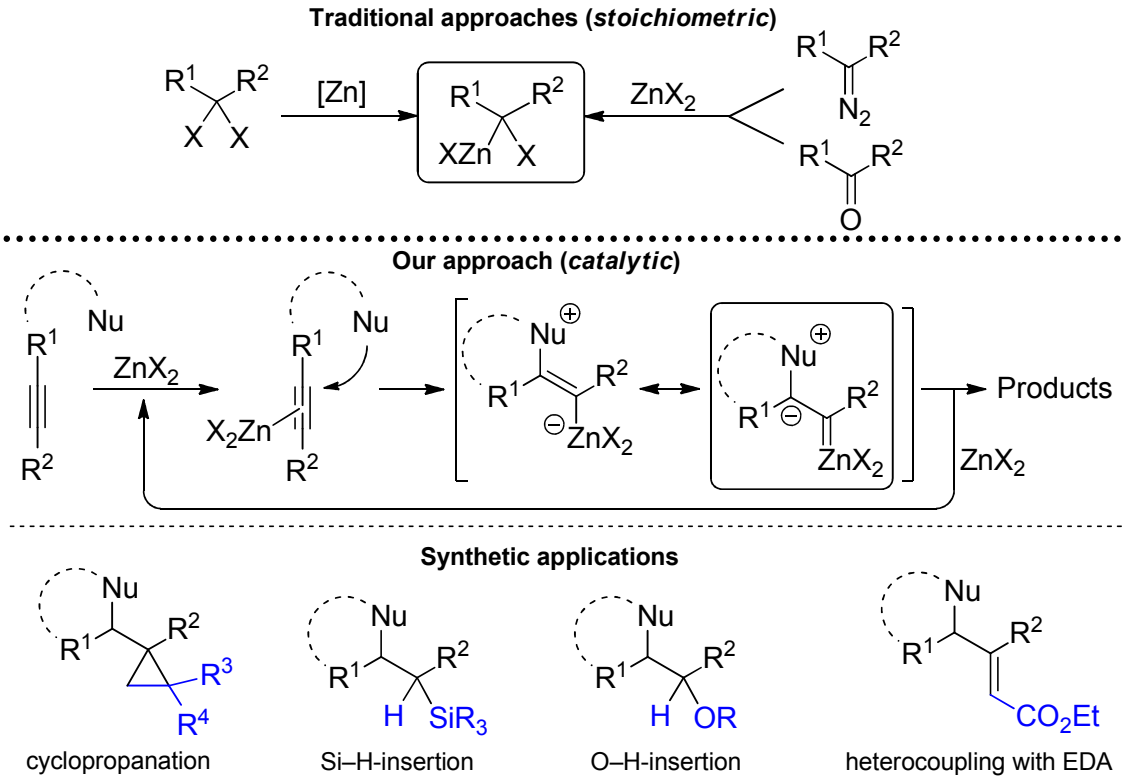
Zinc carbenoids are intermediates of relevance in organic synthesis since they are precursors of an important class of compounds like cyclopropanes. To date, zinc carbenoids are stoichiometrically generated from dihaloalkanes, diazocompounds or carbonyl compounds.[1] On the contrary, zinc complexes proved capable to activate alkynes in both stoichiometric and catalytic manner.[2] We envisioned that an alkyne activation promoted by zinc, followed by nucleophilic attack, could afford a new access to zinc carbene intermediates. Thus, we found that zinc(II) carbenes could be catalytically generated from alkynes bearing a carbonyl group as nucleophile. These intermediates were trapped with alkenes, silanes, alcohols or diazocompounds, providing a variety of compounds.



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CO-5

Enantioselective 1,3-Dipolar Cycloadditions of Azlactones and Electrophilic Alkenes Catalyzed by Dimeric BinapAuTFA Complexes

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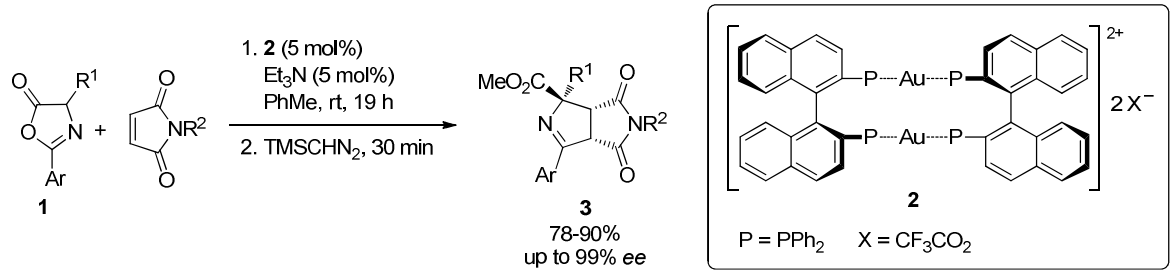
Azlactones **1** are very interesting substrates for the synthesis of both quaternized or non quaternized α-amino acid derivatives.[1] They are also important since the synthetic point of view because they exhibit a nucleophilic part and an electrophilic site. When a Lewis acid and a base reacted with an azlactone a cyclic stabilized azomethine ylide (münchnone) is formed, which is able to react with alkenes to yield, after an amidation or esterification protocole, Δ^1-pyrrolines. The asymmetric version of this transformation was first accomplished by Toste´s group using (*S*)-Cy-Segphos(AuOBz)$_2$ as catalyst.[2]

According to our previous experience in gold(I) catalyzed 1,3-DC of α-iminoesters and alkenes using chiral Binap as privileged ligand, the dimeric chiral gold complex **2** resulted to be the optimal catalyst.[3] Thus, glycine derived azlactones **1** (R^1 = H) reacted with maleimides using (*S*)- or (*R*)-dimeric BinapAuTFA complexes **2** affording the corresponding cycloadducts in good yields and high enantioselections (up to 99% *ee*). The intermediate carboxylic acids (non isolated) were treated with trimethylsilyldiazomethane and then isolated as Δ^1-pyrroline methyl esters **3**. These cycloadducts could be transformed into *exo*-proline derivatives by reduction with $NaBH_3CN$ in acidic media or, even, underwent a further thermal 1,3-dipolar cycloaddition with several dipolarophiles. On the other hand, *N*-benzoylalanine derived oxazolone **2** (R^1 = Me) reacted with *tert*-butyl acrylate providing the cycloadduct with the ester group at the 3-position with a *trans*-relative configuration with respect to the methyl ester group.[4,5]



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5 This work has been supported by the Spanish Ministerio de Ciencia e Innovación (MICINN), Generalitat Valenciana and by the University of Alicante.

Stoichiometric and Catalytic Selective Functionalization of Heterocycles Mediated by Ru and Pd Complexes

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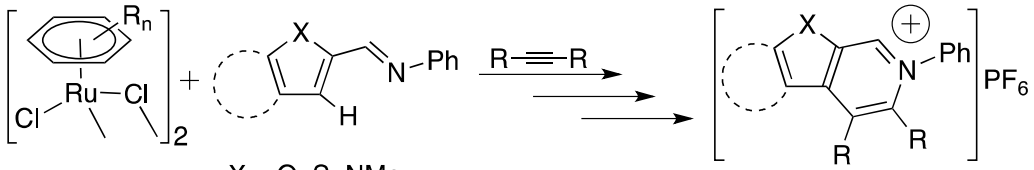
The coordination-directed functionalization of organic species through C-H bond activation, promoted by transition metals, is one of the most active areas of the chemistry nowadays because it provides alternative synthetic pathways to the classical organic methods. The use of organometallic complexes allows for the activation of C-H bonds under mild conditions and, in addition, the use of directing groups affords fully regio- and chemoselective processes.

The present contribution reports the synthesis of functionalized molecules, which are derived from a wide variety of heterocycles, employing orthometallated complexes of Ru[1] or Pd,[2] and imines or amines as directing groups. Several processes, either stoichiometric or catalytic, will be presented. The halogenation of different thiophene-based imines affords substituted 2-halo-3-formyl-thiophenes and 3-halo-2-formylthiophenes, being this process mediated by orthoruthenated complexes. On the other hand, valuable molecules such as thieno[3,2-c]pyridines and their respective isomers thieno[2,3-c]pyridines have been regioselectively obtained by reaction of the corresponding thieno-imines and internal alkynes through an adequate choice of the metal. This reactivity is not limited to thiophene compounds and has been expanded to the selective modification of other heterocycles such as benzothiophene, furane, benzofurane, pyrrole and indole. In all cases we have been able to obtain the two- or three-fused annulated products, derived from the coupling with internal alkynes, as shown in the figure.



X = O, S, NMe
R = Et, Ph, CO_2Et

Therefore, the present methodology allows for the selective synthesis of modified heterocycles through non-conventional preparative pathways, alternative and complementary to classical organic methods.

Acknowledgment. The authors thank the MINECO (Project CTQ2011-22589) for financial support.

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CO-7

Origins of the Stereocontrol in (3+2) Metal-Catalyzed Cycloaddition Reactions

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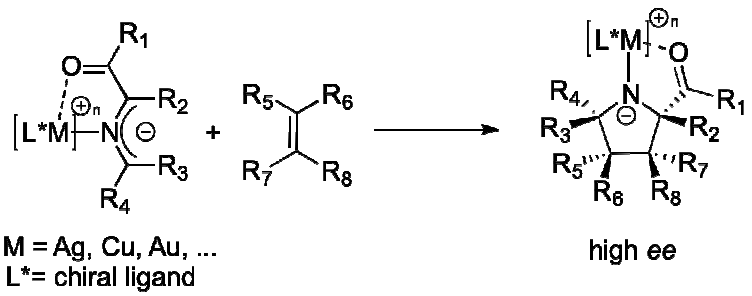
(3+2) Cycloaddition reactions constitute highly powerful methodologies for the assembly of five-membered heterocyclic structures from easily available starting materials. In fact, the employment of chiral metal complexes is widely used for the convergent and stereocontrolled chemical synthesis of valuable heterocyclic compounds.

It is found that there is no general mechanism for these reactions since both concerted aromatic [$\pi 4_s + \pi 2_s$] mechanisms and stepwise processes involving zwitterionic intermediates can be found. [1]

The observed stereocontrol stems from remote and unexpected origins in many cases.

In this work, we will present and discuss examples of stereocontrolled cycloadditions including 1,3-dipolar reactions between π-deficient alkenes and metallated azomethine ylides derived from imines (Scheme 1). The role of different homochiral catalysts will be analyzed using computational tools.[2]



Scheme 1

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CO-8

Síntesis de inhibidores de α-tubulina: análogos e híbridos de pironetina

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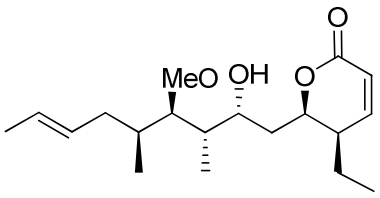
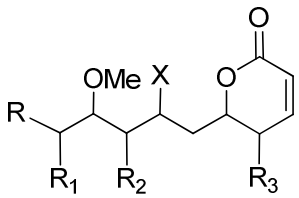
La pironetina **1** es una α-pirona que fue aislada casi a la vez de dos microorganismos diferentes del género *Streptomyces*.[1] La importancia de la pironetina **1** radica en su capacidad para unirse a la α-tubulina, una diana biológica de enorme importancia en el proceso de división celular. Únicamente se conocen cinco compuestos capaces de interactuar con la α–tubulina[2] y su potencial aplicación terapéutica en el tratamiento del cáncer ha suscitado recientemente gran interés sobre este tipo de sustancias.
En esta comunicación se expone la síntesis de diversos análogos simplificados de pironetina y la evaluación de la capacidad de éstos para unirse a α-tubulina.[3]

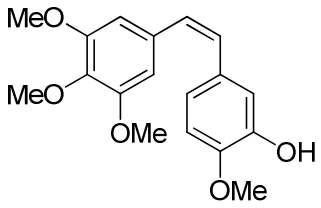


Pironetina 1

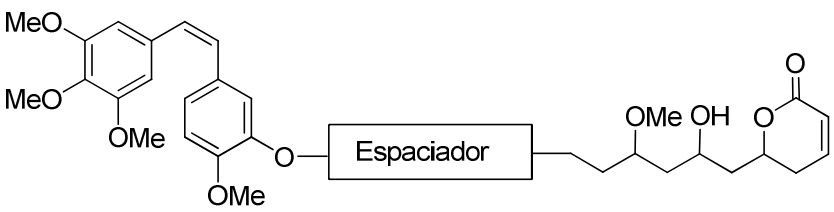


Análogos no naturales de pironetina (R_1-R_3 = H o alquilo, X = H, OH)

La combretastatina A4 **2** es un compuesto estilbénico con una demostrada actividad disruptora del sistema de microtúbulos debida a su capacidad para unirse a la β-tubulina. Se han sintetizado diversas moléculas híbridas pironetina-combretastatina A4 mediante el empleo de diversas cadenas espaciadoras:



Combretastatina A4 2



Híbridos de pironetina-combretastatina

[1] (a) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot.* **1994**, *47*, 697. (b) Kobayashi, S.; Tsuchiya, K.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Iitaka, Y. *J. Antibiot.* **1994**, *47*, 703. (c) Yasui, K., Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem*. **1995**, *60*, 7567-7574.
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CO-9

Scalable Total Synthesis of (–)-Berkelic Acid Using a Protecting-Group-Free Strategy

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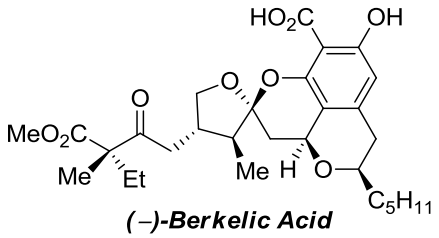
Berkelic Acid is a stereochemically dense secondary metabolite isolated by Stierle and co-workers in 2006 from an extremophile *Penicillium* species found in the hostile environment of Berkeley Pit Lake, Montana (USA).[1] This lake was formed when an abandoned copper mine was filled with infiltrating ground water to give an extremely acidic (pH= 2.5) and metal-contaminated ecosystem. Berkelic acid is one of the increasing numbers of novel secondary metabolites isolated from extreme dwelling microorganisms that have been found to present unique structure and bioactivity. Specifically, this molecule showed high and selective biological activity towards the human ovarian cancer line OVCAR-3 and also it was found to inhibit the cysteine protease capase-1 and matrix metalloprotease MMP-3.



(–)-Berkelic Acid

The necessity for an in depth study on the biological activity of the compound besides the more than likely future elimination of its natural source mandates a secured material supply. In this communication we would like to show our approach to the total synthesis of (–)-Berkelic Acid based on an strategy wherein all but the last step were executed on a gram-scale. This level of practicality was enabled by a highly stereoconvergent and modular strategy. Thus, our synthesis involves a seven step linear sequence where tedious protection/deprotection steps were avoided. Notably, the polycyclic core of (–)-Berkelic acid was constructed in just one step with a high control of the stereoselectivity and from very simple starting materials.[2]

[1] Stierle, A. A.; Stierle, D. B.; Kelly, K. *J. Org. Chem.* **2006**, *71*, 5357.
[2] Fañanás, F. J.; Mendoza, A.; Arto, T.; Temelli, B.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2012**, *51*, in press (*DOI: 10.1002/anie.201109076*)

CO-10

Iododesilylation of TIPS-, TBDPS- and TBS-Substituted Alkenes in Connection with the Synthesis of Amphidinolides B/D

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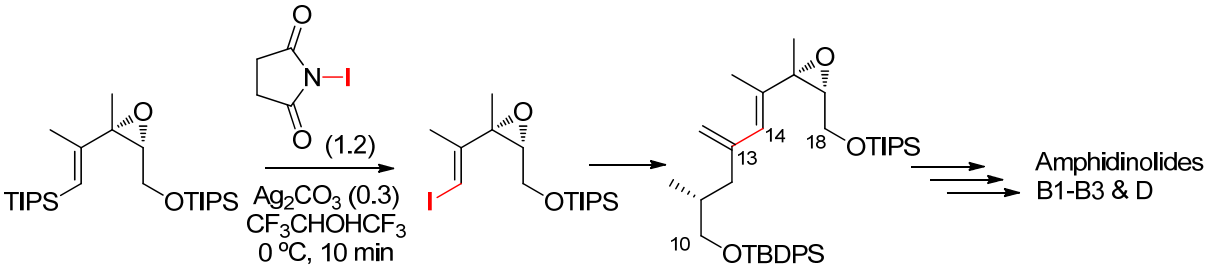
The C–Si bonds of triisopropylsilyl-substituted alkenes, 1,3-dienes, and related multifunctional substrates, as well as analogous C–TBDPS and C–TBS bonds, are readily and chemoselectively cleaved with NIS (or other sources of I^+, such as *N*-iodosaccharin, 1,3-diodohydantoin, and Ipy_2BF_4). The desired iodoalkenes are obtained stereospecifically without byproducts, provided that the reactions are carried out in $CF_3CHOHCF_3$ and, in general, with 30 mol% of Ag_2CO_3 (or AgOAc/2,6-lutidine) as an additive. Fragment C10–C18 of cytotoxic amphidinolides B1–B3 and D has been synthesized using this improved procedure.



CO-11

Synthesis of polycyclic amines with anti-influenza A virus activity

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Influenza is an infectious disease caused by virus of the *Orthomyxoviridae* family. Influenza spreads in seasonal epidemics infecting one out of five humans worldwide. Eventually these viruses cause pandemics with high morbidity and mortality.

The influenza virus possesses some "druggable" surface proteins that have been targeted by several drugs. The M2 influenza channel, a pH-gated proton channel which triggers the intracellular uncoating of the virus, is one of the targeted viral proteins.[1]

Amantadine was the first clinically approved compound able to inhibit the M2 channel of influenza A.[2] It has been shown that this inhibition is due to its ability to impede the flow of protons through the M2 channel.[3] However, its therapeutic use has been recently limited due to the rapid occurrence of resistances.[4]

Recently, our research group has synthesized new analogs of amantadine using several novel polycyclic scaffolds (Figure 1).[5]

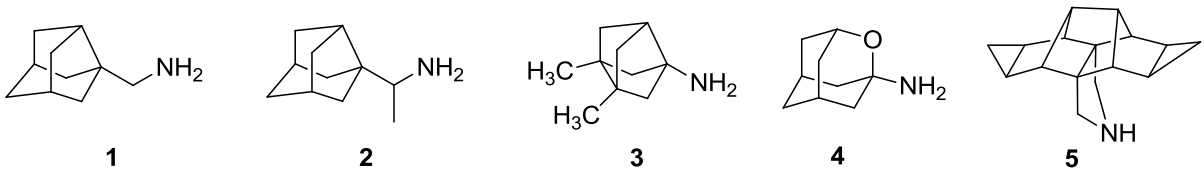

Figure 1.

Some of our polycyclic amines were more potent than amantadine against the influenza A/H1N1 strain. Surprisingly, the antiviral activity of several of these amantadine-inspired compounds was not mediated through M2 inhibition.

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CO-12

Synthesis of Polycavernoside A

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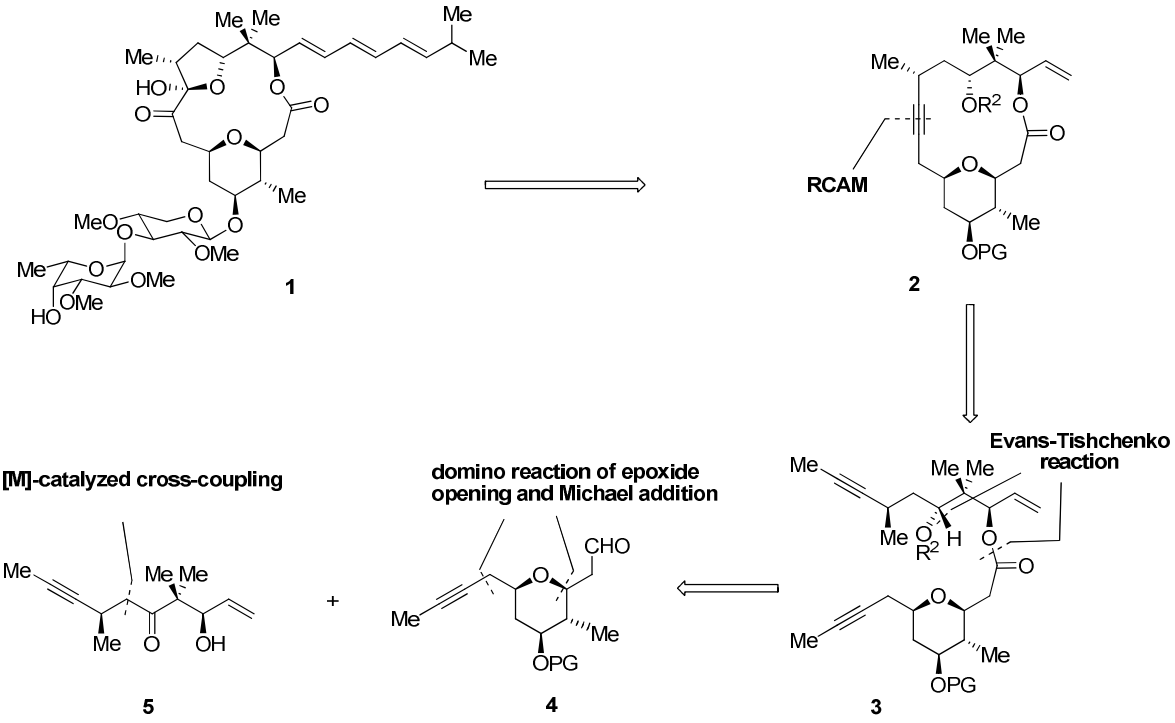
Polycavernoside A (**1**) was isolated from red alga *Polycavernosa tsudai* as a causative toxin of sudden human intoxication in Guam in 1991.[1] The structure was confirmed by the first total synthesis described by Murai and coworkers;[2] subsequently three total syntheses have been reported highlighting the attraction exerted by this architectural and biological features challenging target.[3]

In this communication, we report a novel formal synthesis of **1** demonstrating the power of metal-catalyzed reactions. Ring Closing Alkyne Metathesis (RCAM) utilizing Mo-based catalyst developed in our laboratory[4] was chosen as macrocyclization strategy. Further steps include a Sm-mediated Evans-Tishchenko reaction of fragments **4** and **5** as well as Noyori-reduction, cross-metathesis, Jacobsen-epoxidation and Sonogashira-coupling to construct these fragments.



1. a) Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147-1148.
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CO-13

La deleción de los genes BcPKS9 y BcPKS6 reveló una ruta biosintética común en las toxinas policétidas excretadas por *Botrytis cinerea*

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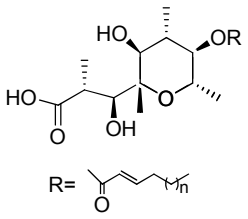
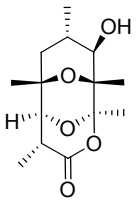
Las especies de *Botrytis* pertenecen al grupo de patógenos de plantas más extendido geográficamente. Las pérdidas producidas por este hongo en numerosos cultivos comerciales son cuantiosas. *B. cinerea* utiliza en su proceso de infección dos familias de toxinas: una familia de sesquiterpenos que contienen el esqueleto básico de botriano y dos tipos de lactonas policétidas, botcininas[1] (**1**, **2**) y botrilactona[2] (**3**).

Los genes de la biosíntesis de ácido botcínico (**1**) han sido investigados recientemente utilizando aproximaciones de genética reversa y transcriptómica. La inactivación de los genes *BcPKS6* y *BcPKS9*, los cuales codifican para sendas PKSs, puso de manifiesto que actúan conjuntamente en la síntesis de botcininas.[3] La acumulación de botrylactona (**3**) en el mutante *bcpks9*Δ, junto con la homología estructural e incluso características estereoquímicas de ambos tipos de lactonas policétidas, apunta a un origen biosintético común para ambas familias de compuestos.



1 n=3; Botcinic acid
2 n=5; Botcineric acid



3 Botrylactone

En esta comunicación se presentan experimentos de marcaje isotópico con [1-^{13}C]-, [2-^{13}C]-, y [1,2-$^{13}C_2$]-acetatos sódico, [2-^{13}C]-malonato sódico y L-[$^{2}H_3$-metil]-metionina. El patrón de marcaje de las botcininas y botrilactonas aisladas, junto a los resultados obtenidos con los mutantes *bcpks6*Δ y *bcpks9*Δ, son consistentes con un origen biosintético común de ambas lactonas policétidas. *B. cinerea* biosintetiza un policétido C_{10} por condensación de 4 unidades de malonil-SCoA y una unidad de acetil-SCoA, el cual se metilaría en los grupos metilenos activados para dar un ácido bicíclico hipotético. Este intermedio sería clave como punto de ramificación conducente a derivados de botrilactona o botcininas.

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CO-14

Diversity Oriented Synthesis: Stereoselective Total Synthesis of Gabosines and Anhydrogabosines

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The gabosine family comprises a group of secondary metabolites isolated from various *Streptomyces* strains that present a polyhydroxylated methyl cyclohexane system as the common constitutional feature. Their structural diversity is originated by differences in the substituent positions, unsaturation degree, and/or relative and absolute configuration of their stereogenic centers.[1] Some other compounds isolated from natural sources display also a structural pattern within the gabosine family. There are also several known epoxyquinone natural products with anhydrogabosine structure (Figure 1).

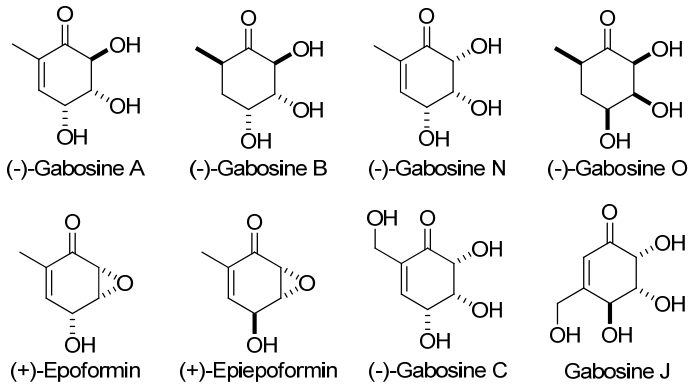

Figure 1: Some members of the gabosine and anhydrogabosine families.

In the last years, we have developed a flexible, diversity oriented methodology starting from a common material. This strategy has been designed aiming to cover the variety of substitution patterns found in gabosine and anhydrogabosine families. Based on this new approach, the stereoselective syntheses of gabosines N, O,[2] A, B, F[3] and J[4] as well as epoformin and epiepoformin have been accomplished. Furthermore, our work has contributed to establish the correct structure of some of these metabolites.

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CO-15

Validation of FtsZ protein as a new potential therapeutic target for the discovery and development of new antibacterial agents

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Emergence and spread of antibiotic-resistant strains of pathogenic bacteria have boosted an urgent need for new antibacterial agents with novel modes of action. In this sense, FtsZ (Figure 1) "a widely conserved tubulin-like GTPase" has recently been proposed as an attractive target for antibacterial drug discovery due to its essential role in bacterial cell division.[1] Approaches based on the FtsZ and tubulin resemblance and on the GTPase function, combined with high throughput screening techniques, have allowed the identification of compounds that specifically target FtsZ and inhibit its function in bacterial division.[2] Among them, the most promising FtsZ inhibitor discovered so far is PC190723.[3] This compound binds an alternative site different from the classical GTP binding site,[4] and has shown potent activity both in vitro and in vivo against *Staphilococcus* but it is inactive against a range of Gram-positive and Gram-negative pathogenic bacteria. Therefore, the development of new inhibitors of FtsZ able to act as broad spectrum antibacterials still needs to be addressed and will be the focus of the present work.

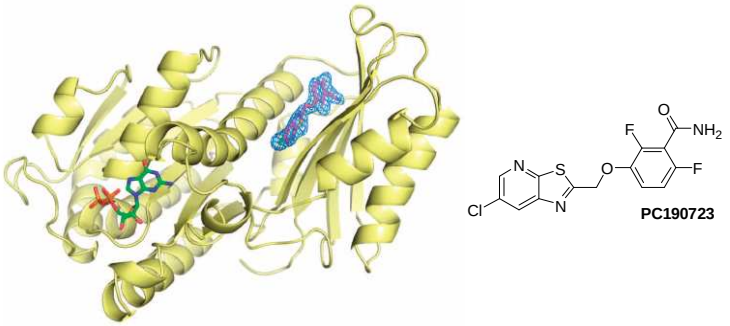

Figure 1. Crystal structure (2.0 Å) of *S. aureus* FtsZ-GDP in complex with PC190723

Here, we will present our latest results on the discovery of FtsZ inhibitors targeting the GTP-binding pocket and the newly described PC-binding site, using two different strategies: the design of GTP-mimetics and virtual screening. In addition, synthesis of fluorescent derivatives of PC190723 is being carried out to obtain a valuable tool to set up a fluorescent assay which would allow for the assessment of the affinity of new synthesized compounds for this recently identified binding site.

Acknowledgments: This work has been supported by grants from the Spanish Ministerio de Economía y Competitividad (MINECO, SAF2010-22198) and Comunidad de Madrid (SAL-2010/BMD2353). The authors thank MINECO for a predoctoral grant to M.E.A.

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CO-16

Toll-like Receptor 4 Modulators. Molecular Modelling Insights for Drug Design

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One of the mechanisms by which the innate immune system senses the invasion of pathogenic microorganisms is through the Toll-like receptors (TLRs), which recognize specific molecular patterns present in microbial components (as lipopolysaccharides, LPS, in the outer membrane of Gram-negative bacteria). In particular, TLR4 forms a heterodimeric complex with MD2, its accessory protein myeloid differentiation factor 2. Thus, the TLR4-MD2-LPS complex (Figure 1) is responsible for triggering powerful pro-inflammatory cytokine responses.[1] Several new compounds interacting TLRs are now undergoing preclinical and clinical evaluation, for the treatment of sepsis and inflammatory diseases, cancer, and rheumatoid arthritis. Emerging new aspects of TLR-mediated signalling might offer further possibilities of therapeutic manipulation.[2]

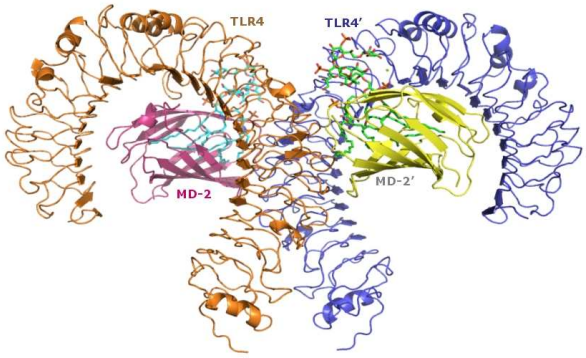
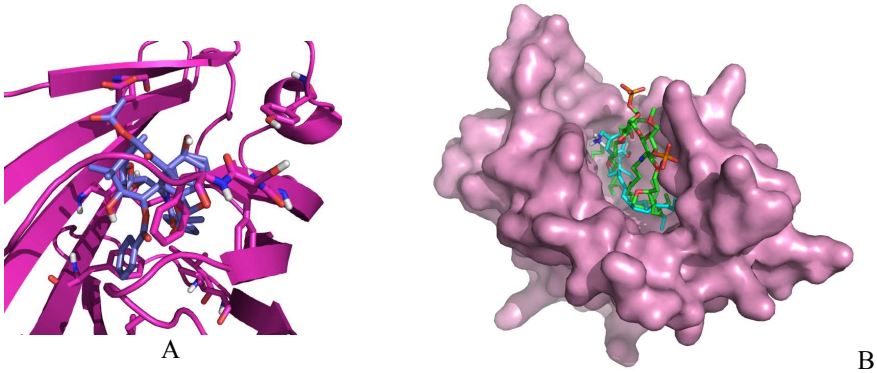


Figure 1. TLR4-MD2 complex with bound endotoxin antagonist **Eritoran** (X-Ray structure, PDB 2z62).

Here we report molecular modelling studies on TLR4 interactions with reported agonists and antagonists (Figure 2). Ligand-protein and protein-protein docking analyses have been carried out to unravel the details regarding molecular recognition processes. Our studies can be very valuable for the understanding of the interaction mechanism of these compounds at atomic level, unknown in most cases, and for further design of new ligands able to modulate TLRs functions.



A B

Figure 2. A) Novel MD2 binding pose for TLR4 agonist **paclitaxel**; B) Superimposition of the docked TLR4 antagonists **Eritoran** (green) and **P03** (cyan) bound to MD2.

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CO-17

The combination of new chemical tools and NMR methodologies open the field of structural elucidation to new molecules

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Recent advances in Nuclear Magnetic Resonance (NMR) give access to new parameters with structural information and methodologies that allow the characterization of complex systems.

In this sense, we present our results on the development of chemical tools, based on lanthanide binding tags, for the conformational study of carbohydrates both in the free state and bound to protein receptors. Herein, diamagnetic carbohydrates have been converted to paramagnetic compounds through attachment of an EDTA-based paramagnetic tag, thus extending the methodology already developed for proteins.[1]

On the other hand, we are interested on ^{13}C direct detection experiments that have emerged as a new solution to overcome the drawbacks of traditional NMR experiments (based on proton detection).[2] These experiments are especially useful to study systems such as; paramagnetic proteins, very large proteins or intrinsically disorder proteins. In this context, we are applying ^{13}C direct detection experiments to the study of the N-terminal domain of CHOP protein. This protein is a transcription factor that induces growth arrest and apoptosis after endoplasmic reticulum stress or DNA damage.[3] While the C-terminal leucine zipper of CHOP is involved in DNA recognition, its N-terminal half contains transactivation domains that are crucial for transcriptional control. Regardless of its importance, the presence of intrinsically unstructured stretches in the N-terminal half of CHOP has hampered a structural characterization of this region using conventional methods.

Financial support in the form of Access to the Bio-NMR Research Infrastructure co-funded under the 7th Framework Programme of the EC (FP7/2007-2013) grant agreement 00088 for conducting N-CHOP experiments is gratefully acknowledged.

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CO-18

Carbohydrate DNA conjugates: a convenient tool to explore biologically relevant binding-motifs

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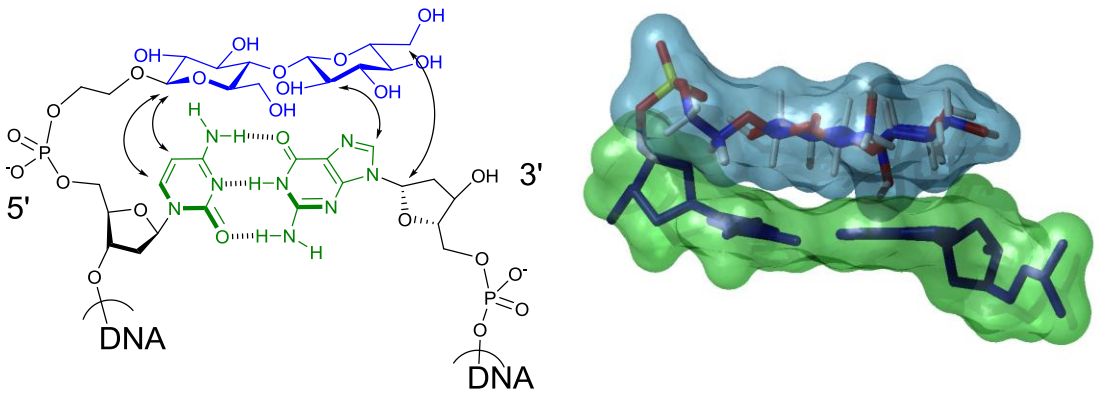
Carbohydrate-nucleic acid contacts are known to be a fundamental part of some drug-DNA recognition processes.[1,2] Most of these interactions occur through the minor groove of DNA, such as in the calichaemicin or anthracycline families. In fact, we have shown that carbohydrate-DNA interactions are also possible through sugar stacking on a DNA double helix. We have observed that mono- and disaccharides attached to the 5'-end of short DNA sequences stabilize a DNA duplex up to 0.9 kcal·mol^{-1} respect to the DNA control. These results are remarkable since these carbohydrates are highly polar molecules in contrast to typical capping agents used in DNA such as hydrophobic aromatic rings. Carbohydrate-DNA stacking has been confirmed by NMR experiments and molecular dynamics calculations.[3] Recently we have reported that apolar sugars are also able to stack onto DNA double helices. Moreover, these permethylated carbohydrates stabilize DNA duplexes much more than the corresponding natural sugars up to -1.8 kcal·mol^{-1} respect to the DNA control.[4]



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CO-19

β-Phenylproline: effect of the β-phenyl substituent on the β-turn propensity and pyrrolidine puckering

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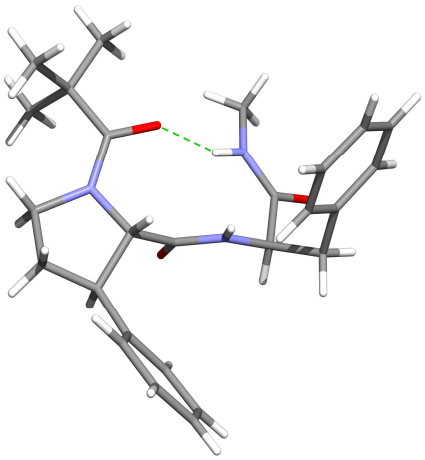
The conformational propensities of the proline analogue bearing a phenyl substituent attached to the β carbon, in either a *cis* or a *trans* configuration relative to the carbonyl group, have been investigated.[1] The behaviour of *cis*(βPh)Pro and *trans*(βPh)Pro has been compared with that of proline in homochiral and heterochiral dipeptide sequences including L- or D-phenylalanine.

NMR and IR studies as well as X-ray diffraction analysis provide evidence that the additional β-phenyl substituent does not disrupt the tendency of proline to occupy the i+1 position of a β-turn. The pyrrolidine conformation is significantly affected by the presence of the β-phenyl group. The puckering modes that alleviate most the steric hindrance introduced by this substituent are preferred. The *cis*(βPh)Pro residue shows a marked propensity for the C^{γ}-*endo*/C^{β}-*exo* arrangement whereas the *trans* compound exhibits a higher flexibility, with different pyrrolidine shapes being accessible.

Interactions between the aromatic ring of (βPh)Pro and the contiguous L- or D-Phe residue are observed in all the dipeptides crystallised. In solution, they seem to occur only for the heterochiral sequences. This intramolecular aromatic-aromatic interaction may be responsible for the higher β-turn ratio observed for such sequences and also seems to affect the conformational preferences of the pyrrolidine ring.



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CO-20

Hybrid cyclobutane containing peptides: design of foldamers and new cell-penetrating agents

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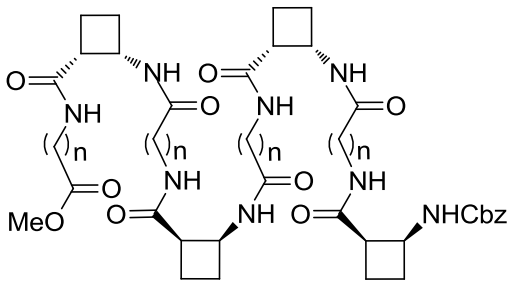
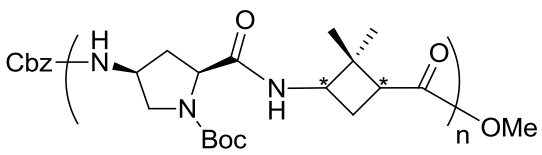
The use of carbocyclic amino acids to construct peptides confers rigidity to the corresponding oligomers. Alternation with linear residues results in new conformational bias in solution. Hybrid tetra-, hexa- and octapeptides that join in alternation an enantiopure cyclobutane β-amino acid and glycine, β-alanine or γ-amino butyric acid (GABA), respectively, have been synthesized. Studies have been carried out by NMR, CD and theoretical calculations and results show that the spacer length has an effect on the folding pattern shown by these peptides.[1] This behaviour contrasts with that of oligomers consisting exclusively of cyclobutane residues.[2]



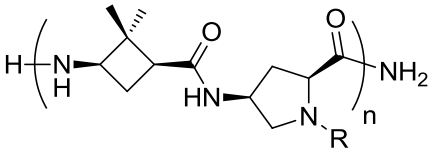
octapeptides

n = 1; β-**sheet**-like folding
n = 2; **14-helical** folding
n = 3; β-**sheet**-like folding

Regarding hybrid peptides that incorporate different cyclic residues joined in alternation, new families of γ,γ-peptides have been synthesized from enantiopure cyclobutane γ-amino acids and *cis*-4-amino-L-proline. The effect of the absolute configuration of the cyclobutane moiety, the length of the peptide and the nature of the side chains have been analyzed in terms of their secondary structure and ability to be up-taken by HeLa cells.[3]



n = 1, 2, 3



n = 3
R = alkyl, acyl, benzyl, guanidinium

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CO-21

α,γ-Cyclic Peptide Nanotubes as Potential Selective Ion Transport Systems

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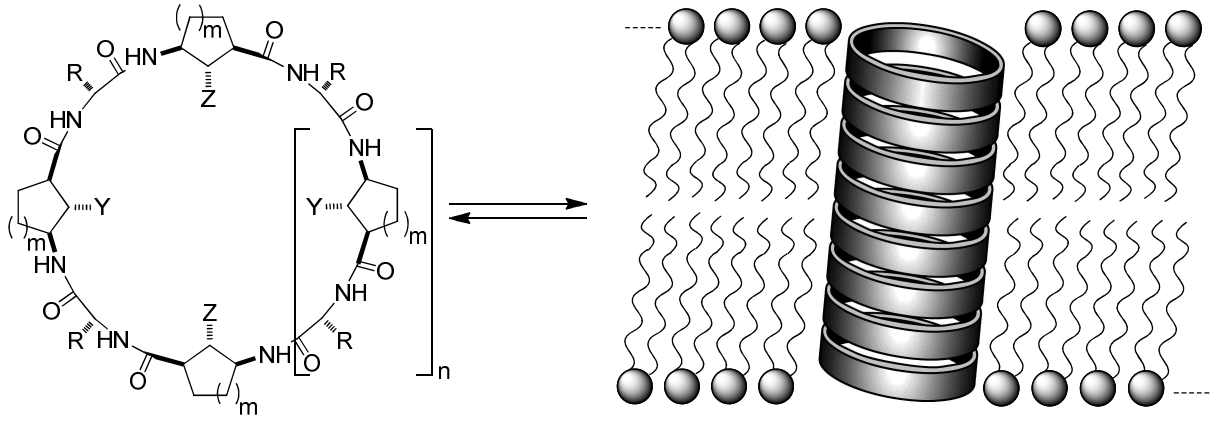
In the last few years considerable effort has been carried out to prepare organic and inorganic nanotubes with selective transport properties.[1] Although the resulting synthetic transporters have been able to mimic some properties of natural systems; still some additional work is need to be carried out it, especially in terms of transport selectivity. One interesting approach to these systems, which allow a precise control of the internal diameter is the self-assembling peptide nanotubes (SPN) made by stacking of cyclic peptides.[2] The SPN formed by *D*,*L*-cyclic peptides have the ability to insert in lipid bilayer and transport ions efficiently,[3] but, because of their design it is not possible to control the inner properties, mainly due to the lack of functional groups projected toward the nanotube cavity. In this presentation we will show our progress toward the design and synthesis of SPN with tunable cavity properties based on α,γ-cyclic peptides.[4]



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CO-22

Propargyl Vinyl Ethers: Synthetic Applications

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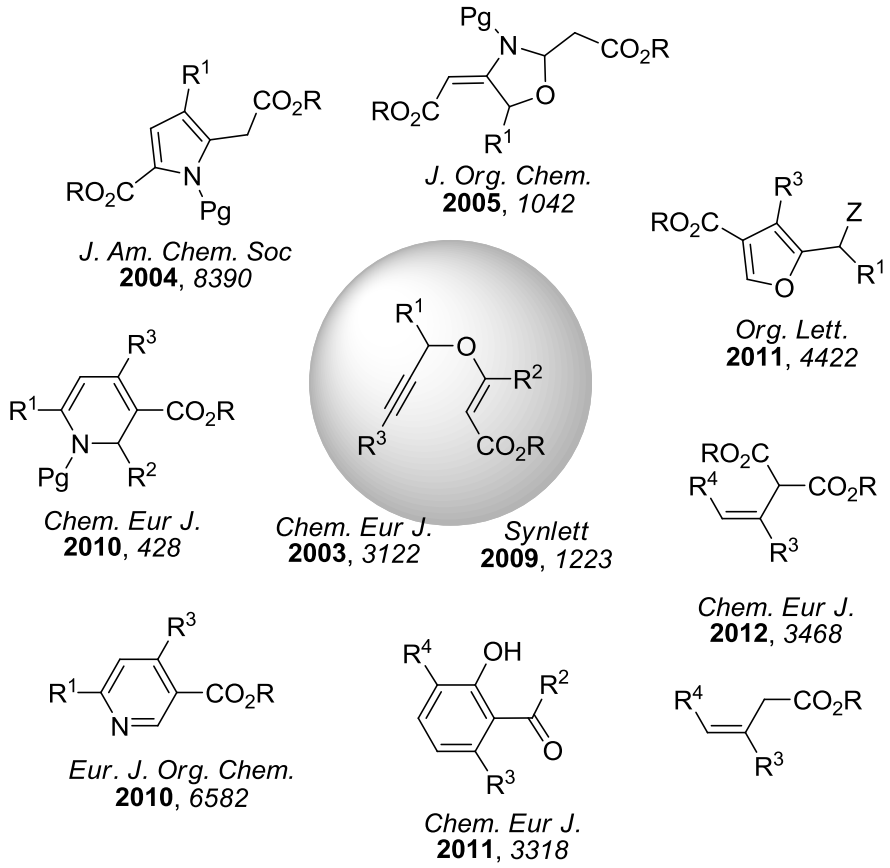
Propargyl vinyl ethers (PVEs) constitute a privileged group of small size, structurally simple, readily available, and densely functionalized scaffolds. Our group has been working on the synthetic potential of these platforms in accessing a large number of different compounds.[1]



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CO-23

Asymmetric Synthesis of Bis-α-Amino Acids through Bis-Alkylations of Chiral Glycine Equivalents

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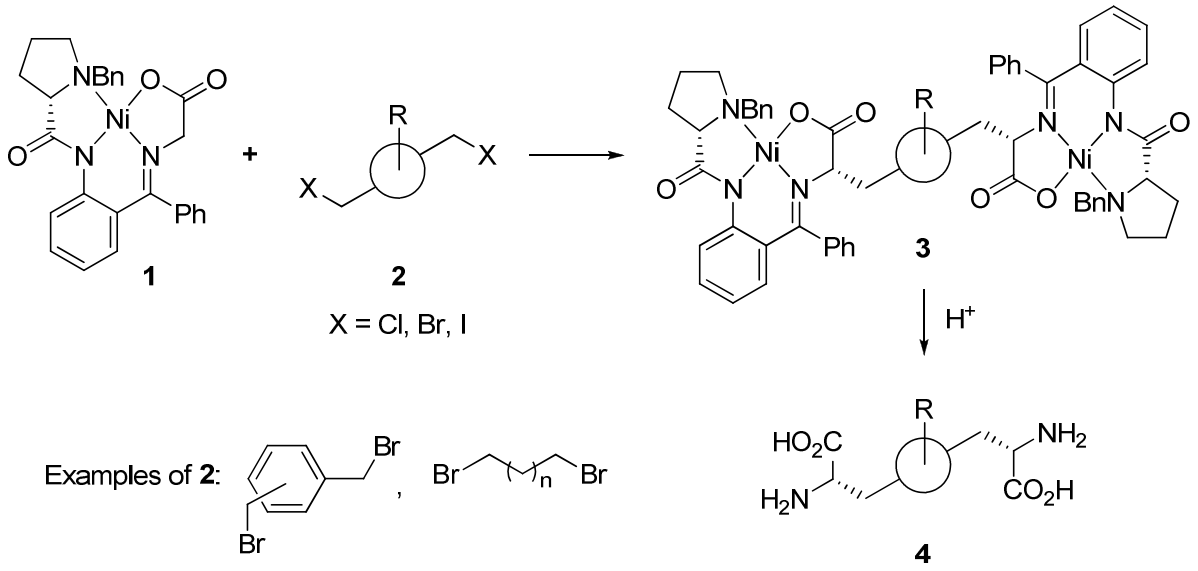
Homologation of glycine equivalents is probably the most practical and direct method for the synthesis of structurally varied and/or conformationally restricted α-amino acids. In this context, nickel(II) complex **1** derived from benzyl-L-proline is a versatile chiral nucleophilic equivalent of glycine widely employed for the synthesis of α-amino acids through alkylation, Michael addition or aldol reactions.[1] On the other hand, bis-α-amino acids can be isolated from different natural sources and display interesting biological activities.[2] However, their preparation in optically pure form usually requires long synthetic routes which may also proceed with low stereocontrol. We envisioned an easy access to symmetrically substituted bis-α-amino acids[3] via alkylation reactions of complex **1** with bis-halogenated reagents **2**. The resulting bis-alkylated compounds **3** were obtained in good diastereomeric ratios, under both homogeneous and heterogeneous (phase-transfer) conditions. Disassembly of complexes **3** by acid treatment finally affords target bis-α-amino acids **4**.



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CO-24

Arylsulfonylacetylenes as Alkynylating Reagents of Csp^2-H and Csp^3 Bonds

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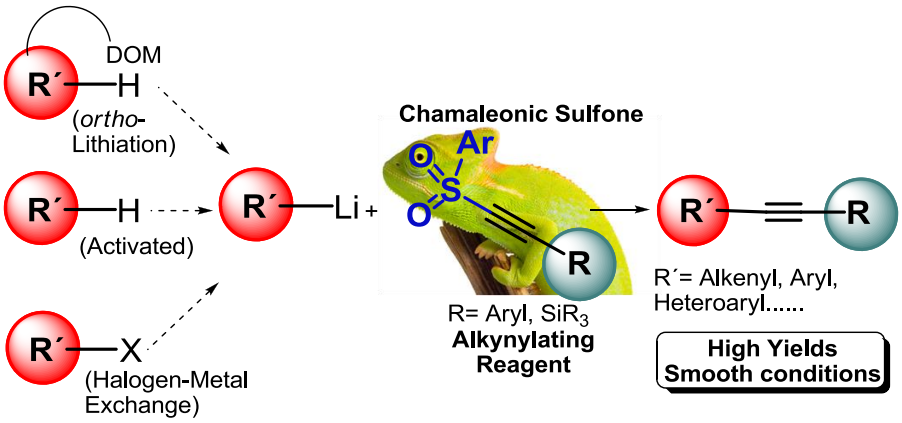
In recent years, acetylene chemistry has become an increasingly attractive topic for chemists due to its importance in the synthesis of bioactive natural products and new materials as well as in biochemistry.[1] A variety of new approaches have appeared for incorporating alkyne moieties into organic molecules. The most common method for the formation of Csp-Csp^2 bonds to provide aryl-acetylenes and conjugated enynes is the well-known Sonogashira cross-coupling reaction.[2] However the direct efficient introduction of alkynyl moeity from organolithium reagents remains a challange in this synthetic area.



In this communication, we will show a new strategy for the synthesis of a wide variety of alkynyl derivatives consisting in the reaction of substituted arylsulfonylacetylenes with organolithium species prepared *in situ* by conventional methods.[3] The excellent yields, the simplicity of the experimental procedure, the broad scope of this reaction, and the formation of Csp-Csp^2 and Csp-Csp^3 bonds[4] without using transition metals, are the main features of this methodology.

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CO-25

Reacciones de alquinilación enantioselectivas catalizadas por complejos de Zn(II) y ligandos de tipo bifenol

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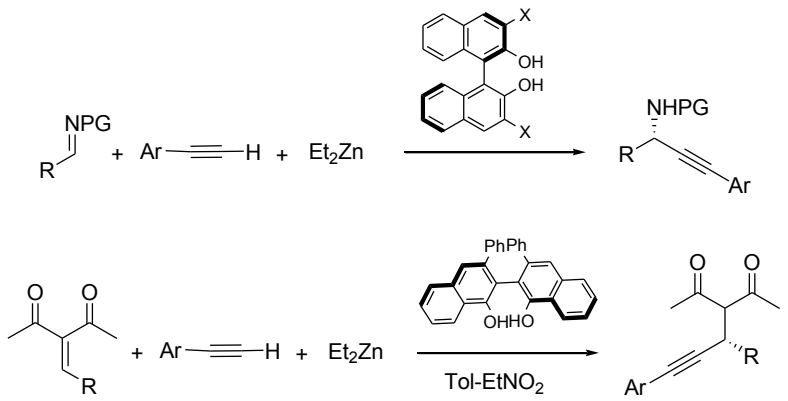
La adición enantioselectiva de alquinos terminales a dobles enlaces electrofílicos constituye un procedimiento muy atractivo para la síntesis de alquinos internos funcionalizados.[1] El triple enlace de los productos resultantes puede ser manipulado para obtener otros grupos funcionales, lo que aumenta el valor de estos compuestos como building blocks.[2] Nuestro grupo de investigación ha desarrollado procedimientos catalíticos para la adición de alquinos terminales a aldehídos[3] y *N*-sulfoniliminas[4] con excelentes rendimientos y *ee*.

Como continuación de nuestra investigación sobre formación de enlaces C-C mediante catálisis asimétrica, en esta comunicación mostraremos nuestros resultados más recientes en la adición 1,2 de alquinos a iminas,[5] así como en la adición conjugada a cetonas α,β-insaturadas, utilizando alquinos terminales, reactivos de dialquilcinc y ligandos de tipo bifenol (BINOL y VANOL).



Agradecimientos: Ministerio de Ciencia e Innovación y FEDER (CTQ2009-13083), y Generalitat Valenciana (ACOMP/2012/212). A M. y A S-M agradecen la concesión de becas pre-doctorales a la GV y al MICINN respectivamente.

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CO-26

Regiocontrolled Cu^{I}-Catalyzed Borylation of Alkynes

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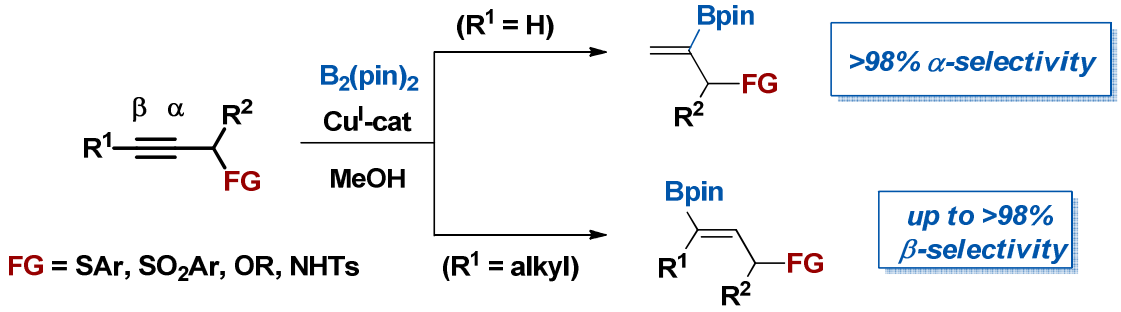
The catalytic hydroboration of terminal alkynes with B–H reagents is regarded as one of the most straightforward methods for the preparation of vinylboronate reagents, which are highly versatile building blocks endowed with numerous synthetic applications. The anti-Markovnikov was the only regiochemical outcome available for the direct borylation of terminal alkynes until the very recent work by Hoveyda and co-workers, who devised a NHC-Cu-catalyzed borylation protocol with $[B_2(pin)_2]$, leading to functionalized branched vinylboronates with high α–selectivity.[1] Despite this significant pioneering study, complementary approaches are highly needed for expanding the substrate scope.

The regiocontrolled borylation of internal alkynes represents an even greater challenge because of their lower reactivity and difficult site-selectivity. Indeed, so far only strongly sterically or electronically biased alkynes have been successfully borylated (aryl-substituted alkynes and conjugated enynes).[2] In contrast, the regiocontrolled hydroboration of simple dialkyl alkynes remains an unmet challenge.

In this communication[3] we present an operationally trivial, room temperature Cu^{I}-PR_3-catalyzed protocol for the regio- and stereocontrolled $B_2(pin)_2$-monoborylation of internal dialkyl-alkynes with only subtle biases between the two acetylenic termini, and the α–selective borylation of terminal alkynes. Further elaboration of the products without affecting the boronate group via allylic substitution reactions have been demonstrated, thereby allowing widening the current structural scope in the synthesis of vinylboronates.



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CO-27

Organocatalytic Enantioselective Intramolecular aza-Michael Reactions

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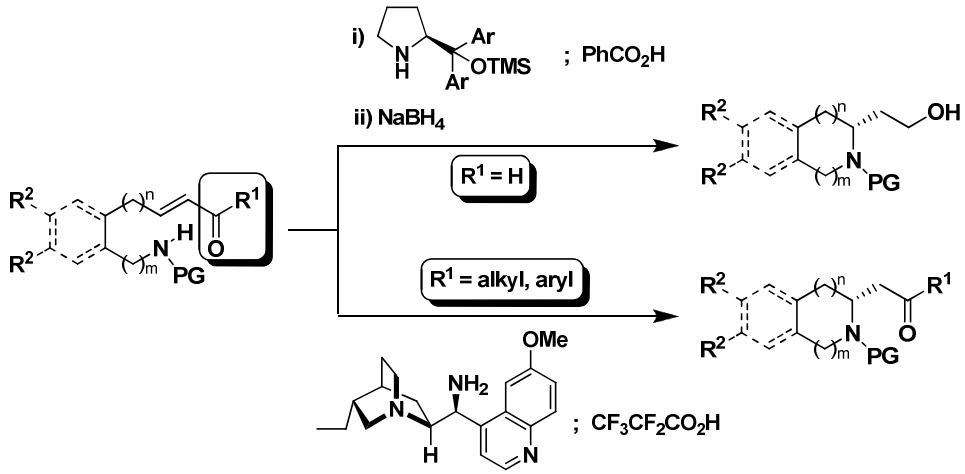
The *aza*-Michael reaction provides one of the best methods for the formation of C-N bonds and has emerged as a very powerful tool for the synthesis of nitrogen-containing heterocycles in its intramolecular version. Despite the synthetic utility of this transformation, the *catalytic enantioselective aza-Michael reaction* remained undeveloped until very recently.[1] Moreover, most of the examples reported in this field are intermolecular processes, while the intramolecular version has remained almost unexplored. In this context, we carried out a catalytic enantioselective intramolecular aza-Michael reaction (IMAMR) of carbamates bearing a remote α,β-unsaturated aldehyde moiety. When these compounds were treated with diarylprolinol ether derivatives, the IMAMR took place with high levels of enantioselection, giving rise to a variety of enantiomerically enriched nitrogen heterocycles.[2]

On the other hand, when the starting carbamates contained conjugated ketones as Michael acceptors, the IMAMR required the use of primary amines as catalysts. Specifically, 9-amino-9-deoxy-*epi*-hydroquinine in combination with pentafluoropropionic acid as a co-catalyst was found to be an efficient catalytic system to carry out this transformation in a highly enantioselective manner. Interestingly, the cyclization under microwave irradiation led to comparable results in terms of yield and *ee* to those obtained at room temperature.[3]

In order to exemplify the synthetic utility of our developed methodology, we performed the total synthesis of different piperidine, quinolizidine and tetrahydroquinoline alkaloids.[2,4]



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CO-28

Rapid access to enantiopure decahydroquinolines via organocatalysis: application to the total synthesis of lycoposerramine Z and cermizine B

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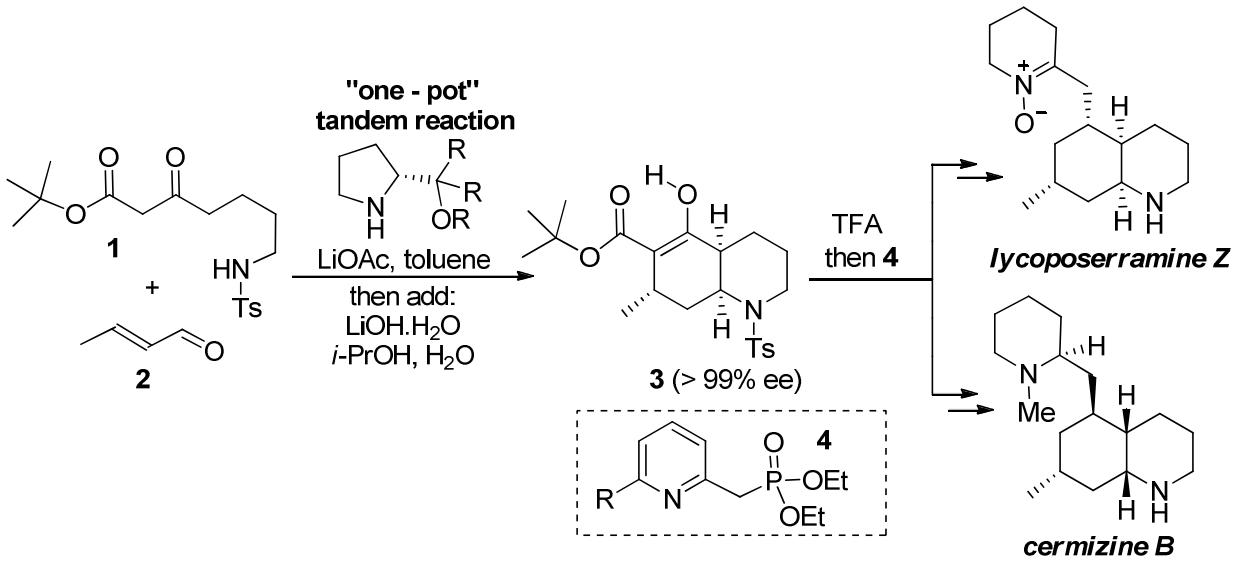
The *Lycopodium* alkaloids have attracted much attention recently not only for their diverse and structurally complex architectures but also as their potential as leads against neurogenerative diseases and cancer.[1] However, despite intense effort many of these compounds require between 25-30 synthetic steps for their construction making their large scale preparation or the synthesis of analogs impractical.

As part of our ongoing work on the application of organocatalysis to the synthesis of complex natural products[2] we have developed a possible solution to this problem utilizing an organocatalysed one-pot tandem reaction that constructs enantiopure decahydroquinoline unit **3** in >99% ee from simple achiral acyclic building blocks **1** and **2**. Subsequent decarbalkoxylation and coupling with piperidine surrogate **4** under kinetic or thermodynamic controlled conditions allowed us to rapidly convert **3** into the natural products lycoposerramine Z and cermizine B. The application of this method to synthesize analogs and other important heterocyclic structures will also be briefly discussed.



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CO-29

Asymmetric Construction of Complex Molecules by Cascade Reactions

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Domino or cascade reactions represent an advantageous approach for the straightforward construction of biologically relevant compounds because they allow construction of complex molecules in an efficient way, thereby minimizing the number of laboratory operations and the generation of waste chemicals. In this sense, between all methodologies described in the literature, organocatalytic enantioselective domino reactions represent a useful and competitive tool for the generation of molecular complexity from readily available and cheap starting materials, as well as display exceptional performance with regard to stereochemical control.[1]

Recently, we have reported several methodologies for the synthesis of carbo- and heterocycles using cascade reactions using chiral secondary amines as catalysts. In particular, we have accessed to pyridazines and pyrazolidines, important heterocycles from a pharmacuetical point of view, using the well known iminium/enamine platform (figure 1). In addition, we have also developed a novel approach to highly functionalized cyclobutanes by formal [2+2] cycloaddition between enals and nitroalkenes using the combination of dienamine and iminium activation (figure 1).

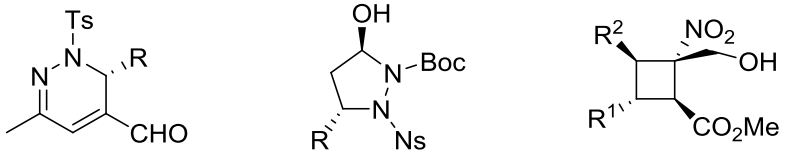

Fig 1. Some products synthesized in our group using aminocatalytic cascade reactions[2]

Aknowledgment: The authors thank the Spanish MICINN (CTQ2011-22790), the Basque Government (Grupos IT328-10 and fellowship to M. F. and G.T.) and UPV/EHU (UFI11/22) for financial support

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CO-30

Evidencias experimentales directas sobre la epimerización en las reacciones de Michael organocatalizadas

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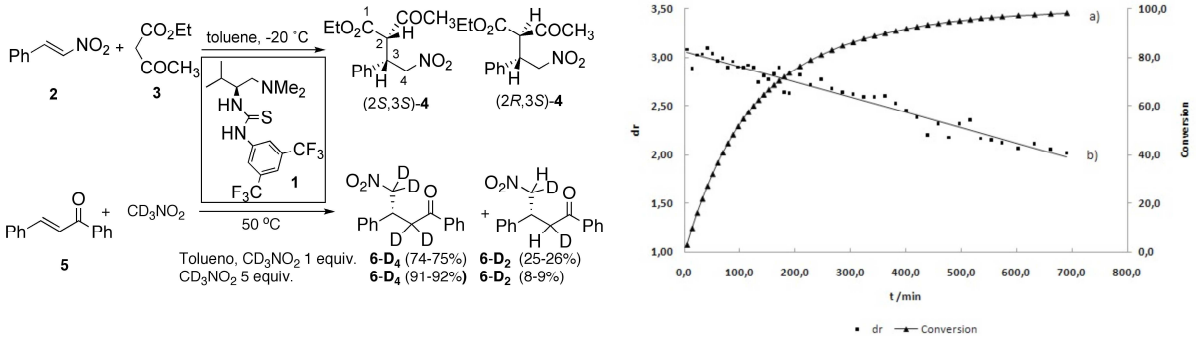
Desde el redescubrimiento de los procesos enantioselectivos catalizados por moléculas orgánicas pequeñas, la reacción de Michael, en sus diferentes versiones, ha sido uno de los procesos más estudiados.[1] Dependiendo de la naturaleza del núcleofilo es posible crear dos estereocentros contiguos con esteroquímica definida y su control es un problema asociado a la naturaleza de los organocatalizadores utilizados y las condiciones de reacción empleadas.

Los resultados descritos en la bibliografía y los nuestros propios[2] ponen de manifiesto que la selectividad estérea depende además de la naturaleza de los nuevos estereocentros creados. Mientras que se obtienen excelentes resultados en la formación de un único estereocentro, o de dos si uno de ellos es cuaternario, la diastereoselección es baja cuando ambos son terciarios.

En el trabajo se presentarán los resultados obtenidos en la adición de metilenos proquirales a nitroolefinas y de nitrometano a cetonas α,β-insaturadas (Esquema).

Se ha comprobado experimentalmente que la diastereoselectividad depende de las condiciones de reacción (tiempo, temperatura) aunque la enantioselectividad se mantiene constante y que, en todo caso, los productos de reacción se epimerizan en presencia del catalizador.



Esquema 1.

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CO-31

terc-Butil Hidrazona del Formaldehído en Nuevas Reacciones Hetero-Carbonil-Énicas Organocatalíticas Enantioselectivas

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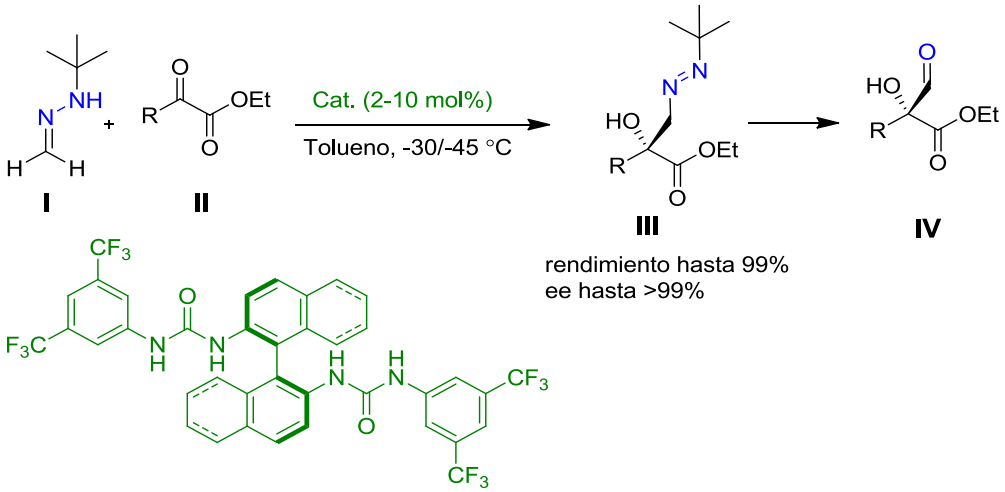
La adición 1,2 asimétrica de equivalentes sintéticos del anión formilo/acilo a compuestos carbonílicos es una herramienta sintética versátil para obtener carbinoles funcionalizados enantioenriquecidos.[1] En este contexto, nuestro grupo de investigación ha explotado el marcado carácter aza-enamina de las *N*,*N*-dialquilhidrazonas del formaldehído para la funcionalización 1,2 de diversos electrófilos,[2] pero este sistema no ha proporcionado niveles aceptables de enantioselectividad en adiciones organocatalíticas a compuestos carbonílicos. Por otro lado, Baldwin y *col*. demostraron la reactividad de monoalquil(aril) hidrazonas como equivalentes de aniones acilo en reacciones énicas térmicas con acrilato de metilo y acrilonitrilo.[3] En esta comunicación se presenta una reacción hetero-carbonil-énica sin precedentes entre la *terc*-butil hidrazona del formaldehído **I** y α-ceto ésteres **II** catalizada por *bis*-ureas derivadas del BINAM para la síntesis de diazenos **III** con excelentes rendimientos y enantioselectividades. Estos azo compuestos son precursores directos de los aldehídos **IV**, carbinoles terciarios de elevado valor sintético.



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CO-32

Regio- and Stereoselective Aziridination of Dienes. Application to the Synthesis of Sphingosine

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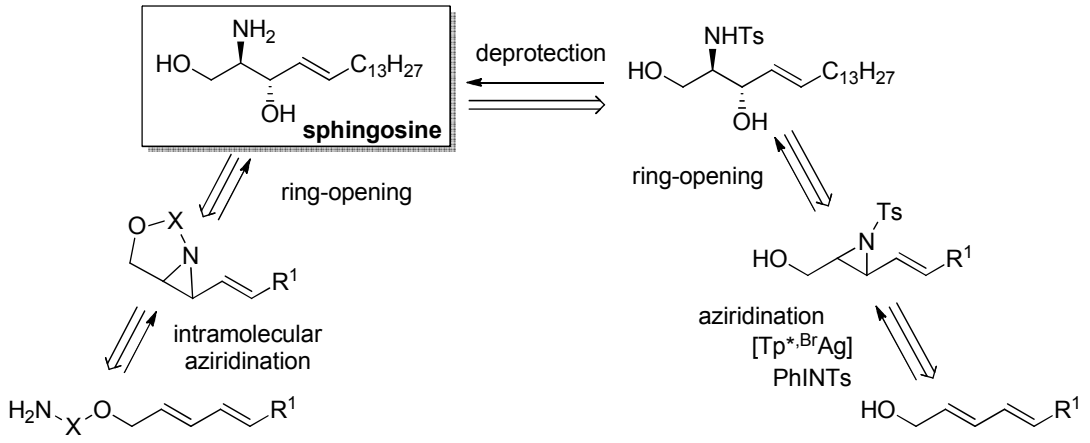
The synthesis of aziridine derivatives through metal-mediated nitrene addition reactions to olefins has been extensively developed in the last decades. [1] However, in spite of the synthetic interest of vinyl aziridines, only few reports have dealt with conjugated dienes as the substrate. Moreover, only symmetric dienes were employed in these cases and the selectivity, as *trans*/*cis* ratio was low. These two drawbacks strongly prevent the synthetic application of this method.

Looking for new and efficient methods for synthesizing sphingoid bases, especially D-*erythro*-sphingosine, we proposed a synthetic route based in the regio- and stereoselective synthesis of vinyl aziridines, which by a ring-opening reaction afforded precursors of the target compound. To achieve this objective, we studied the aziridination of non-symmetric 2,4-diene-1-ols using nitrene transfer protocols.



In this communication we present an efficient methodology for the aziridination of conjugated dienes bearing an allylic hydroxyl group, catalyzed by complexes containing Tp^xM fragment (M=Cu, Ag) and by using PhINTs as nitrene source.[2] The corresponding vinyl aziridines have been obtained with a low catalyst loading, with silver complexes being highly regioselective and stereospecific with an array of dienes. The study and scope of this methodology, its application to the synthesis of sphingosine as well as the preliminary work to develop an intramolecular version of the process will be presented.

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CO-33

Synthesis of α-Iminophosphonates Derived From Ketones. Applications to the Stereoselective Synthesis of Quaternary α-Aminophosphonates

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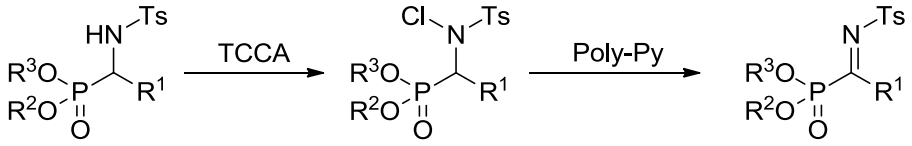
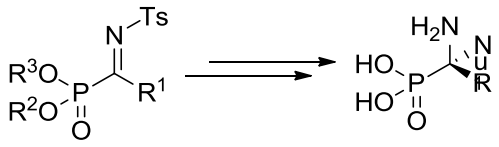
The synthesis of ketimines is, in general, more difficult than aldimines, due to the decreased reactivity of the parent ketones relative to aldehydes.[i] Although some α iminophosphonate molecules derived from aldehydes have been reported,[ii] the synthesis of α-ketiminophosphonate derivatives remains a challenge, due to the ability of the phosphonate group to undergo elimination and the intrinsic tendency of imines to hydrolyze. In this communication, the development of a methodology for the synthesis of α ketiminophosphonates **3** will be shown, through a formal oxidation of the parent aminophosphonates **1**, comprising a chlorination followed by elimination of HCl.



1 **2** **3**

The resulting α-iminophosphonates **3** derived from TADDOL phosphate can be used for the enantioselective synthesis of quaternary α-aminophosphonic acid derivatives **4** through catalytic asymmetric nucleophilic addition to the C=N iminic bond.



3 **4**

The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia e Innovación (MICINN, Madrid DGI, CTQ2009-12156) and by the Departamento de Educación, Universidades e Investigación del Gobierno Vasco and Universidad del País Vasco (GV, IT 422-10; UPV, GIU-09/57). J. V. thanks the Ministerio de Ciencia e Innovación for a "Ramón y Cajal" contract.

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Synthesis of enamides and indoles via cesium carbonate-promoted hydroamidation of alkynes. The effect of iron salts.

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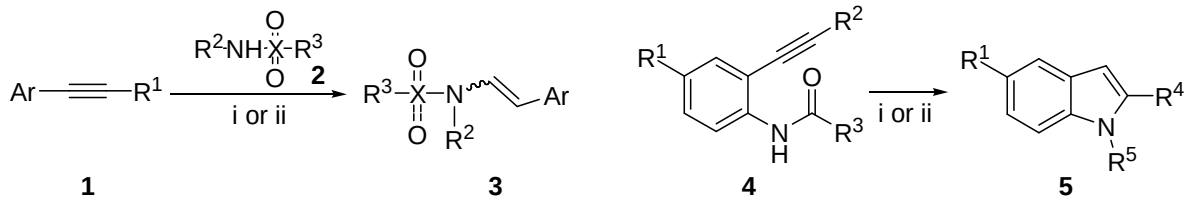
The abundance of enamide-like motifs in nature, synthetic drugs and relevant intermediates has encouraged research on new protocols for their preparation. Considering the relatively harsh conditions required for classic approaches or the limited availability of vinyl derivatives required for metal catalyzed cross-coupling reactions,[1] hydroamidation of alkynes has appeared as a very promising alternative approach.[2] This is the reason why we decided to follow our research on the development of methods for the synthesis of heterocyclic motifs by working on alternative procedures for the hydroamidation of alkynes, strategy that could provide not only valuable enamides but also nitrogen heterocycles via its intramolecular version.

As a result of our work, a number of enamides **3** were successfully synthetized by adition of amides **2** to alkynes **1** promoted only by Cs_2CO_3. The research showed that, in some cases, iron salts exerted a beneficial effect on reaction yields. The developed protocols were also applied to the cyclization of *ortho*-alkynilanilides **4** which enabled easy access to indole derivates.



1 **3** **4** **5**

i. Cs_2CO_3, PhMe, 150 ºC. ii.Cs_2CO_3, $FeCl_3$, py, PhMe, 150 ºC

It is worth pointing out that, although metal-catalyzed or base-promoted aminations of alkynes have been described, as far as we know, this is the first report on the use of such a mild base as cesium carbonate as the sole promoter of the reaction.

Acknowledgements: We thank the University of the Basque Country/Basque Government (Projects GIC10/52/IT-370-10, S-PC10UN10, UFI QOSYC 11/12) and the Spanish Ministry of Science and Innovation (CTQ2010-20703) for financial support.. Technical and human support provided by SGIker (UPV/EHU, MICINN, GV/EJ, ESF) is also gratefully acknowledged.

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[2] For selected examples: a) *J. Am. Chem. Soc.* **2011**, *133*, 7428; b) *J. Organomet. Chem.* **2010**, *696*, 170; Pd: c) *Adv. Synth. Catal.* **2010**, *352*, 2667; d) *J. Org. Chem.* **2010**, *75*, 3671; e) *Org. Lett.,* **2009** 11, 1309; f) *Adv. Synth. Catal.* **2011**, *353*, 2653.

CO-35

Fe(III) en la síntesis de oxaciclos de tamaño medio

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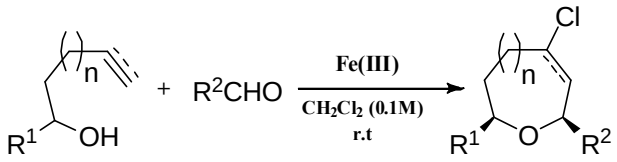
Los oxaciclos de tamaño medio son unidades estructurales presentes y ampliamente distribuidas en una gran variedad de productos naturales bioactivos sobre todo de origen marino.[1]

El desarrollo de nuevas tecnologías encaminadas a la síntesis de este tipo de oxaciclos ha crecido enormemente en los últimos años y se ha basado principalmente en dos tipos de estrategias de ciclación: a través de la formación de enlaces C-C y de enlaces C-O.[2] Sin embargo, la formación de oxaciclos de forma directa y simple no es obvia; se hace necesario productos de partida fácilmente accesibles y que la metodología controle la estereoquímica de las posiciones adyacentes al átomo de oxígeno. En este punto la ciclación de Prins se muestra como una metodología muy potente, ya que nos permite usando el catalizador adecuado, el acceso a este tipo de oxaciclos de forma directa. Usando catálisis con las sales de Fe(III) conseguimos, en un solo paso, ciclaciones que conllevan la formación de enlaces C-O, C-C y C-X con la estereoquímica controlada.[3] En esta comunicación se abordará un estudio sintético y mecanístico de la implicación del hierro (III) en esta ciclación.



n = 0, 1

Esquema 1: Síntesis de oxaciclos de tamaño medio mediante catálisis sostenible con Fe(III).

Agradecimientos: Este trabajo ha sido financiado por el Ministerio de Economía y Competitividad (MINECO), cofinanciado con fondos FEDER (CTQ2011-28417-C02-01 y CTQ2010-20714-C02-01, Consolider-Ingenio CSD2007-00006, S2009/PPQ-1634). MAP agradece a la ULL por la concesión de una beca SEGAI. SJP agradece al MINECO una beca FPU. IF agradece la concesión de un contrato RyC.

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CO-36

Development of a New Library of Neurokinin 1 Receptor Antagonists Based on a Ligand-Supported Homology Model

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The neurokinin-1 (NK1) receptor belongs to the family of G-protein-coupled receptors (GPCRs), which represents one of the most relevant target families in small-molecule drug design.[1] The NK1 receptor mediates responses to, e.g., visual, olfactory, hormonal, or neurotransmitter signals. Based on the structural requirements of the recently published NK-1 pharmacophore,[2] in this communication, we present part of our ongoing research directed toward the use of 2-amino-4-*H*-pyrans[3] (Figure 1) as a new family of NK-1 antagonists.

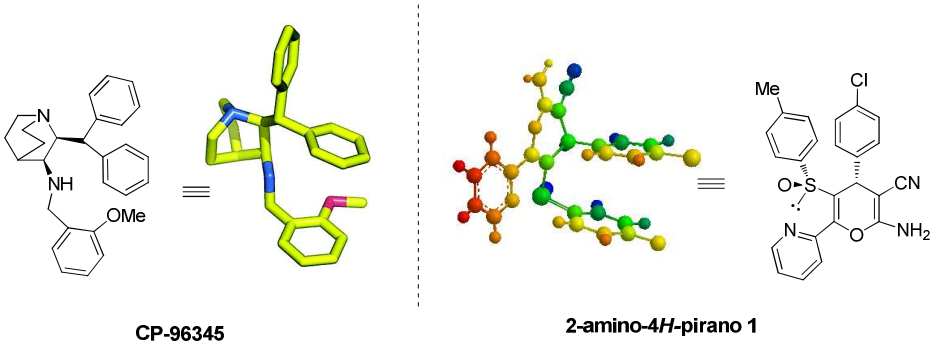

Figure 1

In silico studies on the conformational space of these compounds showed good matching between non-peptidic antagonist CP-96345-NK1 complex and 2-amino-4-*H*-pyrans- NK1 interactions (figure 1). Moreover, optimization with "onion method"[4] gave a good correlation between the calculated ligand-receptor interaction energies and the corresponding ligand activities, experimentally determined as NK-1 binding affinity in IPone test.[5]

Acknowledgements: Financial supports from the "Ministerio Economía y Competitividad" (grant No. CTQ2010-21755-C02-02) and the "Junta de Andalucía" for financial supports for scientific stays.

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CO-37

Polyatomic anion assistance in the assembly of [2]pseudorotaxanes based on Calix[4]pyrrole macrocycles

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Rotaxanes are mechanically locked structures with potential application in molecular machinery.[1,2] A key intermediate for their construction is the non-covalent pseudorotaxane, where a linear molecule is threaded through the annulus of a macrocycle.[3] We present the synthesis of a homoditopic calix[4]pyrrole macrocycle that exhibits H-bonding complementarity with ditopic linear *meta*-bis-amide-pyridyl-*N*-oxides inducing the assembly of non-covalent neutral interwoven receptors. These receptors have pseudorotaxane topology and its components feature a binding site cavity of six convergent hydrogen bond NH donors: two from bound bis-amide and four from the opposing calix[4]pyrrole cap of the macrocycle. The complexation of bidentate polyatomic anions that are complementary in size and shape to the receptor's cavity induces the exclusive formation of four particle threaded assemblies.[4] We are currently involved in exploting this self-assembly methodology for the synthesis of rotaxanes by stoppering the pyridyl-*N*-oxide diamide with porphyrin units. Most likely, these interlocked molecules will present interesting properties as polyatomic anions receptors.

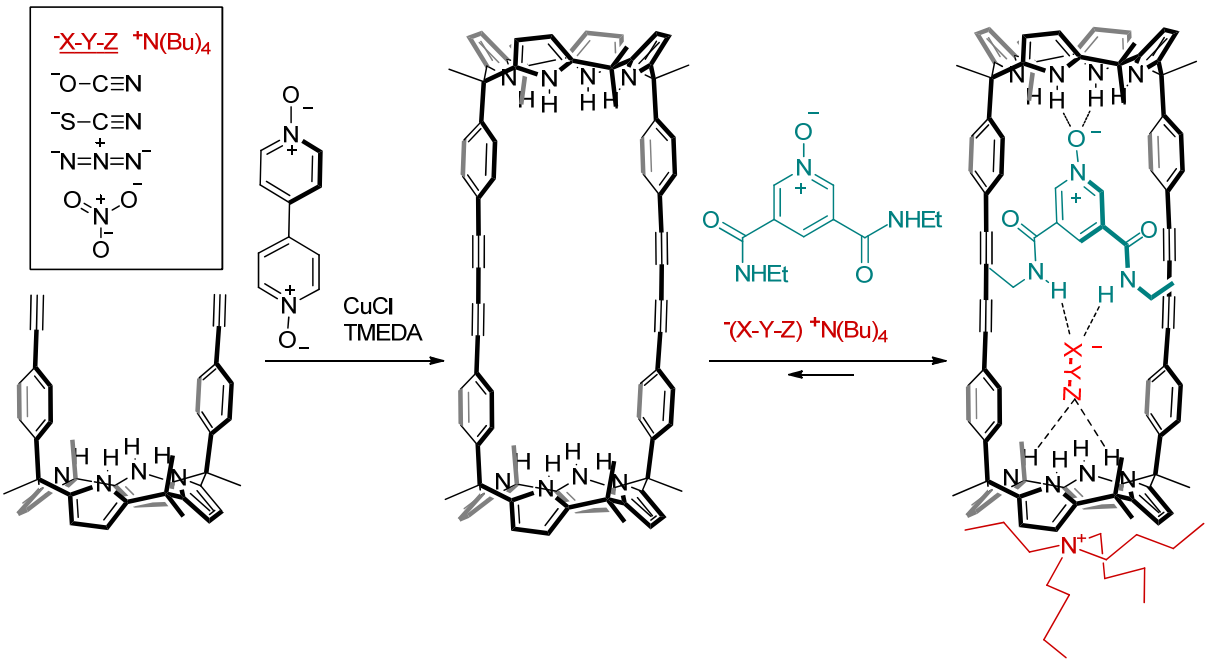

Figure 1. Synthetic scheme for the preparation of a homoditopic calix[4]pyrrole macrocycle used in the quantitative self-assembly pseudorotaxane formation mediated by polyatomic anion template effect.

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CO-38

Pyrido-allenophanes as promising chiral molecular switchers and molecular channels

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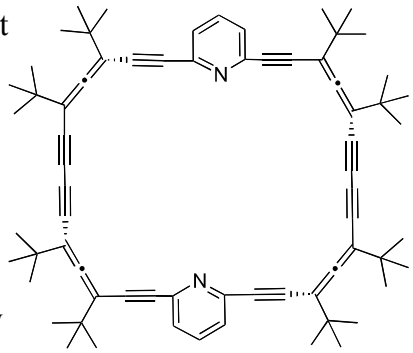
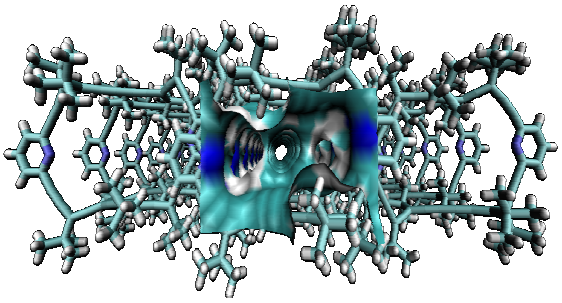
Chiral shape-persistent macrocycles containing signaling or responsive functional groups as an integral part of the macrocyclic framework are of great interest because they offer the possibility for chirality sensing, chiral molecular recognition, and chiral self-assembled architectures. In particular, allenophanes are attractive compounds for creating new nonplanar, chiral topologies and for developing new functional materials. We previously reported the synthesis of (2,5)pyrido-[7_4]allenoacetylenic cyclophanes, in which para-substituted pyridine rings allow direct communication between diethynylallenes attached to the aromatic core.[1] However, free rotation of the pyridine ring makes difficult the analysis of the relationship between electronic and chiroptical responses. This rotation can be locked by changing para to meta-substitution. Hence, we present herein the synthesis, and characterization of the chiral meta-substituted (2,6)pyrido[14_2]allenophane **1**. All isomers were characterized through their symmetry properties revealed in NMR, CD, ORD, and single crystal X-ray diffraction studies.[2]

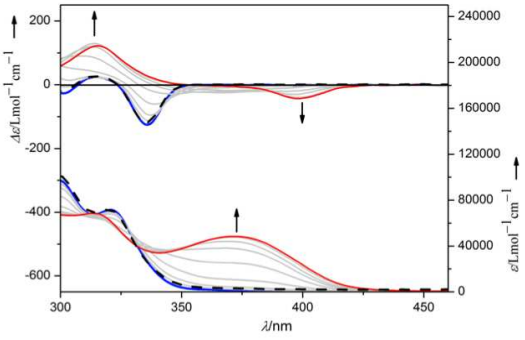


(*P*,*P*,*P*,*P*)-2,6-Pyridoallenophane **1**

The chiral (+)-(*P*,*P*,*P*,*P*)-**1** behaves as a reversibly switchable bistable system with very different CD spectra upon pH change. Moreover, the structural channels formed by this molecule in the solid state show the potentiality of these systems as encapsulation hosts.[3]



Channels along the crystallographic *b* axis of (*P*,*P*,*P*,*P*)-**1**



Change of the UV/Vis and CD spectra of (*P*,*P*,*P*,*P*)-**1** upon addition of TFA. [TFA] = 0 (blue solid line) to 0.38 M (red solid line). UV/Vis and CD spectra after addition of Et_3N in dashed black line.

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CO-39

Functional Oligothienylenevinylene-based Materials for optoelectronics

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Linear π-conjugated oligomers with well-defined chemical structures have been used as molecular wires in molecular electronics or nanoscopic systems; among the different π-conjugated oligomers, oligothienylenevinylene (*n*TVs) are excellent wires besides good electron donors. Here, we will report on the synthesis and properties of some new derivatives (Figure 1) were *n*TVs behave as wires in different systems, in donor-bridge-acceptor linking porphyrins and fullerenes,[1] were the phophysical events were studied, and in acceptor-bridge-acceptor or donor-bridge-donor systems, studying the mixed valence systems.[2] This type of oligomers has also been used as dyes in dye sensitized solar cells.[3]

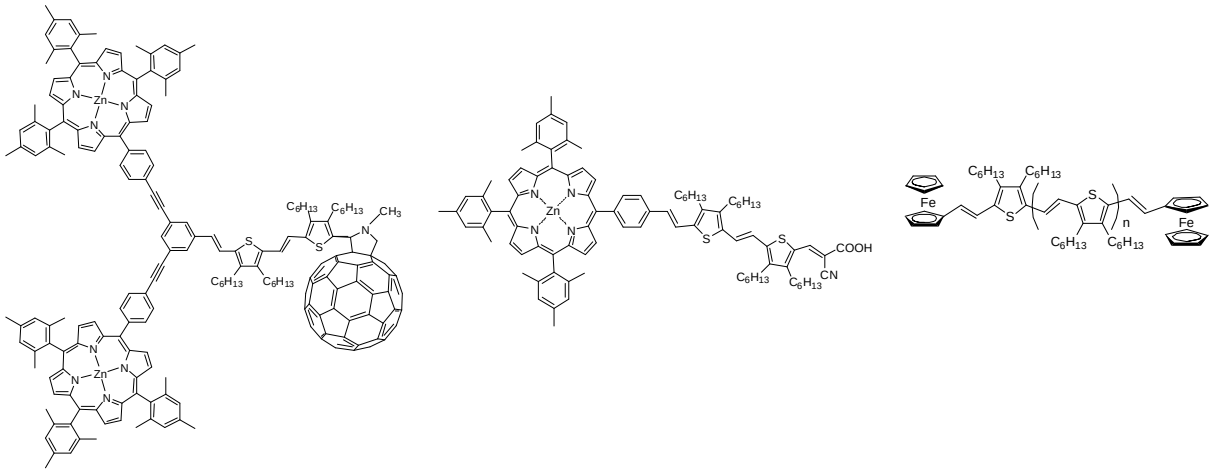

Figure 1

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CO-40

Supramolecular discotic liquid crystalline phosphorous dendrimers decorated with 15-membered triolefinic azamacrocycles

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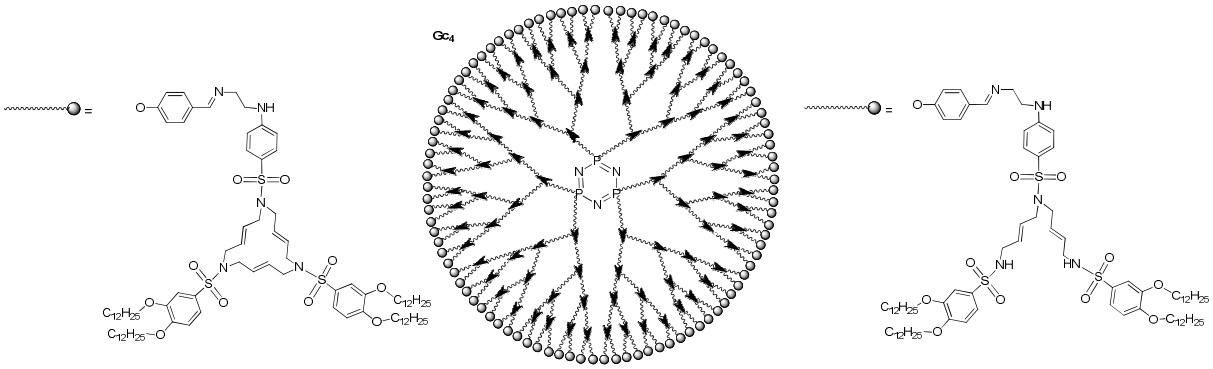
Supramolecular assemblies of disc-shaped compounds into columnar mesophases have been widely investigated for several applications, such as one-dimensional conductors, light-emitting diodes, photovoltaic solar cells and polar switchable phases.[1] The advantages of supermolecular liquid crystals usually arise from their high molecular weights, which provide them with properties similar to those of liquid-crystal polymers (i.e. processability) but starting from monodisperse molecules with a well-defined structure. This fact leads to more reproducible properties in comparison with polymeric materials. Most of these supermolecular liquid crystals are usually based on a dendritic central core upon with mesogenic units are linked, generally on the periphery.[2]

We have prepared and studied the mesomorphic properties of a new series of phosphorous dendrimers derived from cyclotriphosphazene (Gc_0, Gc_1 and Gc_4) decorated on the surface with 15-membered triolefinic azamacrocycles as promesogenic units[3] (6, 12 and 96 cycles respectively). All the compounds exhibit liquid crystalline properties which were studied by optical microscopy, DSC and X-ray diffraction. Models for the supramolecular organizations on the mesophases will be proposed.



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CO-41

Refuerzo del Reconocimiento Quiral

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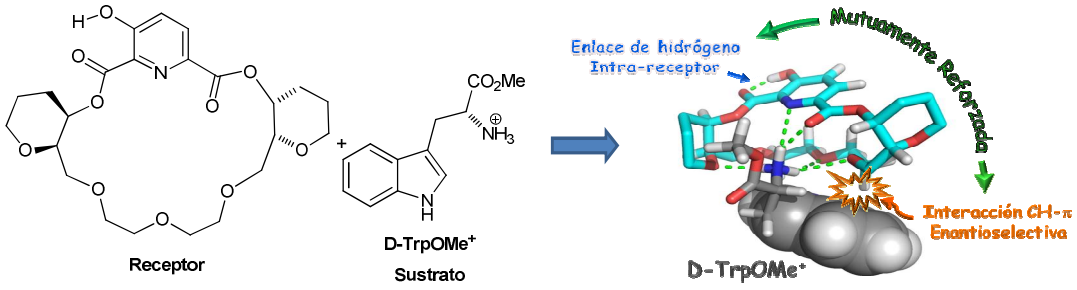
Numerosos procesos biológicos y químicos tienen como etapa determinante el fenómeno de reconocimiento quiral. Varios factores participan en la enantiodiscriminación, sin embargo, es bien sabido que las interacciones no covalentes juegan un papel fundamental como los principales factores en el reconocimiento quiral.
Dentro de nuestro programa orientado a la búsqueda de nuevas unidades estructurales apropiadas para el reconocimiento de cationes, hemos centrado nuestra atención en la unidad de 2-oxymethyl-3-oxi tetrahidropirano, como motivo estructural para el diseño de nuevos receptores quirales de cationes.[1] Recientemente, hemos sintetizado un nuevo receptor que muestra una alta enantiodiscriminación con sales de amonio quirales, y demostramos que una sola interacción CH-π es la principal responsable de este evento.[2] A través del diseño hemos podido sintetizar un receptor análogo al anterior que muestra una cooperatividad positiva bastante peculiar que surge del refuerzo mutuo entre las interacciones receptor-sustrato y las interacciones no-covalentes internas del receptor, las cuales no participan directamente en la complejación.[3] Este tipo de cooperatividad ha sido escasamente descrito en receptores sintéticos, sin embargo, se considera como una de las grandes responsables de la alta afinidad de los receptores bióticos. En nuestro sistema, demostramos que existe un enlace de hidrógeno intra-receptor, que no participa directamente en el reconocimiento del aminoácido, pero que es capaz de reforzar una interacción CH-π entre el receptor y el sustrato. Debido a que dicha interacción CH-π se forma exclusivamente con el enantiómero D del sustrato, su refuerzo conlleva un refuerzo de la discriminación quiral.



Agradecimientos: Esta investigación está financiada por MICINN-FEDER (CTQ2008-03334 y CTQ2011-22653). AFV agradece al MICINN por la beca pre-doctoral FPU.

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CO-42

Reacciones de Kumada con haluros heteroaromáticos y aril éteres catalizadas por el complejo [(IPr)Ni(π-alilo)Cl]

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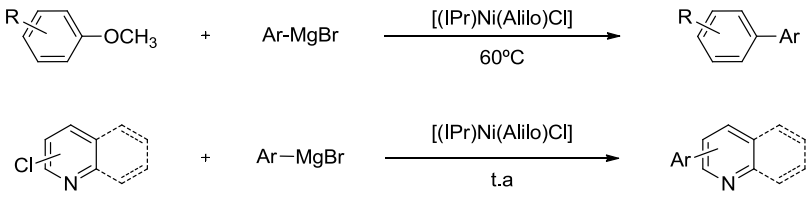
Las reacciones de acoplamiento cruzado catalizadas por metales de transición son herramientas muy importantes para la construcción de nuevos enlaces C-C.[1] En este sentido, las denominadas reacciones de Kumada, que implican la utilización de reactivos de Grignard, ofrecen acceso directo a los productos deseados con una alta economía atómica. En estas reacciones, los electrófilos más empleados son los yoduros y bromuros de arilo siendo escasos los ejemplos descritos con electrófilos más débiles como los cloruros orgánicos[2] o los basados en derivados de fenol, como los éteres.[3] Recientemente, nuestro grupo de investigación ha descrito con éxito la activación del enlace C-Cl de haluros de arilo en reacciones de formación de enlaces C-N llevadas a cabo a la temperatura ambiente, empleando el complejo [(IPr)Ni(π-alilo)Cl] como catalizador.[4] En esta comunicación se describe la actividad catalítica de dicho complejo en reacciones de Kumada empleando cloruros heteroaromáticos y aril éteres como electrófilos.



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CO-43

Hidrazonas como grupo director y ligando en la borilación *orto*-dirigida de arenos.

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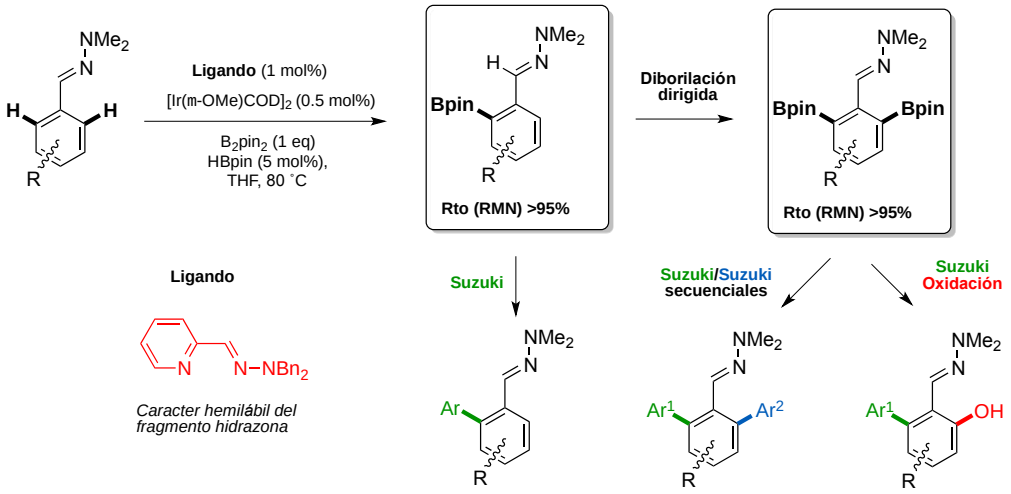
La borilación directa de enlaces C-H de arenos desarrollada por Smith, Hartwig, Miyaura y Marder,[1] ha alcanzado un alto nivel de eficiencia química para el sitema que se basa en el empleo de B_2pin_2 (pin = $Me_4C_2O_2$) or (HBpin) como agente borilante y $[IrX(cod)]_2$ (X = Cl, OMe) / bpy o *t*Bu-bpy como precatalizador. La regioselectividad de esta reacción está típicamente controlada por factores estéricos, y salvo excepciones como el empleo de grupos sililéter[2] o éster[3] como grupos *orto*-directores, la borilación tiene lugar enlace C-H menos impedido. El análisis del mecanismo ha permitido a nuestro grupo de investigación el desarrollo una nueva metodología para la borilación *orto*-dirigida de 2-arilpiridinas e isoquinolinas así como de hidrazonas aromáticas.[4] El método se basa en el caracter hemilábil de ligandos como piridino-hidrazonas, y ha sido extendido a la diborilación *orto,orto'*-dirigida de *N,N*-dimetilhidrazonas aromáticas, cuyos productos pueden ser derivatizados secuencialmente mediante acoplamientos Suzuki–Miyaura sucesivos o acoplamiento seguido de oxidación.[5] La interacción disimétrica del grupo hidrazona con ambos grupos borilo juega un papel fundamental en la selectividad.



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CO-44

Dendritic Phosphoramidite Ligands for Rh-catalyzed [2+2+2] Cycloaddition Reactions: Unprecedented Enhancement of Enantiodiscrimination

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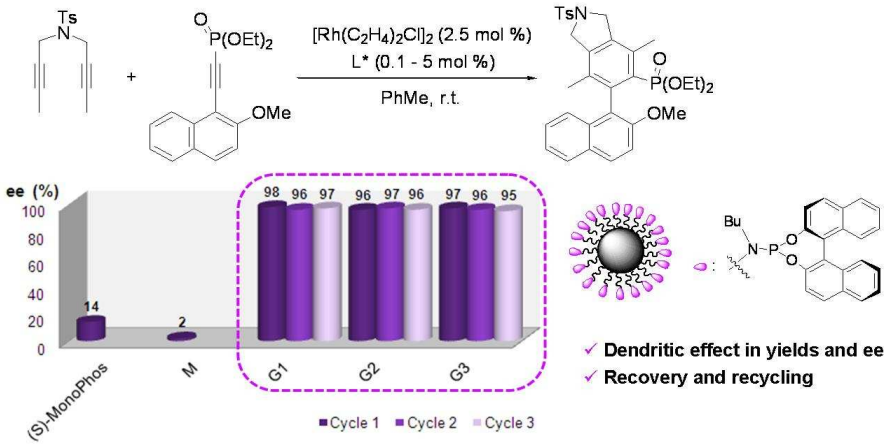
The metal-catalyzed [2+2+2] cycloaddition reaction of three alkynes is a powerful method for the construction of polysubstituted benzenes.[1] Some catalysts based on transition metals have been shown to catalyze effectively the [2+2+2] cycloaddition but the recovery and reuse of the catalyst is an unresolved aspect in the study of this kind of processes.

Dendrimers,[2] nano-objects with astonishing applications in areas ranging from biology to material science, have also been successfully applied in catalysis. The precise incorporation of ligands in the different domains of the dendrimeric structure has enabled the complexation of metals leading to good catalysts in a number of reactions, which can furthermore be easily recovered and reused.

We present here the synthesis of phosphorus dendrimers from generation 1 to 3 containing terminal phosphoramidite ligands. These new materials have been found to be highly effective catalysts for the rhodium(I) catalyzed [2+2+2] cycloaddition. A strong positive dendritic effect is observed both in the activity and enantiodiscrimination leading to axially chiral biaryl compounds. Moreover, the dendrimeric catalyst can be recovered and reused in these alkyne cycloadditions with no significant reduction in the yields and enantioselectivities obtained for three consecutive cycles.



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CO-45

Organocatalysis and controlled release with amino acid-derived molecular gels.

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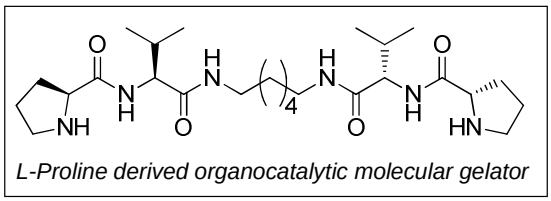
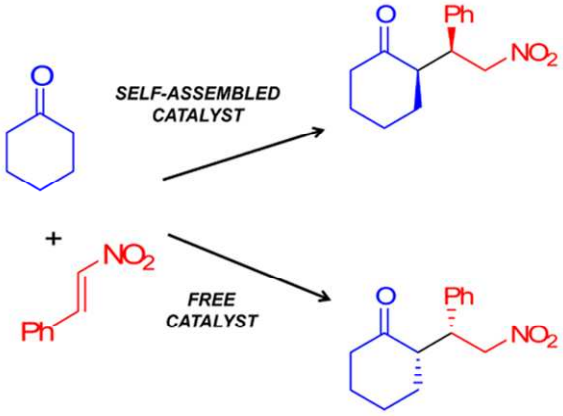
Molecular gels are formed by aggregation of low molecular weight species into nano(micro)fibrilar structures that preclude solvent fluxion. Therefore, this type of soft material contains a very finely divided solid (the nanofibrilar network) with a very high aspect ratio. The introduction of appropriate functionalities in the gelator molecules allows for the preparation of functional molecular gels with applications, among other areas, in catalysis. Additionally, molecular gels are stimuli responsive smart materials that can be used, for example, in controlled release.[2]

The incorporation of L-Proline amino acid in the gelator structure provides organocatalytic organogels with application in nitroaldol (Henry) reaction and conjugate addition of cyclohexanone to *β-trans*-nitrostyrene. Hydrogels are also prepared which are active and efficient catalysts in the direct aldol reaction.[3]

On the other hand, molecular gels sensitive to different chemical stimuli such as aldehydes, pH, phenolic derivatives or enzymes have been prepared and studied in controlled release of entrapped substances.[4]





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[1] Now at Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands.

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CO-46

Tuning Chloride Binding, Encapsulation and Transport by Peripheral Substitution of Pseudopeptidic Tripodal Small Cages

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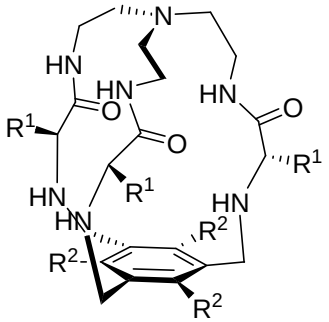
The synthesis of small pseudopeptidic cages[1] from simple precursors has been achieved by an efficient triple S_N2 reaction where the success of the macrobicyclization strongly depends on the correct pre-organization of the intermediates. The chloride binding[2] abilities of the protonated pseudopeptidic cages have been studied in the solid state (X-ray diffraction), in solution (NMR and ESI-MS) and gas (CID MS) phases. Both the amino acid side chain (R^1) and the substitution in the aromatic tripodal ring (R^2) have a strong impact on the chloride binding properties. According to the obtained structural data (X-ray and NMR), we propose a different mode of binding depending on the receptor structure. Finally, the transport of the chloride anion through lipid bilayers as a model for cell membranes[3] has been studied for selected cages, showing important differences due to the receptor structure. Thus, slight changes in the structure of these pseudopeptidic cages produce important differences as chloride receptors and transporters, even bearing essentially the same binding pocket.



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CO-47

Electroactive Molecules on Surface for Charge-Storage Memory Devices

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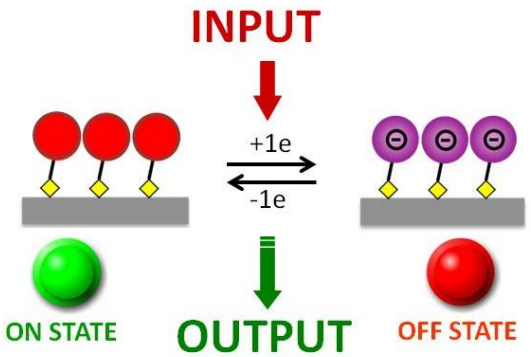
The increasing interest in miniaturizing electronic devices to achieve denser circuits and memories will eventually entail the utilization of molecules as active components. In particular, self-assembled monolayers of bi-stable molecules offer great perspectives to develop memory devices.

Here, we describe the functionalization of surfaces (SiO_2, ITO and Au) with appropriately functionalized polychlorinated triphenylmethyl (PTM) radicals. Such hybrid organic/inorganic surfaces behave as chemical and electrochemical redox switches with bistable optical (absorption and fluorescence), wettability and magnetic responses. Importantly, these systems exhibit an exceptionally high long-term stability and excellent reversibility and reproducibility.[1] Moreover, these surfaces can be patterned as well as electrochemically locally addressed.

Further, following the same methodology, the switch behaviour of surfaces functionalised with other electroactive molecules such as tetrathiafulavalenes has also been investigated.[2] These systems exhibit three-stable states and, thus, can allow for the execution of more complex logic operations.

All these robust molecular platforms permit hence to write, store and read information, which is very promising for developing non-volatile memory devices based on immobilized molecules, of great interest in Molecular Electronics.



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CO-48

Click Assembly of Di-Functionalized Octasilsesquioxanes and Their Application in Bioimaging

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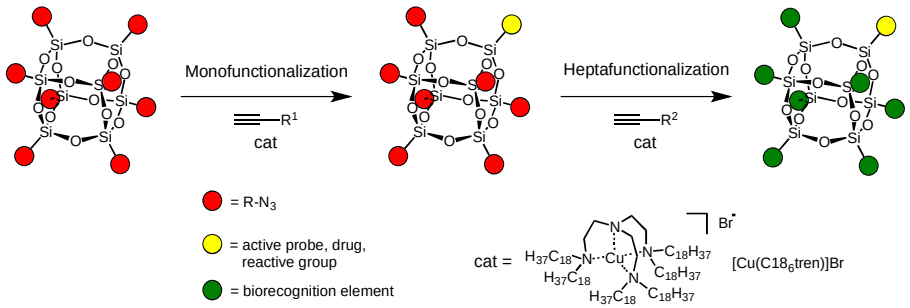
The synthesis of cubic octasilsesquioxane platforms (POSS)[1] with two different reactive functional groups is a complex and as yet largely unsolved problem of great importance for the development of new hybrid nanomaterials. The functionalization of the POSS core with both a bio-recognition element (e.g., a peptidic or carbohydrate epitope) and an "active" molecule, such as a fluorescent dye, a magnetic resonance imaging probe or a drug will open potential applications as bioimaging agents for the study of biological receptors and for vectorized drug transport.



The irreversible character and high efficiency of the CuAAC reaction could allow controlling the degree of functionalization by a judicious selection of the stoichiometry of the reactants and the catalytic system used for the reaction. Armed with this efficient synthetic methodology, we have prepared a series of difunctionalized POSS derivatives (scheme), including a fluorescent glyco-POSS equipped with a BODIPY dye and seven carbohydrate units that we have tested as bioimaging agent for dendritic cell membrane receptors.

Acknowledgements: This work was supported by the former Ministerio de Ciencia e Innovación (project MAT2010-20646-C04-03), and by the European Social Fund and Comunidad de Madrid (project S2009/PPQ-1634 "AVANCAT"). CSIC is gratefully thanked for a JAEPRE contract to M.E.P.O.

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CO-49

Chemo-enzymatic preparation of N-glycan arrays and their Applications

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Glycan arrays have emerged as versatile platforms in Functional Glycomics for the high-throughput screening of binding specificities for lectins and antibodies or to determine the substrate requirements of carbohydrate processing enzymes.
A remaining major bottleneck for a more extended use of glycan arrays is the supply with sufficiently pure and well-characterized ligands. Focusing on N–glycans our laboratory has combined the synthesis of N-glycan core structures with their enzymatic modification on the chip using recombinant glycosyltransferases to generate a library of structures with systematic variations in number of antennae, terminal sugars and core modifications.[1-3] A surface-based MALDI-Tof MS method has been developed to evaluate the enzymatic on-chip glycosylation[4] and as a powerful tool to analyze biomass degrading enzymes in environmental samples.[5]
The printed and modified glycan arrays have been employed in the screening of substrate specificities of carbohydrate processing enzymes[6] and to determine lectin and antibody specificity employing fluorescent, MALDI-Tof[4] and autoradiography as complementary readout techniques.

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PRESENTACIONES *FLASH*

Flash-1

C_2 Symmetric Bis-Sulfoxides as Chiral Ligands in Rh(I)-Catalyzed 1,4-Addition of Boronic Acids to Activated Ketones

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In the last decades, chiral sulfinyl derivatives have been used with success in a plethora of asymmetric chiral C-C and C-X bond formation.[1] Surprisingly, despite their interesting metal-coordinating abilities, the great efforts devoted to their applications in asymmetric catalysis have met with little success. Within our interest toward the synthesis of chiral sulfinyl derivatives,[2] and their applications in organic and organometallic asymmetric catalysis,[3,4] in the present work we report our preliminary results on the synthesis of C_2-Symmetric bis-sulfoxides "BiSox" and their application in highly enantioselective 1,4-addition of boronic acids to cyclic and acyclic α,β-unsaturated ketones. The designed "BiSox" ligands **I**, Figure 1, with a chiral sulfur atom as the sole chiral center are obtained by the Cu(I) catalyzed dimerization of methylsufoxides, obtained in high enatiopurity using the DAG methodology.[2]

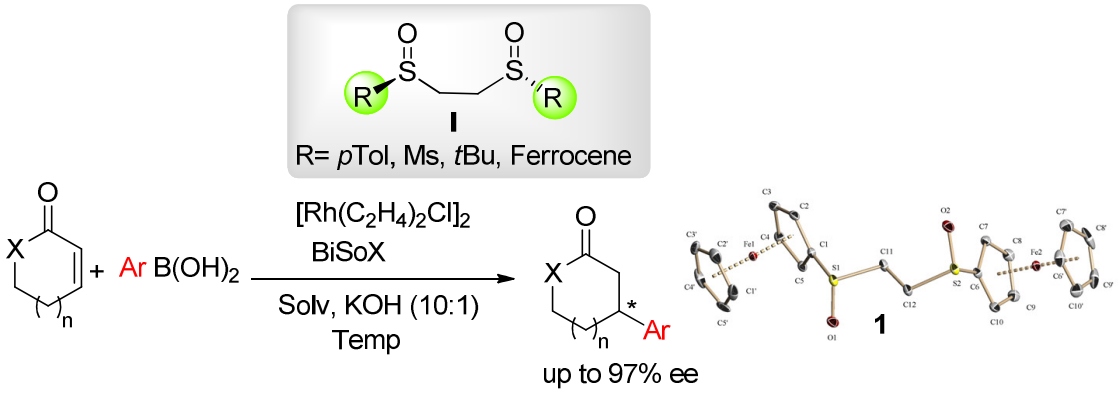

Figure 1.

The screening of this new family of ligands in the model reaction of 2-cyclohexanone and phenyl boronic acid, reveals that bis-ferrocenylsulfoxide **1** is the optimal ligand. Indeed, ligand **1** exhibits an excellent behavior and general electrophile scope, such as cyclic enones, lactones and, what is more interesting, the challenging acyclic substrates. These and others investigations directed toward the determination of the scope and limitations of the "BiSox" ligands will be discussed in this communication.

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Aerobic Oxidations Catalyzed by Palladacyclic Compounds

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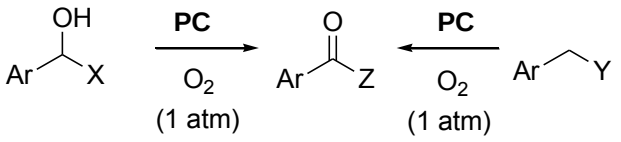
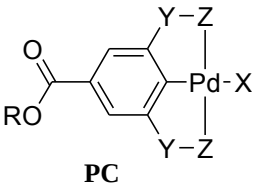
Considering environmental and safety issues, oxygen is an ideal oxidant for organic transformations. Aerobic oxidation of alcohols has been successfully applied to several types of hydroxy derivatives, including 1,2-diols and polyols, α-hydroxy- and alkoxy-carboxylic acids, simple aliphatic, allyl and benzyl alcohols, *inter alia*.[1] To be precise, much effort has been devoted to the aerobic oxidation of benzyl alcohols, and on the basis of the higher selectivity and efficiencies observed, several palladium sources have been employed as catalysts for this reaction. However, relatively high amounts of palladium salts and/or complexes (0.1-10 mol% of Pd) are required,[2] and problems arising from the removal of palladium traces from final products still remain.

In this communication, we wish to present the application of several pincers as catalysts in aerobic oxidation of benzyl alcohols and methylene compounds. A number of products have been synthesized by procedures based on the use of infinitesimal amounts of palladium pincers in environmentally friendly media. Further details about reaction scope and experimental conditions will be discussed.



X, Y: H, R
Z: H, OH, R



PC

R: H, Me, Et
Y, Z: C, N, O
X: Br, Cl, $OCOF_3$

Acknowledgements: This research was supported by the University of the Basque Country (UPV/EHU)/Basque Government (Projects GIC10/52/IT-370-10) and the Spanish Ministry of Science and Innovation (CTQ2010-20703). G.U. thanks UPV/EHU for a predoctoral scholarship and for financial support (UFI QOSYC 11/22). Finally, technical and human support provided by SGIker (UPV/EHU, MICINN, GV/EJ, ESF) is gratefully acknowledged.

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Flash-3

Novel Oxamate-Containing Palladium(II) Catalysts for Cross Coupling Carbon-Carbon Reactions

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[b] *Equipe de Chimie Moléculaire, Matériaux et Modélisation- C3M, Faculté Polydisciplinaire de Safi, Université Cadi Ayyad, Safi, Morocco.*

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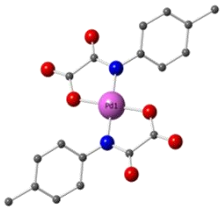
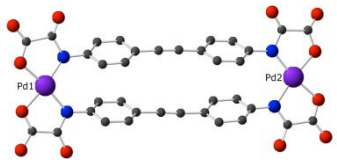
The palladium-catalyzed carbon-carbon coupling reactions, namely Suzuki and Heck reactions have received considerable attention, primarily due to the synthetic potential to generate *sp*-*sp* and sp^2-sp^2 carbon-carbon bonds. Several approaches towards the catalyst design and its improvement have been described. Most efforts focused on electron-poor chloroarenes by the use of highly basic, sterically hindered phosphines, *N*-heterocyclic carbenes (NHC), palladacycles, a large excess of coordinating ligands such as triphenylphospine or colloidal palladium nanoparticles.[1]

In search for new free-phosphine, highly stable and water-soluble palladated catalysts; we developed new palladium (II) complexes based on the use of oxamate type ligands. In fact, these ligands are very versatile and their preparation is straightforward and very cheap. The electronic state and steric environment of the palladium center can be modulated by fine-tuning these ligands, in view of controlling the catalytic reactivity/selectivity of the palladium(II)-oxamate system in carbon-carbon bond cross coupling processes.[2]

In the present communication, we focus on the preparation and structural characterization of mono- and dinuclear oxamate-containing palladium(II) complexes with different alky/aryl-substituted oxamate ligands. The successful use of these palladium complexes as catalysts for both Suzuki and Heck reactions in a variety of solvents such as organic, water and ionic liquid media shows their potential as promising robust, multifunctional and greener catalysts for synthetic targets involving cross-coupling reactions.



Perspective view of the mononuclear [Pd(*N*-4-methylphenyloxamate]$^{2-}$ anion unit



Perspective view of the dinuclear [Pd(*N,N'*-4,4'-Diphenylethynedioxamate]$^{2-}$ anion unit

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Flash-4

Síntesis de oxaciclos de nueve eslabones mediante hidroarilación de alenos catalizada por oro

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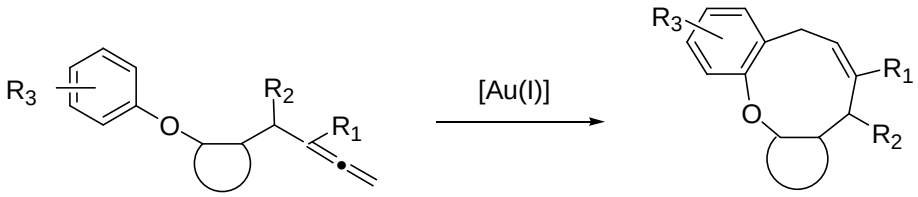
En la última década, el número de reacciones catalizadas por complejos de oro ha aumentado notablemente, debido a su comportamiento como ácidos de Lewis suaves. Por otro lado, los alenos han pasado de ser una mera curiosidad de laboratorio a convertirse en un grupo funcional versátil con una reactividad única, permitiendo a los químicos preparar una gran variedad de compuestos de alto interés químico y biológico. La mayoría de las reacciones de carbociclación intramolecular catalizadas por oro en alenos utilizan como nucleófilos anillos aromáticos o heteroaromáticos ricos en electrones,[1] permitiendo la síntesis de anillos de cinco o seis eslabones. Continuando con nuestro estudio sobre procesos catalizados por metales y química de alenos,[2] se describe por primera vez una carbociclación 9-*endo* de alenil-arenos catalizada por oro, como una herramienta sintética útil para la obtención de oxaciclos de nueve miembros benzocondensados.



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Flash-5

Synthesis of 2-Indol-3-ylbenzofulvenes through a Tandem Reaction Catalyzed by Cationic Au(I) Complexes

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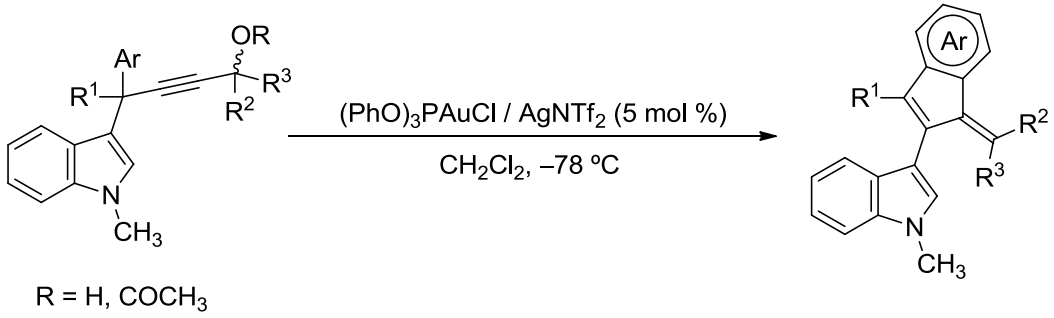
Benzofulvenes are interesting compounds that have found versatile applications in material science, as precursors of indenyl ligands and other indene derivatives, and in medicinal chemistry. On the other hand, tandem reactions posses a great interest because they offer a convenient and economical manner to access to complex organic molecules from simple starting materials in a one-pot process.

In the last years, we have been involved in the study of the reactivity of 3-propargylindoles in the presence of cationic gold complexes.[1] We have found that the indole nucleus is able to undergo a 1,2-migration process triggering a metalla-iso-Nazarov reaction affording 2-(indol-3-yl)indene derivatives. As propargilic esters are also able to undergo different tandem reactions started by 1,2- or 1,3-acyloxy migrations, we wondered about the reactivity of an internal alkyne containing an indole at one of the propargylic positions and an acetate group at the other propargylic position.



Scheme 1.

In this communication, we report the behavior of 3-propargylindoles possessing an additional acetate/hydroxyl group at the other propargilic position under gold-catalysis (Scheme 1). New benzofulvenes derivatives bearing an indol-3-yl substituent at C-2 were formed indicating that the migration of the indole has selectively occurred.

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New Pd-Catalyzed Cross-Coupling Reactions of α-Alkoxytosylhydrazones and Aryl Nonaflates

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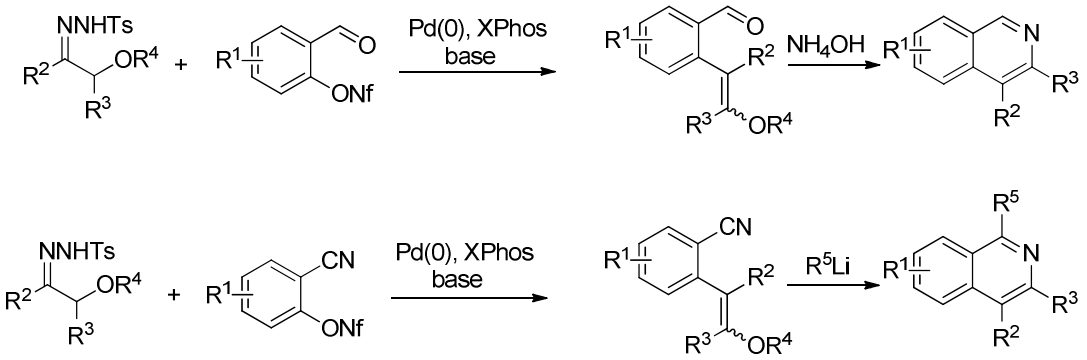
Pd-catalyzed cross-coupling reactions can be considered nowadays amongst the most reliable methods for the formation of $C(sp^2)$- $C(sp^2)$ bonds.[1] In our research group, it was recently developed an efficient synthesis of polysubstituted olefins through a new type of Pd-catalyzed cross-coupling reaction that employs *N*-tosylhydrazones as nucleophilic coupling partners and organic halides as the electrophiles.[2] Continuing with our interest on this transformation, we have expanded the scope of the reaction to the employment of sulfonates as nucleophilic partners giving rise to the polysubstituted olefins in very high yields and high stereoselectivity.[3]

In this context, we have recently uncovered a new Pd-catalyzed cross-coupling reaction of *o*-functionalized nonaflates, readily available from salicyl aldehydes or *o*-cyanophenols, with α–alkoxytosylhydrazones. This transformation gives rise to protected 1,5-dicarbonyl and 1-cyano-5-carbonyl derivatives, that are useful intermediates in heterocyclic synthesis. This transformations have been applied to the preparation of isoquinolines substituted at any position of the heterocyclic ring.[4]



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Flash-7

A New Mode of Cyclization of Enynes. Synthesis of Cycloalkyl Ketones through a Platinum-Catalyzed Hydrative Cycloisomerization Reaction

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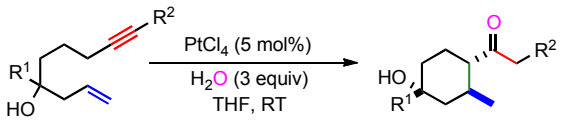
The use of π-acids in homogeneous catalysis has emerged from a mere curiosity a few years ago to a now very useful tool to achieve reactions of value.[1] Particularly interesting is the application of these carbophilic Lewis acids in the catalytic cycloisomerization of enynes.[2] In this context, we have recently developed an efficient method for the preparation of [3.3.1]bicyclic compounds from easily available enynol derivatives[3]
Following our interest on this kind of reactions, we have discovered a new cascade reaction catalyzed by platinium(IV) chloride that may be considered as an unusual cyclization of enyne derivatives. Details on this process are given in this communication.



This operationally simple, air- and moisture-tolerant reaction affords diastereomerically pure cycloalkyl ketone derivatives in a straightforward manner. The global process could be considered as an unprecedented abnormal platinum-catalyzed cyclization of enynes. The role of the platinum-catalyst promoting at least three different reactions in this auto-tandem catalytic process is remarkable. The regiochemistry of the reaction is controlled by a hydroxy-group directed site-selective hydration of a practically symmetric carbon-carbon triple bond. Finally, the reaction also includes a step that supposes the first platinum-catalyzed intramolecular hydroalkylation of an unactivated olefin with a simple dialkyl ketone under very mild reaction conditions.

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Flash-8

Hidrazonas Monosustituídas como Reactivos *Umpolung* para la Adición Conjugada Aminocatalítica

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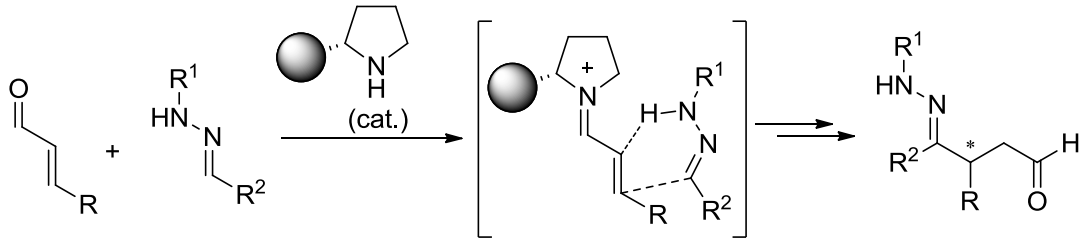
La adición conjugada de equivalentes sintéticos de aniones acilo es uno de los ejemplos de la denominada reactividad *umpolung*, posibilitando la preparación de compuestos 1,4-dicarbonílicos de una forma directa y sencilla. En este sentido, se han llevado a cabo diversas aproximaciones mediante el cuidadoso diseño de reactivos nucleofílicos en los que la función carbonílica se encuentra enmascarada, para posteriormente ser liberada tras el proceso de adición conjugada. También se han diseñado diversas variantes estereocontroladas para la obtención de productos enantioméricamente enriquecidos, generalmente basadas en la incorporación de auxiliares quirales, o bien mediante el empleo de catálisis metálica u organocatálisis.[1]

Nuestro grupo de investigación se ha centrado en los últimos años en el diseño de nuevos procedimientos para la construcción de compuestos ópticamente activos, empleando para ello los diferentes métodos de activación asociados al empleo de aminas secundarias quirales como organocatalizadores. Así, hemos descubierto el empleo de hidrazonas monosustituídas como pronucleófilos[2] adecuados capaces de participar en adiciones conjugadas a aldehídos α,β-insaturados empleando activación vía iminio. Se trata de una reacción diaza-énica formal que da lugar a la formación de γ-hidrazonoaldehídos, en los que la función hidrazona se puede considerar como grupo carbonílico enmascarado que se podrá liberar bajo las condiciones de reacción apropiadas.[3]



Agradecimientos: Este trabajo ha sido financiado por el MICINN (CTQ2011-22790), Gobierno Vasco (Grupos IT328-10, beca pre-doctoral a M.F. y post-doctoral a U. U.) y Universidad del País Vasco (UPV/EHU). M. F agradece a UPV/EHU (UFI QOSYC 11/22) la ayuda económica.

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Flash-9

Biomimetic organocatalysts derived from carbazole for the synthesis of the Hajos-Wiechert and Wieland-Miescher ketones

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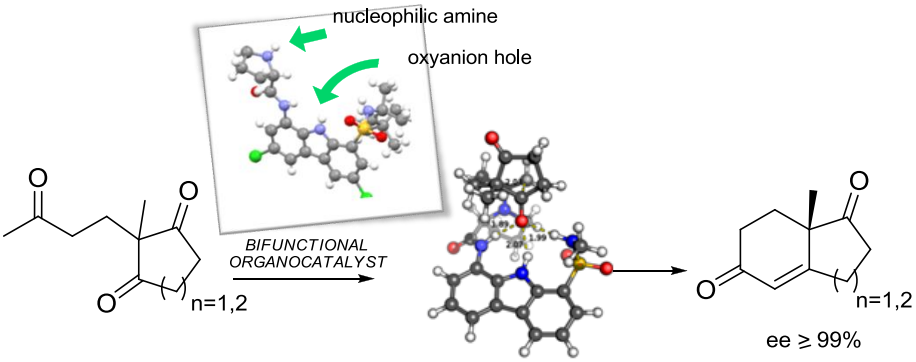
In this work we describe the synthesis of new organocatalysts that have been used in the preparation of the Hajos-Wiechert and Wieland-Miescher ketones with excellent enantioselectivities, up to ≥ 99.9%.[1]

The design of the catalysts is based on the action mode of natural enzymes. The strategy employed by class I aldolases in nature was mimicked by either a chiral cyclohexanodiamine or a proline unit, able to form an enamine with the donor carbonyl group. Also, the 'oxyanion hole' present in natural peptidases was recreated with two acidic NHs derived from sulfonamide moieties. In order to arrange these functional groups within a structural pattern with distances similar to those of enzymes, a carbazole framework has been used.

The catalyst structure obtained by X-ray diffraction experiments showed an H-bond disposition similar to that of the acetylcholinesterase active-center.

Finally, some calculations were made in order to fully justify the results obtained.[2]



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Flash-10

Novel Thiourea Organocatalyzed aza-Michael Addition of Hydrazides to Nitroalkenes

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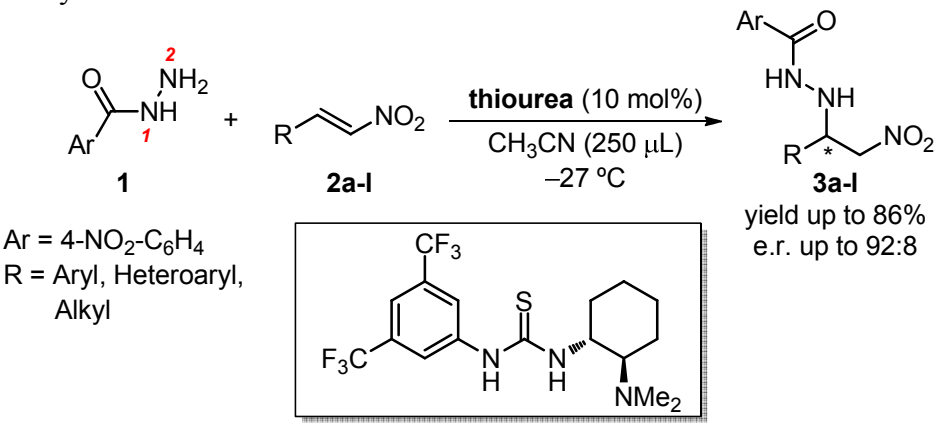
The aza-Michael addition reaction is one of the most important protocols for C-N bond formation. This field has undergone an impressive growth in the last decade, especially concerning the area of asymmetric organocatalysis.[1]

The hydrazide is a privileged structural motif present in many bioactive heterocyclic compounds with biological properties.[2] Additionally, its use as starting material is also attractive due to the challenging aim of modulating the regiochemistry between the two competitive NH groups.

We report here an unprecedented approach of thiourea catalyzed aza-Michael addition reaction of hydrazides to nitroalkenes providing easy access to inspiring building blocks with biological activity.[3,4] Further mechanistic studies are required in order to understand and to probe the role of the catalyst in this reaction and to gain insight the preferential N^2 reactivity shown by the hydrazide.[5]



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Flash-11

Síntesis Diastereodivergente de Ciclohexanos Enantioenriquecidos Densamente Funcionalizados Mediada por Catalizadores Quirales no Covalentes.

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La reacción de Michael es uno de los procesos de formación de enlaces C-C más importantes en el ámbito de la síntesis orgánica. Esta transformación destaca por la gran cantidad de sustratos que admite y por tanto, la gran diversidad de productos que se pueden obtener. Además, el propio perfil mecanístico de la reacción posibilita realizar reacciones en cascada para de esta manera conseguir moléculas de elevada complejidad estructural en un solo paso de reacción. La versión asimétrica de esta reacción ha sido potenciada desde la aparición de organocatalizadores quirales capaces de controlar el curso estereoquímico de la misma y, en este sentido, de entre los distintos sistemas descritos, destaca el empleo de la organocatálisis *via* interacciones no covalentes.[1] En este contexto, la estructura de escuaramida aparece como una arquitectura aventajada por su capacidad para formar puentes de hidrógeno tanto con el aceptor de Michael como con el dador, así como por su carácter aromático que la dota de la rigidez necesaria para una buena discriminación facial en procesos enantioselectivos.[2]

En nuestro grupo de investigación hemos desarrollado una reacción en cascada Michael/Henry utilizando diferentes escuaramidas como catalizadores del proceso, oxohexanoatos y nitroalquenos para llegar a la síntesis diastereodivergente de ciclohexanos enantioenriquecidos densamente funcionalizados (Figura 1).

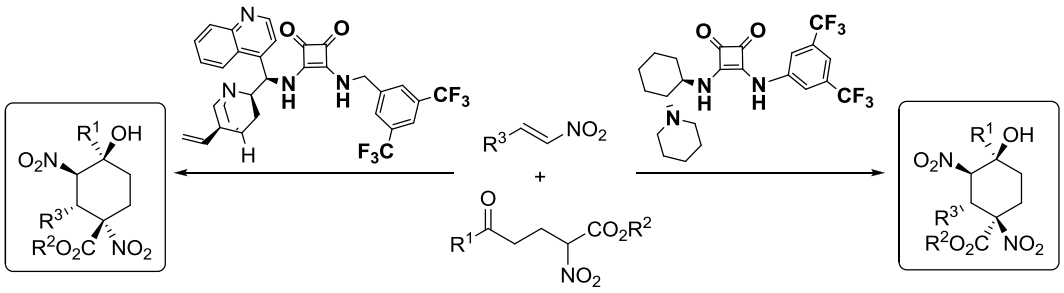

Figura 1

Agradecimientos: Los autores agradecen al MICINN (CTQ2011-22790), al Gobierno Vasco (IT328-10) y a la Universidad del País Vasco (UPV/EHU) por el soporte económico. Jose I. Martínez agradece a Gobierno Vasco la Beca para Formación y Perfeccionamiento de Personal Investigador y a UPV/EHU (UFI-11/22) por la ayuda económica.

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Aminocatalytic Enantioselective 1,6-Additions of Alkyl Thiols through Vinylogous Iminium Ion Activation of Cyclic Dienones

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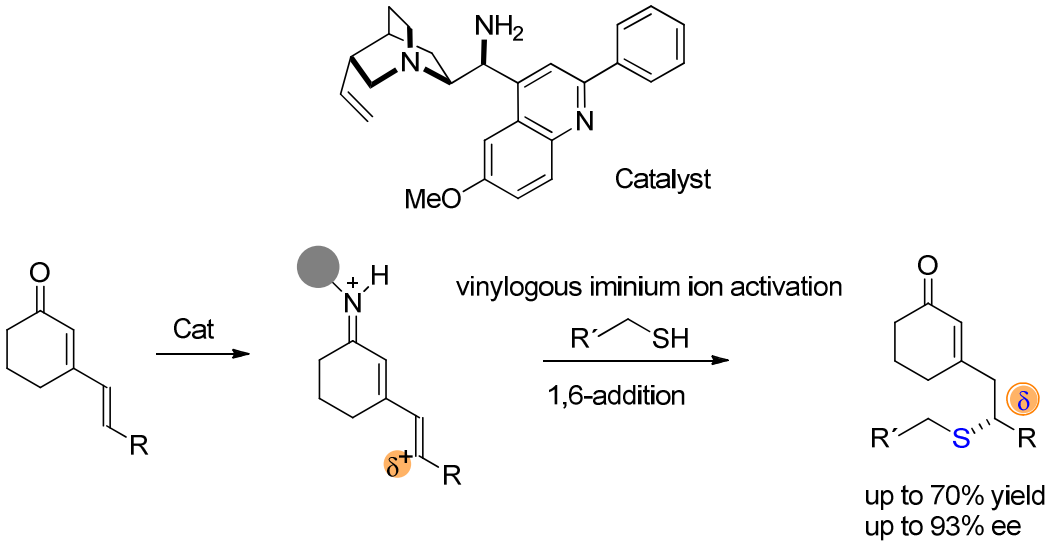
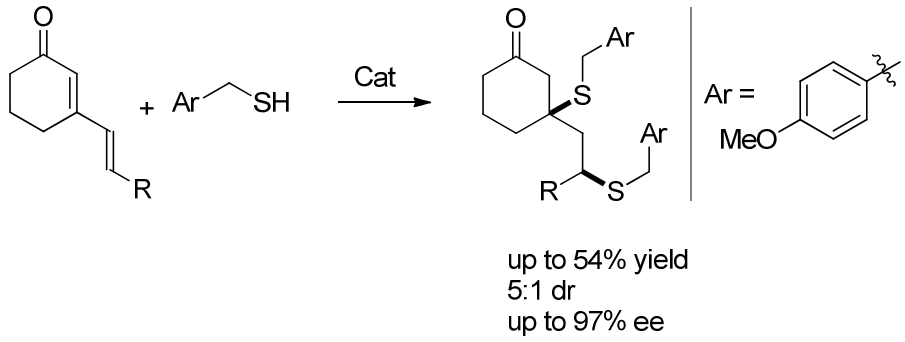
We have discovered that the LUMO-lowering activating effect can be transmitted through the conjugated π-system of 2,4-dienones upon selective condensation with a chiral amine. The resulting aminocatalytic activation mode, termed vinylogous iminium ion catalysis, contributes a strategy for the direct, stereoselective δ-functionalization of unsaturated carbonyl compounds. Specifically, the 1,6-addition of alkyl thiols to β-substituted cyclic dienones catalyzed by a cinchona-based primary amine proceeds with high stereocontrol and δ-site selectivity[1].



In addition, a cascade reaction was successfully implemented by using a large excess of the thiol and prolonging the reaction time. This change in the reaction conditions allowed the synthesis of more sophisticated adducts with moderate diastereoselectivity but high control over the absolute configuration.



[1] *Angew.Chem.Int.Ed.2012.* just accepted

Flash-13

Direct Enantio- and Diastereoselective Organocatalytic α-Alkylation of Aldehydes with β-Substituted 2-(Bromomethyl)acrylates

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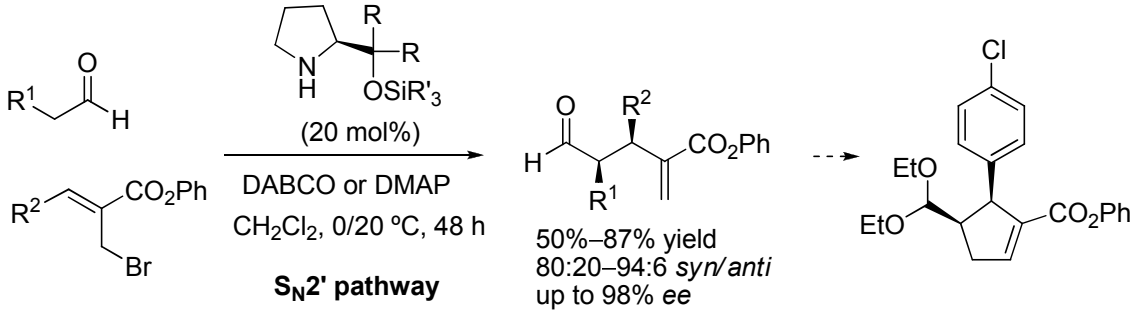
Despite impressive advances in the field of catalytic asymmetric methodologies, the enantioselective α-alkylation of aldehydes, an elemental carbon-carbon bond forming process, remains challenging. Recent achievements based on the chemistry of transiently formed enamine intermediates have open new perspectives, and several methods have been reported for amine-catalyzed enantioselective α-alkylation of aldehydes which proceed via either intramolecular S_N2 mechanism, radical or organophotoredox mechanisms, or a S_N1 pathway and involve a variety of electrophilic alkylating reagents.[1] We have found[2] that direct α-alkylation of aldehydes with 2-(bromomethyl)acrylates is feasible via a double activation approach, i.e. the enamine-mediated activation of the aldehyde component and the tertiary amine-promoted activation of the alkylating halide reagent via ammonium salt formation. Results show that combined use of a prolinol ether catalyst and DMAP or DABCO as the amine coadyuvant leads to alkylated products with remarkable levels of reaction enantio- and diastereocontrol. In this talk we will present the scope of the method, some mechanistic aspects as well as synthetic applications.



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Evaluación de la Tendencia Relativa de los Compuestos Carbonílicos a Formar Enaminas y Oxazolidinonas

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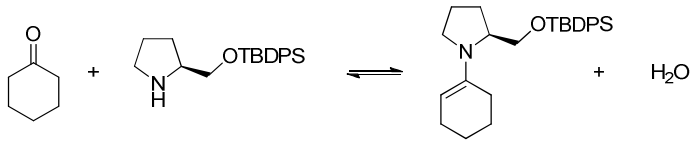
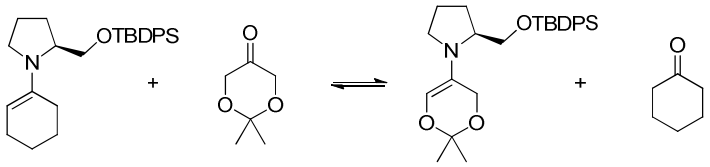
Se han estudiado por espectroscopia de RMN en DMSO-d_6 los equilibrios de formación de las enaminas de diferentes aldehídos y cetonas,[1] como el ejemplo que sigue:



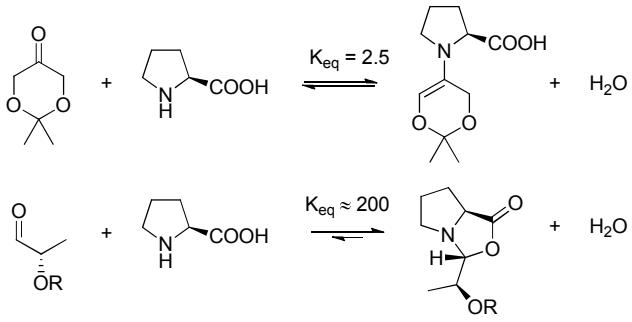
El uso de *O*-TBDPS-prolinol como amina secundaria es lo que nos ha permitido comparar una gran variedad de compuestos carbonílicos.

Los aldehídos tienden a formar enaminas más estables que las cetonas. No obstante, hay algunas excepciones a esta regla: por ejemplo, la 2,2-dimetil-1,3-dioxan-5-ona muestra una mayor tendencia a formar enaminas que algunos aldehídos α-sustituidos. Hemos seguido por RMN reacciones de intercambio tales como la siguiente:



A partir de estas comparaciones por parejas, hemos obtenido una escala de la estabilidad relativa de las enaminas (derivadas del prolinol mencionado y de pirrolidina).

En este contexto, hay que indicar que las reacciones aldólicas entre 2,2-dimetil-1,3-dioxan-5-ona y aldehídos α-sustituidos, catalizadas por prolina, se han utilizado mucho en síntesis de polioles.[2] Hemos demostrado que, en DMSO-d_6, 2,2-dimetil-1,3-dioxan-5-ona y L-Pro forman la enamina correspondiente, mientras que el aldehído α-sustituido da la oxazolidinona (pero no enamina, con lo que no se observa racemización del estereocentro):



Una larga serie de resultados experimentales inconexos o inexplicados en el campo de las reacciones aldólicas catalizadas por prolina y derivados pueden ahora interpretarse a la luz de nuestros estudios sobre los equilibrios existentes.

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Flash-15

Regioselective Preparation of Benzo[b]furans from Phenols and α-Bromoacetophenones.

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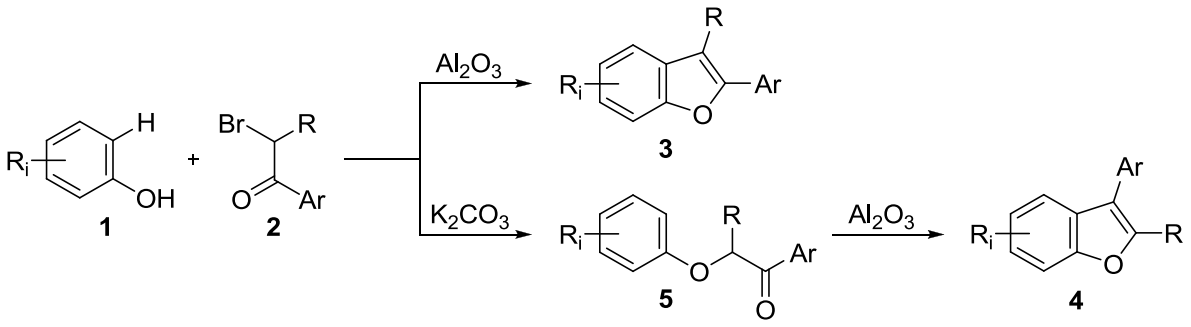
Benzo[*b*]furans have attracted considerable interest because of their presence in natural products, biologically active compounds and other compounds of pharmaceutical interest. In particular, 2-arylbenzo[*b*]furans possessing methoxy and/or hydroxy groups are attractive compounds because of their wide spectrum of biological activity which includes anticancer,[1] antioxidative[2] and antiinflammatory[3] properties.

In the present work, a fully regiocontrolled synthesis of either 2- or 3-substituted benzo[*b*]furans is described. Reaction between phenols **1** and α-bromoacetophenones **2** in the presence of neutral alumina yields 2-aryl benzo[*b*]furans **3** with complete regiocontrol. When a basic salt such as potassium carbonate is used instead of alumina, the corresponding 2-oxoethers **5** are obtained.[4] Cyclization of these latter compounds promoted by neutral alumina yields the corresponding 3-aryl benzo[*b*]furans **4**.

In addition, in order to get a better understanding of the of the paths these reactions go through, reasonable mechanisms to explain the formation of both 2-aryl and 3-aryl derivatives are proposed based on DFT calculations.



Agradecimiento: L. A. agradece a la Universidad del País Vasco (UFI QOSYC 11/22) la ayuda económica.

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Flash-16

Intramolecular carbolithiation reactions for the synthesis of six-, seven- and eight-membered nitrogen heterocycles.

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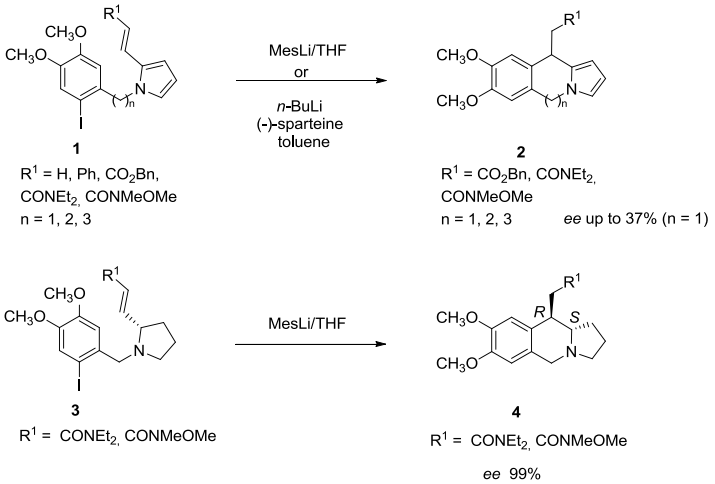
The intramolecular carbolithiation of alkenes constitutes an interesting approach for the synthesis of functionalized carbocyclic and heterocyclic systems. The attraction of this methodology lies in the high regio- and stereoselectivity when a carbon–carbon bond is formed and in the possibility of trapping the resulting cyclized organolithium with electrophiles to introduce diverse functionality into the cyclized products. Intramolecular carbolithiation reactions are particularly well suited for the construction of five-membered rings through 5-*exo*-trig cyclization processes. Althoguh some examples of formation of three, four or six-membered cycles have been reported, it is still not clear if these cyclizations would provide the same degree of stereo- and regiochemical efficiency.[1]

In this context, the intramolecular carbolithiation reaction of 2-alkenyl susbtituted *N*-benzyl pyrroles **1** (n = 1) proceeded efficiently.[2] An electron-withdrawing group in the alkene is required to favour the cyclizations, and MesLi has shown to be a highly effective metalating agent, avoiding side reactions. The procedure is applicable to the construction of six, seven and eight membered rings, thus opening new routes to pyrroloisoquinolines **2** (n= 1), benzazepines **3** (n = 2), and benzazocines **4** (n = 3). In the presence of a chiral ligand for lithium as (–)-sparteine, only low levels of enantioselectivity (up to 37 % *ee*) were obatined. However, the cyclization reaction proceeds with complete diastereoslectivity[3] to obtain the *trans* adducts when pyrrolidines **5** are used, and allowing the synthesis of enantiomerically pure pyrroloisoquinolines **6** (99 % ee). Details of these transformations will be given.



We wish to thank the Ministerio de Ciencia e Innovación (CTQ2009-07733), and UPV/EHU for their financial support. E.C. thanks UPV/EHU (UFI QOSYC 11/22) for financial support, and GV for a grant.

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Flash-17

Pd(0) and Pd(II) catalyzed intramolecular alkenylation reactions for the synthesis of quinolines.

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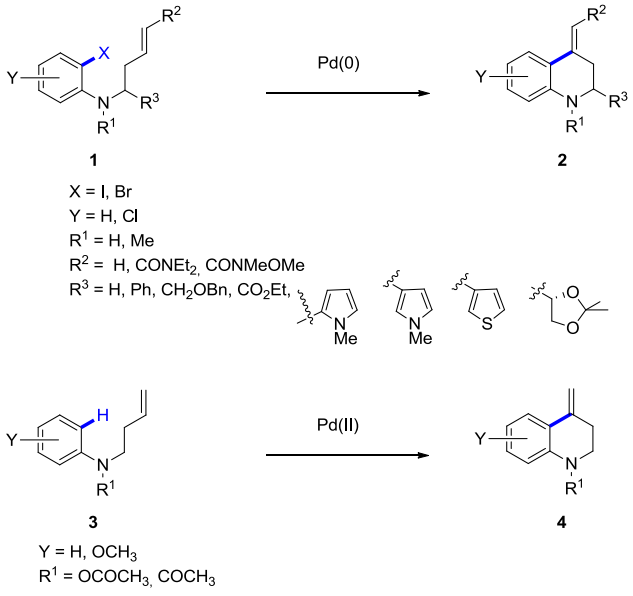
The quinoline framework is a motif common to natural products and pharmaceutically active compounds, as well as agrochemicals, dyestuffs, and materials. In particular, 2-substituted 4-akylidenetetrahydroquinolines have shown promising biological activity. Thus, considerable efforts have been dedicated to developing new methods for the preparation of these pharmacophores.[1] In this context, palladium-catalyzed coupling reactions and, in particular, the intramolecular Heck reaction[2] is of special relevance here. An interesting variant of this alkenylation reaction is the Fujiwara-Moritani reaction, that implies the activation of a C-H bond with a Pd(II) catalyst[3]

In connection with our interest in the application of Pd(0)-catalyzed reactions to the synthesis of heterocyclic systems,[4] we decided to study the intramolecular Heck reactions of alkenyl *o*-halo anilines **1**, to afford 4-alkylidenequinolines **2**, with different substituents on C-2. The procedure has been applied to the synthesis of enantiopure heterocycles. The alternative Pd(II)-catalyzed reaction avoids the use of an halogenated substrate, but requires the presence of an activating group to favor the C-H activation on anilines **3** to obtain quinolines **4**. Details of these transformations will be discussed.



We wish to thank the Ministerio de Ciencia e Innovación (CTQ2009-07733), and UPV/EHU for their financial support. V.O. E. thanks UPV/EHU (UFI QOSYC 11/22) for financial support, and GV for a grant.

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Flash-18

Synthesis and Reactivity of New Cyclobutanes

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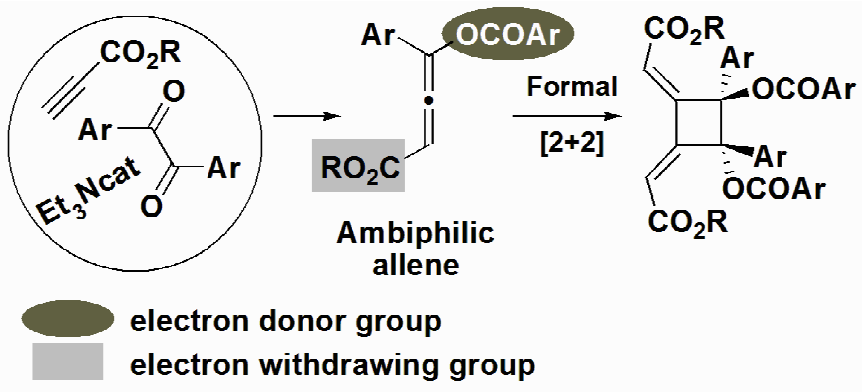
In this communication we present the generation of fully-substituted cyclobutanes in a regio- and highly stereoselective manner.[1]

The manifold involves the organocatalytic generation of a propiolate anion and a novel and highly effective rearrangement of a conjugated γ-acyl propargylic alkoxide intermediate followed by the formation of an ambiphilic allene that performs a thermally-driven dimerization reaction to generate the corresponding cyclobutane.



In addition, the reactivity of these cyclobutanes and their derivatives towards different conditions and reactants (acid media, basic media, nucleophiles, reducing agents…) is under study in our lab.

Acknowledgments: This research was supported by the Spanish and European MICINN RDF (CTQ2008-06806-C02-02 and CTQ2011-28417-C02-02), and FUNCIS (REDESFAC PI01/06). G. M-A thanks MEC for the FPU fellowship.

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Flash-19

Aminoalquilación regioselectiva de indoles y heterociclos relacionados con α-amidosulfonas

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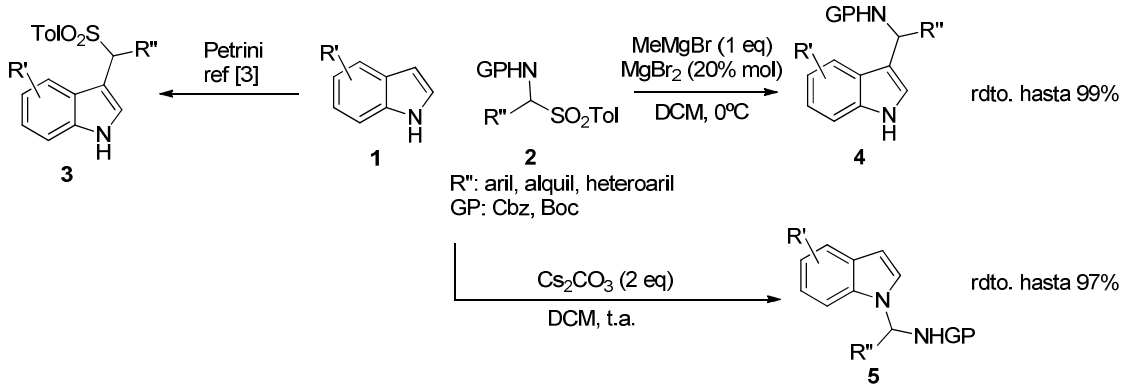
La introducción de diferentes tipos de cadenas funcionalizadas en la posición C-3 del núcleo de indol (**1**) es una práctica común dirigida a la síntesis de compuestos biológicamente activos.[1] La mayor parte de métodos disponibles para alcanzar este resultado utilizan la reacción de Friedel-Crafts entre el núcleo de indol, con elevada densidad electrónica, y reactivos altamente electrofílicos generados bajo condiciones ácidas. Esta activación ácida del electrófilo es particularmente necesaria cuando se utilizan electrófilos débiles como las iminas.[2] Alternativamente, podría llevarse a cabo la reacción de Friedel-Crafts mediante la formación in situ de iones *N*-aciliminio por tratamiento ácido de α–amidosulfonas (**2**). Sin embargo, en todos los casos descritos en la bibliografía, la reacción del indol con α–amidosulfonas conduce al indol sustituido en la posición 3 con un grupo alquilo que retiene el grupo sulfonilo (**3**) en lugar del grupo amido.[3]

En esta comunicación presentaremos una síntesis regioselectiva de 3-(carbamoilalquil)indoles (**4**). La reacción se ha llevado a cabo a partir de α–amidosulfonas como equivalentes sintéticos de iminas, indoles diferentemente sustituidos y bromuro de metilmagnesio/bromuro de magnesio.

También presentaremos la síntesis regioselectiva de *N*-(carbamoilalquil)indoles (**5**), la cual se ha llevado a cabo a partir de α–amidosulfonas e indoles diferentemente sustituidos por reacción con carbonato de cesio.



Agradecimientos: Ministerio de Ciencia e Innovación y FEDER (CTQ 2009-13083) y Generalitat Valenciana (ACOMP/2012/212) . M.M. agradece a la Universitat de València la concesión de una beca pre-doctoral.

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Flash-20

Síntesis Controlada de Selenolactamas Espirocíclicas y Selenoquinolonas

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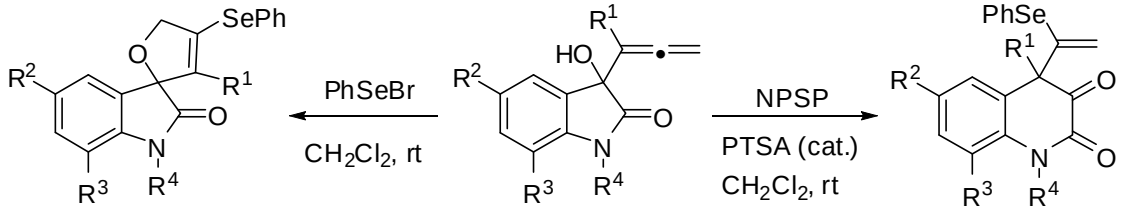
La química de los compuestos orgánicos de selenio ha experimentado un gran desarrollo en los últimos años debido a su interesante actividad biológica y farmacológica.[1] La reacción de selenociclación inducida por reactivos electrófilos de selenio en sistemas insaturados que contienen una especie nucleófila, permite obtener productos cíclicos de forma estereoespecífica.[2] La reactividad de alenos frente a compuestos electrófilos de selenio ha despertado un gran interés ya que permite obtener diferentes derivados funcionalizados.[3] En la presente comunicación se describe un estudio de la reactividad de diferentes lactamas alénicas frente a reactivos electrófilos de selenio, lo cual ha permitido la síntesis selectiva de compuestos de expansión y de productos de selenoeterificación. Las alenil-lactamas **1** se obtuvieron fácilmente a partir de α-oxolactamas, y se utilizaron como materiales de partida en el estudio de la reactividad divergente con diferentes reactivos electrófilos de selenio. La preparación de productos de oxiciclación **2** o de expansion de anillo **3** puede modularse en función de los reactivos y sustratos elegidos. Las reacciones de selenofuncionalización se han desarrollado experimentalmente con muy buenos resultados y algunos de los heterociclos sintetizados han sido sometidos a ensayos de actividad biológica en cuatro líneas celulares de cáncer.[4]



2 **1** **3**

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Flash-21

Reorganización Inesperada del Núcleo Heterocíclico de la Variolina. Síntesis de Nuevos Derivados de Indol.

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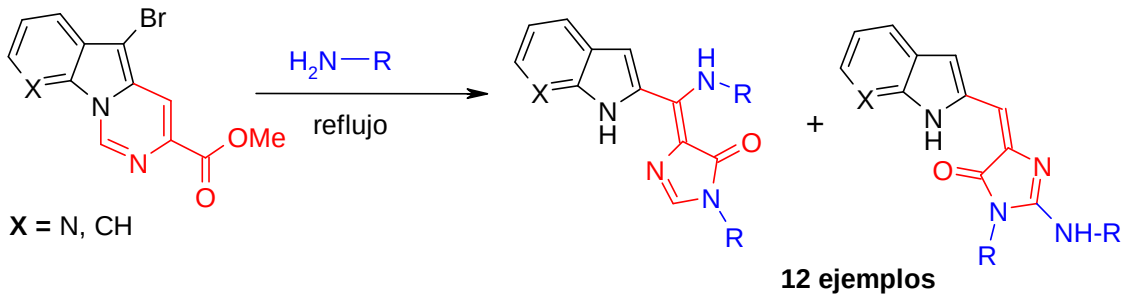
El sistema de pirrolo[1,2-*c*]pirimidina es el análogo de indolizina más interesante y contiene un átomo de nitrógeno extra en su estructura. Este sistema heterocíclico, aunque raro en la naturaleza, está presente en las variolinas, una familia de alcaloides que tienen actividad antitumoral y antiviral.

Recientemente, durante el estudio centrado en el diseño y síntesis de nuevos inhibidores de calpaína,[1] se consideró que el núcleo heterocíclico de la variolina, el sistema pirido[3',2':4,5]pirrolo[1,2-*c*]pirimidina, y otros derivados de azolopirimidinas podrían ser utilizados como sistemas heterocíclicos para el desarrollo de nuevos inhibidores de calpaína.

Como parte de este estudio se llevó a cabo la reacción del bromo-pirido[3',2':4,5]pirrolo[1,2-*c*]pirimidina y pirimido[1,6-*a*]indol carboxilato de metilo[2] con diferentes aminas primarias. Aunque la amida esperada se formó, rápidamente derivó en un proceso en cascada inesperado que implicaba el ataque de la amina al anillo de piridimidina, reacción de apertura del mismo, pérdida de bromo y por último un proceso de reciclación, dando lugar a la formación de indoliden o azaindoliden imidazolonas sustituidas.



Agradecimientos: Los autores agradecen al Ministerio de Economía y Competitividad (proyecto CTQ2008-04313) e Instituto de Salud Carlos III (Red de Investigación Renal, REDinREN, RD6/0016/0016) por la ayuda económica, y a la Universidad de Alcalá por la beca de investigación (M.M).

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Flash-22

(+)-3,4-Dihydro-γ-ionone, a versatile building block for the efficient preparation of a wide variety of bioactive molecules

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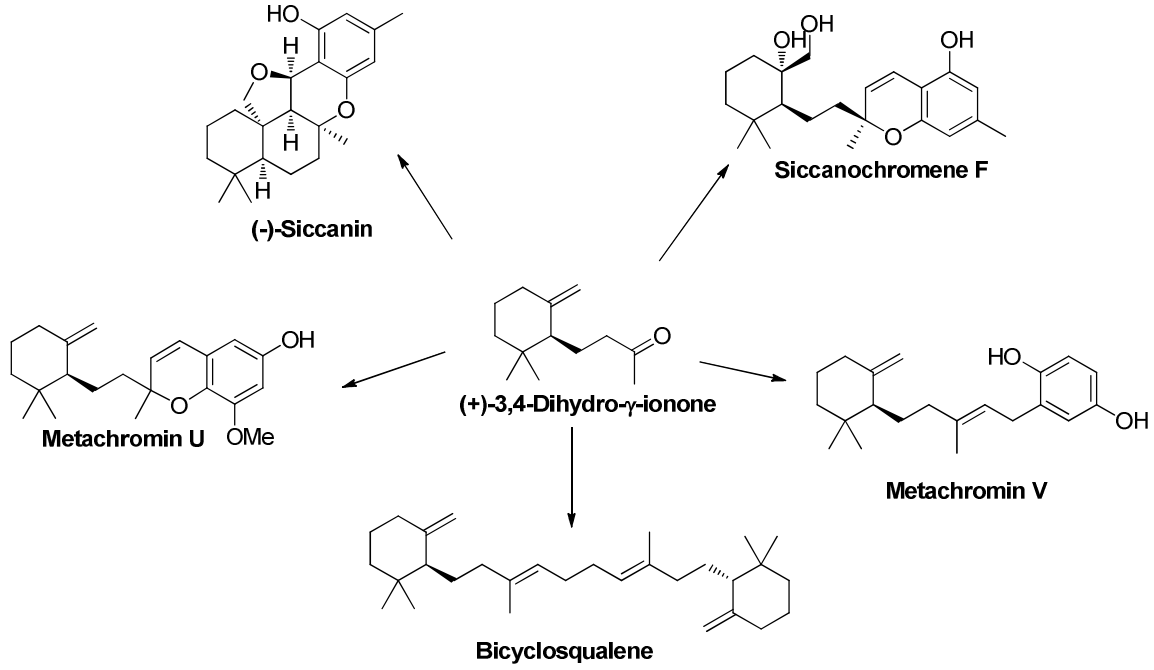
In the field of the synthesis of potent bioactive natural products, it should be remarked that the efficiency of synthetic approaches including the use of renewable enantiopure starting material is generally far ahead of the current capabilities of chemical total synthesis. In this sense we believe that structure and functionality of (+)-3,4-dihydro- γ-ionone, a natural compound obtained in multigrams scale after oxidative degradation of the ethereal extract from *Bellardia trixago*,[1] may well serve as a versatile building block for the efficient preparation of a wide variety of bioactive molecules. In our attempt to show the viability of our chiral pool approach, we report the recent advances in the preparation of the biologically active (-)-siccanin[2] and metachromins U and V[3], among others. For the preparation of the chromene ring present of some of these molecules, an enamine-based organocatalytic domino process has been used.



Acknowledgement: This research was supported by the Ministerio de Educación y Ciencia, Project CTQ2010-16818 (subprogram BQ) and Junta de Andalucía, Excellence Project P08-FQM-3596.

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Flash-23

Towards the Total Synthesis of Amphidinolide B_1

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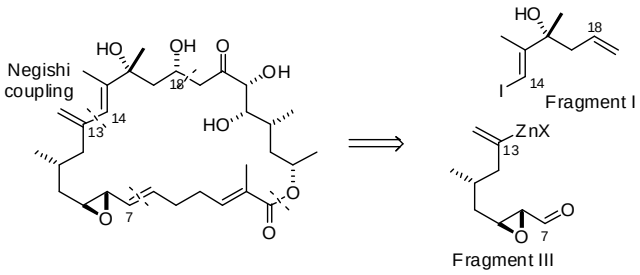
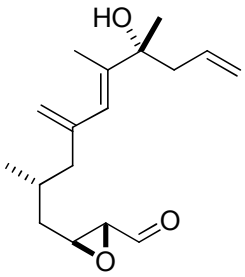
Amphidinolide B_1 is a 26-membered macrolide, isolated[1] from the dinoflagellate *Amphidinum sp*., which is a potent cytotoxic molecule against several cancer cell lines. It represents a synthetically attractive target due to the complexity of its structure. Only two total syntheses of Amphidinolide B_1 have been reported to date.[2]

Herein we report a retrosynthetic strategy, which is a versatile route to reach amphidinolide B congeners. Our approach to the West Part (Fragments I and III) is shown below:



We have already accomplished the syntheses of the fragments. A key Negishi coupling step (C13-C14 bond formation), followed by appropriate transformations, provided the West Fragment.



WEST
FRAGMENT

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Síntesis de Análogos de Acetogeninas

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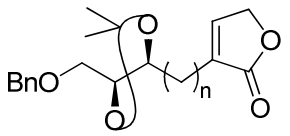
Debido a la importancia que poseen las acetogeninas desde el punto de vista de su actividad biológica, [1] se plantea en este trabajo el desarrollo sintético de una serie de análogos teniendo en cuenta la estructura básica de estos productos naturales y los elementos característicos que le confieren sus propiedades biológicas.

Las acetogeninas son compuestos de 35 ó 37 átomos de carbono que han sido aislados de especies de la familia *Annonaceae*.[2] Estructuralmente, se caracterizan por la presencia de una larga cadena alifática, no ramificada, que porta una γ-lactona terminal, y en las posiciones intermedias uno o más anillos de éter cíclico combinados con diferentes grupos hidroxilo. Constituyen una amplia familia de productos orgánicos con una interesante complejidad estructural, y variadas e importantes actividades biológicas.[1]

Se ha llevado a cabo la síntesis de una serie de butenólidos 2-sustituidos, del tipo del que se muestra en la figura, estructuralmente relacionados con las acetogeninas naturales de acuerdo con el principio de simplificación molecular, variando el tamaño de la cadena lateral situada entre el anillo de butenólido y el dioxolano. Posteriormente, los productos obtenidos se han sometido a un estudio como potenciales agentes antitumorales.



n = 0, 2, 4, 6, 13

Agradecimientos:

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Flash-25

Fosfonatos vs Fosforanos: Aplicación a la Síntesis del Ácido 6,10-(*E*,*E*)-Thymifodioico

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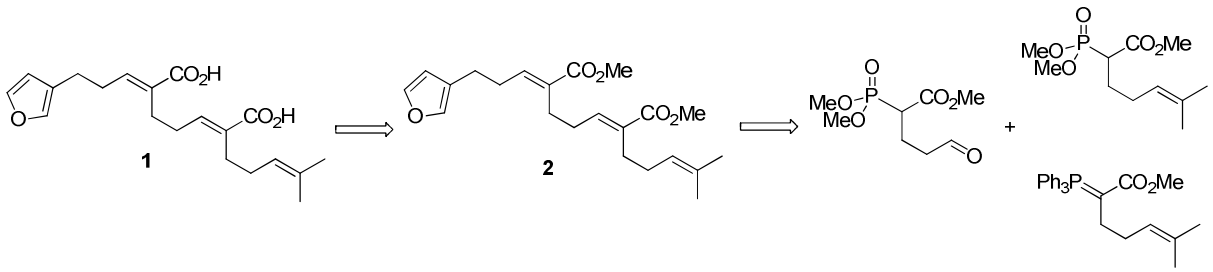
El ácido 6,10-(*E*,*E*)-thymifodioico (**1**) es un diterpeno lineal aislado de las partes aéreas del arbusto argentino *Baccharis thymifolia* Hook & Arn.[1] Este producto natural, su diéster dimetílico (**2**) y otros derivados sintéticos, presentan actividad hormonal frente a las larvas del coleóptero *Tenebrio molitor*,[2] que son causantes de plagas en producciones de grano y posibles transmisores de parásitos a humanos y otros animales. La aplicación tópica de los compuestos **1** y **2** en el quinto estadio del desarrollo de las larvas de *T. molitor* induce la metamorfosis prematura de las larvas y malformaciones en las mismas.[2]

En el trabajo que se presenta, se plantea la síntesis de estos compuestos involucrando la condensación entre un aldehído portador de un grupo fosfonato y un compuesto organofosforado como etapa clave de la ruta sintética.[3] Se ha estudiado la reactividad que presentan los fosfonatos frente a los fosforanos en reacciones de Horner-Wadsworth-Emmons y reacciones de Wittig, respectivamente, frente a este tipo de aldehídos. Las conclusiones de este estudio se han aplicado al desarrollo de una síntesis total y eficiente, en pocos pasos de reacción, del diéster **2**, cuya reacción de hidrólisis permite la obtención del diácido **1**. De esta forma se podrá profundizar en el estudio del potencial biológico de estos productos como posibles insecticidas.



Agradecimientos

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Flash-26

Aproximación a la Síntesis Formal del (+)-Isolaurepinnacin

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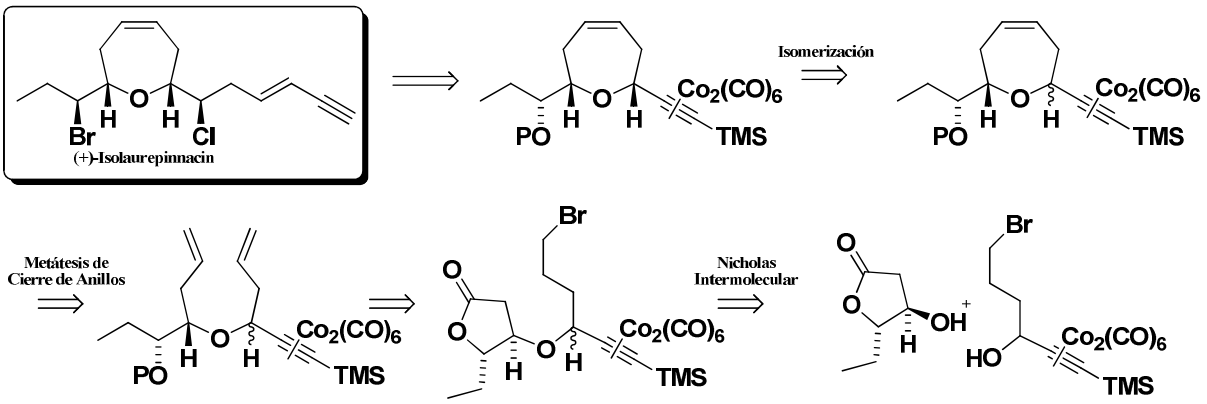
Los Lauroxanos son una serie de metabolitos secundarios, aislados de las algas del género Laurencia, que presentan un gran número de actividades biológicas (antimicrobiana, antitumoral, pesticida, etc).[1] Éstos compuestos presentan como característica estructural un esqueleto carbonado C15, formando un éter cíclico de entre 5 y 9 miembros, y con la presencia de átomos de halógenos.

En esta aproximación a la síntesis formal del (+)-Isolaurepinnacin[2] se ha aplicado una metodología desarrollada en los últimos años en nuestro laboratorio.[3] Las etapas claves para la obtención de este compuesto son la formación de un éter lineal a través de una reacción de Nicholas intermolecular, la ciclación mediante una reacción de metátesis de cierre de anillos y la isomerización del sistema asistida por Montmorillonita K-10.



Agradecimientos: Esta investigación está financiada por el Ministerio de Economía y Competitividad (MINECO), cofinanciado con fondos FEDER (CTQ2011-28417-C02-01 y CTQ2011-22653). JRP agradece al MICINN por la beca pre-doctoral FPI.

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Flash-27

A new multicomponent process for the synthesis of multisubstituted nicotinamide derivatives.

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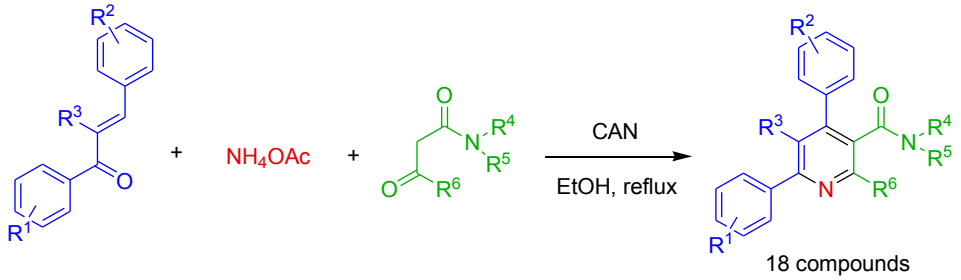
Pyridine motif is among the most important nitrogen heterocycles and shows a wide range of applications widespread in so many different fields of chemistry. Owing to the extensive synthetic utility of this nucleus and to its ubiquitous presence in a wide range of chemical areas from pharmaceutical to agrochemical, a large number of methods to prepare these compounds has been developed.[1] In an attempt to improve the approach to the synthesis of this important building block (and generally of all the heterocycles), in the last decade multicomponent reactions (MCR) have appeared as a powerful instrument in the hands of organic and medicinal chemists showing it as a complementary synthetic alternative to other well-known methods[2]. These processes combine usual requirements such as efficiency and selectivity with current demands of developing environmentally-friendly methods based predominantly on atom- and step-economy[3].

Among the most biologically relevant product containing the pyridine motif we can surely mention nicotinic acid (niacin, vitamin B3) and its amide that are important members of the B-vitamin group and play a key role, as nucleotides NAD/NADP, in various enzymatic oxidation/reduction process of living organisms.

In this communication we present a new facile and efficient one pot multicomponent process for the construction of highly densely substituted nicotinamide derivatives. The synthesis was achieved via a three-component reaction that starts from 1,3-diaryl-2-propen-1-ones, β-ketoamides and ammonium acetate, catalyzed by cerium(IV) ammonium nitrate (CAN), acting as a Lewis acid.



1. For some review of pyridine synthesis see for example: (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052.
2. Orru, R.V.A., Ruijter, E., Eds. *Synthesis of Heterocycles via Multicomponent Reactions*; Topics in Heterocyclic Chemistry, Volumes 23 and 25. Springer Verlag, New York, 2010.
3. For some review of MCR synthesis see for example: (a) B. B. Toure, D. G. Hall, Natural product synthesis using multicomponent reaction strategies. *Chem. Rev.* **2009**, *109*, 4439-4486. (b) H. Eckert, Diversity oriented syntheses of conventional heterocycles by smart multicomponent reactions (MCRs) of the last decade. *Molecules* **2012**, *17*, 1074-1102.

Flash-28

Síntesis de análogos de piranoquinonas bioactivas

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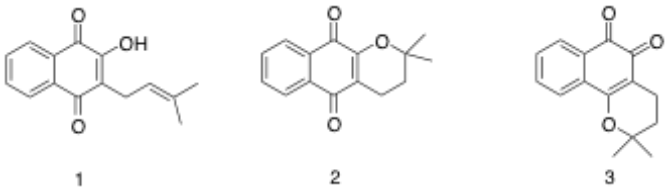
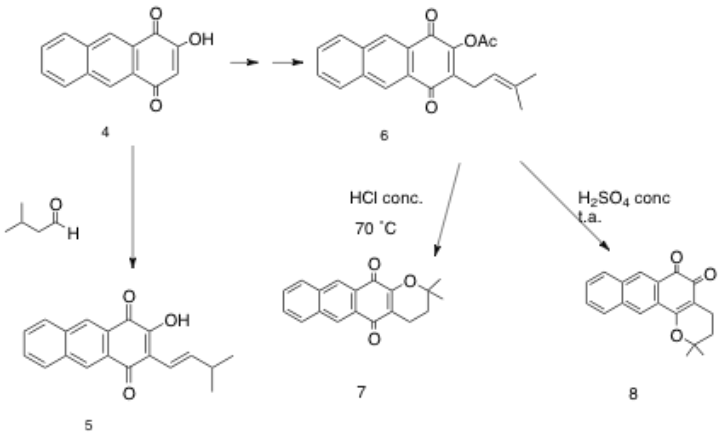
El lapachol (**1)** es un producto natural, originalmente aislado en el siglo XIX por Paterno de árboles de la familia *Tabebuia* (*Bignoniacea*), con notables propiedades terapéuticas[1]: leishmanicida, fungicida, antimalárica, antiviral, antitumoral…. También los productos obtenidos por ciclación del lapachol, α–lapachona (**2**) y β–lapachona (**3**) poseen interesantes propiedades, en particular la β-lapachona que ha llegado a ensayos clínicos en fase II frente a cáncer de páncreas.



Nosotros hemos estudiado la síntesis de análogos de estos productos, a partir del homólogo de lawsona (**4**) y su derivado **6**, obteniendo así el análogo de isolapachol **5**, y las correspondientes piranoquinonas **7** y *o*-quinona **8**. Esta última presenta una actividad semejante a la β-lapachona.



Agradecimientos: programa JAE-técnicos (CSIC) y proyecto SAF-2009-10399 (MICINN)

1. H. Hussain, K. Krohn, V.U. Ahmad, G.A. Miana, I.R. Green. Arkivoc 207, (ii), 145-171

Flash-29

New Copper Catalyzed Reactions

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Over the past decades diaryliodonium salts (Ar_2IX) have emerged as powerful electrophilic arylative reagents for many classical transformations like α-arylation of carbonyl compounds, arylation of a wide range of heteroatom nucleophiles or benzyne generation.[1] In the last years these electrophilic systems have been involved in novel metal–catalyzed C–H arylation of heterocycles and substituted arenes. The Gaunt group have been developing a new strategy for the selective functionalization of these class of molecules using diaryliodonium salts and copper catalysis, observing a remarkable reversal of established metal–catalyzed reactions.[2] This presentation will focus on the development of novel transformations of unsaturated systems with iodonium salts using copper catalysis. A broad range of substrates have been functionalized with excellent levels of selectivity and iodonium salt scope. To explain the outcome of these novel reactions a highly electrophilic copper(III)-aryl species has been proposed.

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Flash-30

Diamination of Internal Alkenes

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[b]Catalan Institution for Research and Advanced Studies (ICREA)
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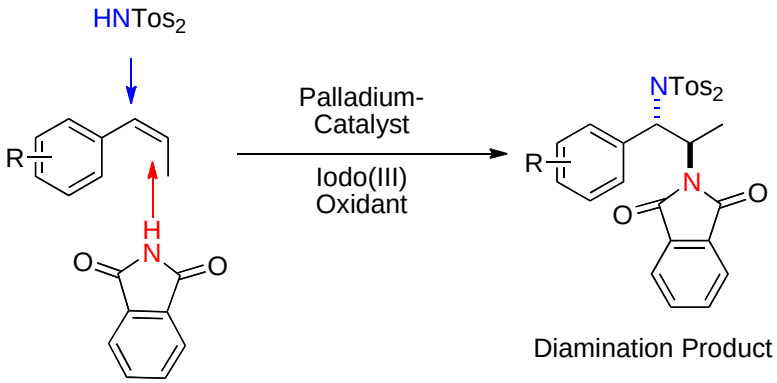
We have recently been interested in the application of palladium catalysts to realise unprecedented diamination reactions of internal alkenes.[1-3] Within this context, the application of suitable high oxidation state palladium catalysis represents the key methodology. We now report the first protocol for palladium catalysed intermolecular diamination reactions of internal alkenes, which employ readily available nitrogen sources. The diamination products are formed with complete regioselectivity, chemoselectivity and diastereoselectivity[4].

Intermolecular diamination of internal alkenes:



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[3] Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542.
[4] Martínez, C.; Muñiz, K. *Angew. Chem. Int. Ed.* accepted.

Gold(I) Catalyzed [2+2] Intermolecular Cycloaddition of Alkenes with *N*-Allenylsulfonamides: approaches towards an asymmetric version.

Samuel Suárez-Pantiga, María Piedrafita, Eduardo Rubio, José M. González and Cristina Hernández-Díaz

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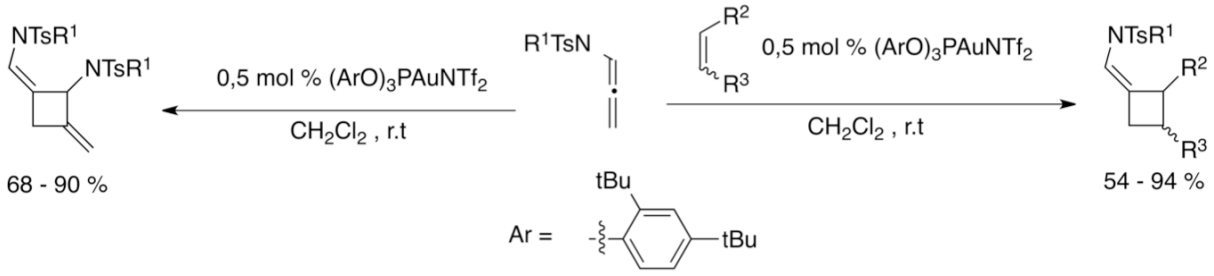
In the last decade gold catalysis has emerged as a useful tool for the synthesis of different scaffolds from accessible starting materials bearing on alkyne or allene moieties.[1]

We report here that the addition of catalytic amounts of a phosphite-based gold(I) catalyst efficiently triggers the intermolecular [2+2] cycloaddition of allenes and alkenes[2] substituted by electron-donor groups. The reaction is fast and furnishes cyclobutane derivatives in a stereoselective manner using low catalyst loadings. Besides, the same catalyst selectively affords homodimerization products from the starting allene, a process that could be conveniently tuned by addition of norbornene.



An asymmetric version of this process will be discussed.

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Flash-32

Gold(I)-Catalyzed [2+2+2] Cycloaddition of Alkynes with Ketoalkenes

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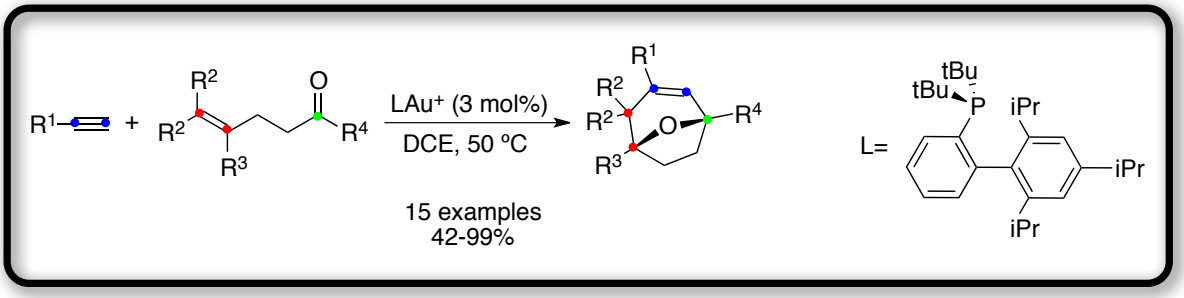
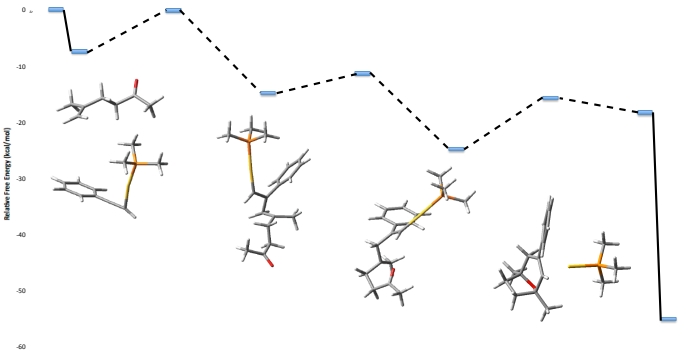
Gold has emerged as an exceptional catalyst for a variety of complex organic transformations through the selective activation of alkynes, allenes and alkenes.[1] An interesting example that leads to elaborated molecular skeletons involves the cycloisomerization of enynes bearing a carbonyl group at the alkenyl chain.[2] We have now developed a new intermolecular version of this reaction for the synthesis of [3.2.1]-oxabicycles from alkynes and ketoalkenes using gold(I) complexes bearing bulky 1,1´-biphenyl-2-dialkylphoshines as catalysts.



The scope of the reaction as well as its mechanism has been studied through DFT calculations and kinetic studies.



Acknowledgements. We thank the MICINN (grant CTQ2010-16088/BQU), the MEC (FPU felloship to C. O.), the AGAUR (2009SGR47), and the ICIQ Foundation for financial support.

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Flash-33

Straightforward Synthesis of Dihydrobenzo[*a*]fluorenes through Au(I)-Catalyzed Formal [3+3] Cycloadditions

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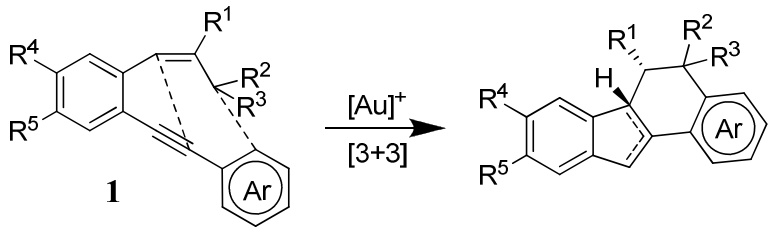
Gold-catalyzed cycloisomerization of enynes has emerged in the last years as a fundamental tool for the synthesis of cyclic structures not easily prepared by conventional methodologies. In this regard, we have recently described a gold-catalyzed cycloisomerization of *o*-alkynylstyrenes that provides an easy enantioselective access to the indene skeleton.[1] Moreover we have developed the synthesis of highly substituted benzene derivatives in a regioselective way from 1,3-dien-5-ynes through a gold(I)-catalyzed tandem reaction.[2]

In this context, we envisioned that compounds **1** could be appropriate substrates for the development of a new route to benzo[*a*]fluorene derivatives (Scheme 1), which are frequently found in diverse natural products possessing biological activity, for instance, in isoprekinamycin, veratramine or nakiterpiosinone.



Scheme 1

In this communication we report a formal Au(I)-catalyzed [3+3] cycloaddition of *o*-alkynylstyrenes **1** leading to the dihydrobenzo[*a*]fluorene skeleton. The asymmetric process, which provides enantiomerically enriched products, has also been developed.

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Estudio por ESIMS y aplicaciones catalíticas de $AuBr_4^-$

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El interés de nuestro grupo por la transformación de grupos nitro en grupos carbonilo (reacción de Nef) en condiciones suaves, con objeto de que puedan aplicarse a sustratos plurifuncionalizados y, en consecuencia, de que pueda aprovecharse la versatilidad de los nitroderivados alifáticos en etapas avanzadas de una síntesis total, viene de antiguo. En los últimos años, hemos publicado que disoluciones acuosas de $AuBr_3$ a pH neutro promueven la hidrólisis de *N*-sulfeniliminas y de oximas (cetoximas y aldoximas) a cetonas o aldehídos.[1] Ningún otro ácido de Lewis ni complejo metálico, entre todos los metales de la Tabla Periódica, es estable y/o cataliza dichas reacciones a pH neutro.

Unos estudios por ESIMS (espectrometría de masas por electrospray), de iones negativos,[2] revelaron que las especies activas durante la reacción son complejos de tipo $[AuBr_x(OH)_y]^-$ (x + y = 4) y que la oxima se coordina al átomo central desplazando HBr. Una de las limitaciones de nuestro protocolo es que las soluciones acuosas de $AuBr_3$ pierden actividad a pH superior a 7.5; partiendo de dicho pH, en las reacciones de hidrólisis en las que usamos 5 mol% de Au^{III}, la acidez del medio va evolucionando hasta llegar a un pH alrededor de 3.

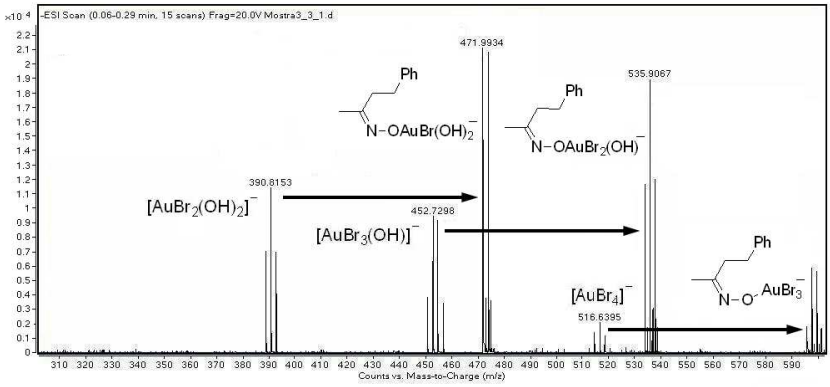

Figura. Interacción de una oxima con auratos de tipo $[AuBr_x(OH)_y]^-$, determinada por ESIMS

Unos estudios más recientes por ESIMS de la distribución de las especies presentes en disoluciones acuosas de otros compuestos de Au^{III} (y también, por comparación, de $FeBr_3$, $InBr_3$ y $LaBr_3$, aunque no son activos en las reacciones antes mencionadas) nos han llevado a evaluar la eficacia de diversas soluciones de $NaAuBr_4$ como catalizadores. Los resultados que hemos obtenido hasta la fecha indican que las soluciones neutralizadas o ajustadas con NaOH 0.10 M hasta valores de pH igual a 7.5, 8.0 e incluso 9.0, siguen promoviendo la hidrólisis de cetoximas, con la gran ventaja de que el pH final no baja de 4.5. Los espectros de masas por ESI muestran que la distribución de las especies presentes, en función del pH, difiere de la observada en el caso del $AuBr_3$. Actualmente estamos realizando estudios adicionales por ESIMS de la interacción de distintos grupos funcionales capaces de coordinarse con auratos, con $NaAuBr_4$ como fuente de Au^{III}. Las principales novedades encontradas se expondrán en la comunicación.

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Flash-35

Fosfino-hidrazonas como Ligandos en la Reacción Asimétrica de Suzuki-Miyaura

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[b]Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, C/ Profesor García González 1, 41012 Sevilla
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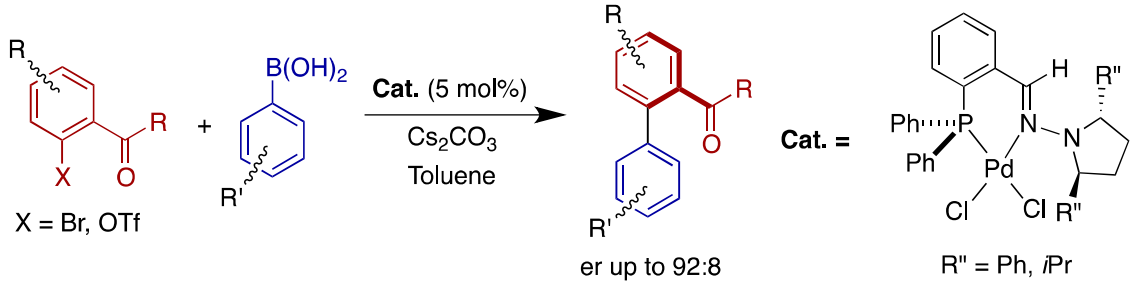
La reacción de Suzuki-Miyaura representa una de las metodologías más simples y eficientes para la formación de enlaces C-C, en concreto para la síntesis de sistemas biarilícos presentes en numerosas moléculas bioactivas.[1] La versión asimétrica de dicha reacción permite la síntesis de derivados quirales configuracionalmente estables, destacándose las metodologías pioneras desarrolladas por Buchwald[2] y Cammidge.[3] Recientemente nuestro grupo de investigación ha desarrollado una versión catalítica asimétrica de la reacción de Suzuki-Miyaura empleando catalizadores de paladio con bis-hidrazonas quirales como ligandos,[4] obteniéndose excelentes niveles de enantioselectividad con una gran variedad de sustratos no funcionalizados. La limitada reactividad y enantioselectividad observada con sustratos funcionalizados (aldehídos, ésteres,…), nos ha llevado a desarrollar una nueva familia de ligandos basados en fosfino-hidrazonas. La nueva familia de ligandos P,N combina una unidad de hidrazona, que introduce el fragmento quiral en el ligando, y una fosfina, que confiere al ligando unas propiedades electrónicas complementarias a las de las bis-hidrazonas de simetría C_2 empleadas anteriormente. En esta comunicación presentamos los recientes resultados obtenidos con dichos ligandos, que mostraron ser más activos y extensibles a otros sustratos como aldehídos, cetonas y ésteres, originando los productos deseados con buenos rendimientos y excesos enantiómericos de hasta el 84%.[5]



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Homogeneous and Heterogeneous Synthesis of Amines Catalyzed by *N*-Heterocyclic Carbene Iridium Complexes

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The development of new methods to prepare amines is very important due to the large number of molecules with biological activity that contain amino functionalities. Our continuous interest in the development of efficient, atom-economical and environmentally friendly processes has prompted us to investigate the synthesis of highly active catalysts for the alkylation of amines using alcohols as latent electrophiles.[1]

We have designed and prepared a family of novel iridium complexes containing bidentate *N*-heterocyclic carbenes (NHC) (Figure 1). The complex with the best catalytic activity is one of the most highly active and efficient catalytic systems for the alkylation of amines with alcohols known to date, and affords a variety of *sec*- and *tert*-amines in excellent yields in short reaction times.[2] Solid supported versions of the catalyst have been also synthesized and tested in the reaction. Mechanistic studies will also be presented.[3]

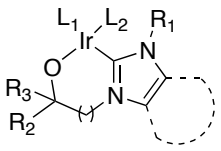
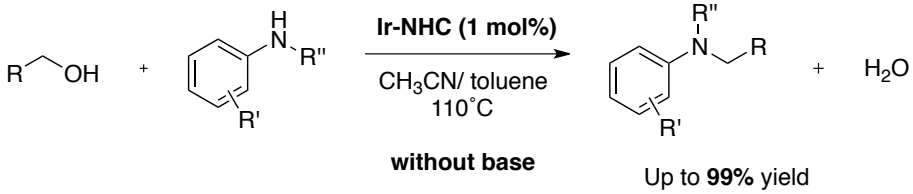


Figure 1



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Flash-37

Aluminium Catalysts for the Synthesis of Cyclic Carbonates

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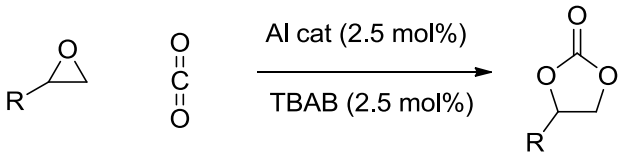
Carbon dioxide has been used in the industrial synthesis of urea, salicylic acid, and inorganic compounds since the 19th century. There is currently considerable interest in preparing a wider range of chemicals from CO_2, and one well studied reaction is the synthesis of cyclic carbonates from CO_2 and epoxides. We have reported[1] that $[Al(salen)]_2O$ complexes will catalyse this reaction under exceptionally mild conditions (atmospheric pressure and room temperature) using TBAB (tetrabutylammonium bromide) as cocatalyst as shown in Scheme 1. Consequently, a new generation of one component catalysts has been designed[2] as well as a more affordable version of the salen ligan derived from acac (acetylacetone)[3] (Figure 1).



Scheme 1.

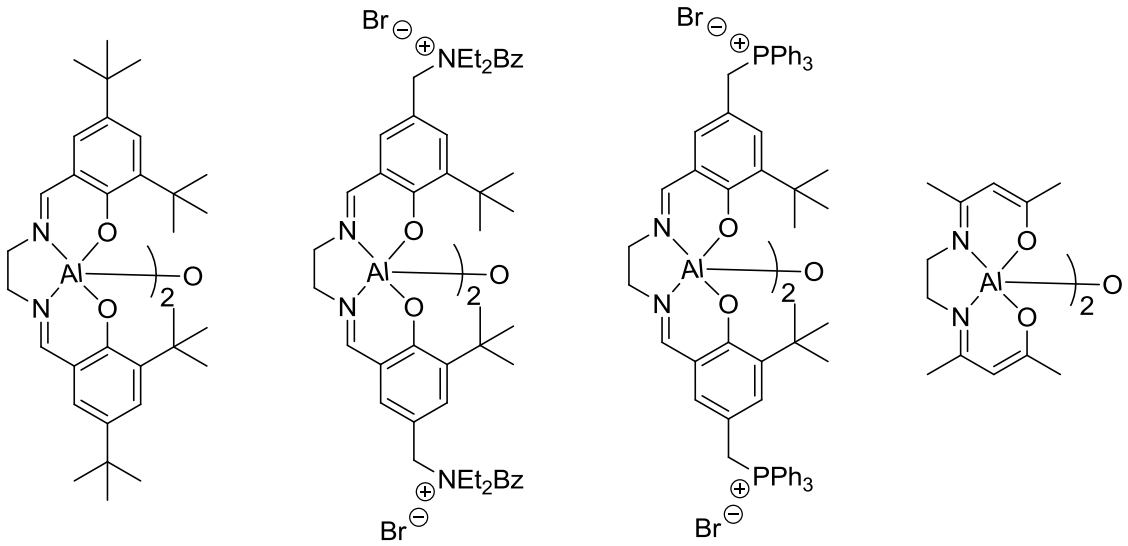


Figure 1

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Flash-38

Síntesis enantioselectiva de 4-alquinil dihidrocumarinas mediante adición conjugada de alquinos terminales catalizada por complejos de Zn(II) y ligandos de tipo hidroxiamida

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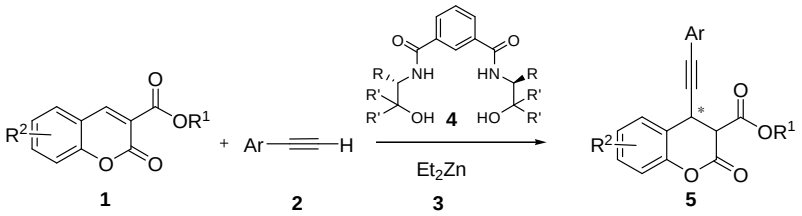
Los núcleos de cumarina y dihidrocumarina se encuentran presentes en un gran número de productos naturales y compuestos de interés biológico y farmacológico.[1] Consecuentemente, el desarrollo de procedimientos que permitan preparar derivados de estos compuestos, especialmente en forma enantioméricamente enriquecida, presenta un gran interés. La adición conjugada de nucleófilos carbonados al doble enlace de cumarinas permite la obtención de dihidrocumarinas funcionalizadas con un centro estereogénico en la posición 4. Recientemente se ha descrito la adición conjugada asimétrica de dialilestaño a 3-alcoxicarbonil cumarinas mediante doble activación con complejos de Yb(III) y Cu(I).[2] Sin embargo, no existen precedentes de adición de alquinos a estos compuestos, lo que resultaría de gran interés debido a las amplias posibilidades de manipulación del triple enlace en los productos resultantes. [3]

En esta comunicación describiremos un procedimiento para la alquinilación enantioselectiva de 3-alcoxicarbonil cumarinas **1** empleando alquinos terminales **2**, dietilcinc (**3**) y ligandos de tipo bis-hidroxiamida **4** desarrollados en nuestro grupo de investigación.[4]



Agradecimientos: Ministerio de Ciencia e Innovación y FEDER (CTQ2009-13083), y Generalitat Valenciana (ACOMP/2012/212). A S-M agradece la concesión de una beca pre-doctoral (FPI) al MICINN.

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Flash-39

Síntesis Regio- y Diastereoselectiva de Híbridos β-Lactama-Triazol Mediante Reacción Secuencial de Passerini/Cicloadición 1,3-Dipolar Azida-Alquino Catalizada por Cu (I)

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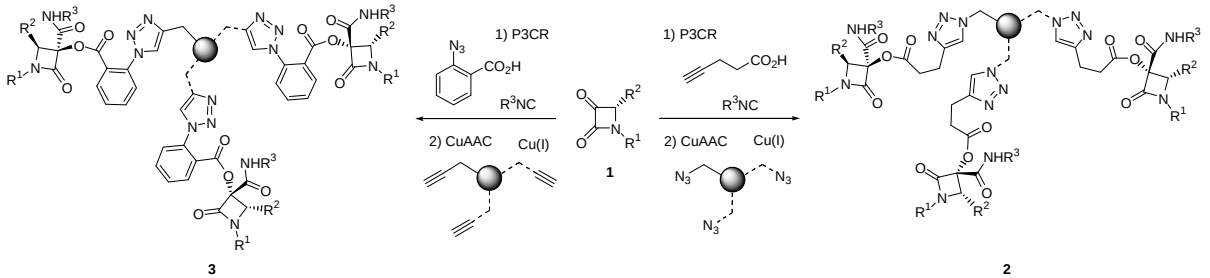
Las reacciones multicomponente (MCRs) son una poderosa herramienta sintética que permite generar elevada complejidad y diversidad estructural en un único paso. En particular, los procesos multicomponente basados en isonitrilos, tales como la reacción de Passerini de tres componentes (P3CR) son especialmente interesantes debido a su versatilidad y selectividad.[1]

Por otra parte, la reacción de cicloadición 1,3-dipolar entre azidas y alquinos, catalizada por cobre (CuAAC),[2] constituye la manera más rápida y eficiente de sintetizar el anillo de 1,2,3-triazol. Esta reacción es, sin lugar a dudas, la más utilizada dentro de todas las transformaciones clasificadas bajo el nombre de "*click chemistry*".[3]

En este contexto, y continuando con nuestro interés por la funcionalización del anillo de 2-azetidinona utilizando procesos multicomponente,[4] se describe la síntesis de híbridos β-lactama-triazol mono-, di- y triméricos, que conjugan ambos rasgos estructurales de reconocida importancia biológica.[5] La combinación de las α-oxo-β-lactamas **1** con diferentes isonitrilos y ácidos carboxílicos funcionalizados da lugar a los correspondientes aductos Passerini con un control total de la diastereoselectividad. La posterior reacción de estos compuestos, sin necesidad de ser aislados, con azidas o alquinos permite obtener diferentes híbridos β-lactama-triazol **2** y **3**, respectivamente, con buenos rendimientos químicos y total regioselectividad.



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Flash-40

Heterogeneous Catalysis with Immobilized Palladium Nanoparticles on Metal-Organic Frameworks (Pd@MOF)

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Due to the growing need for sustainable development, enormous efforts to develop environmentally friendly and efficient catalytic systems have been made. In this context, heterogeneous catalysis offers great advantages from an industrial and environmental point of view. Heterogeneous catalysts can be separated from the reaction media, they can be recycled more easily than homogeneous catalysts, and the production of waste can be minimized. We describe here our latest results on the synthesis and characterization of a novel heterogeneous catalyst that consists of palladium nanoparticles incorporated in a functionalized metal-organic framewrok (MIL-101(Cr), **Figure 1**).[1]

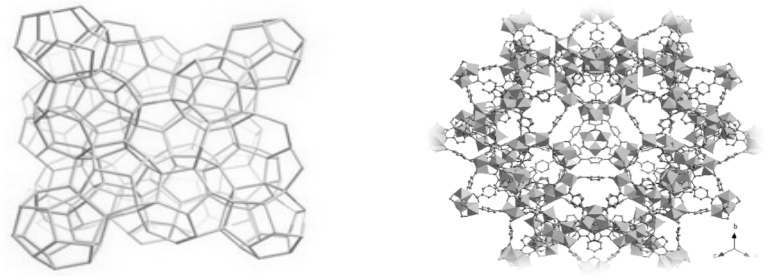

Figure 1. Zeotype architecture of MIL-101(Cr) (left) and structure of the large cage (right).

We also present the catalytic activity of the palladium catalyst (**Figure 2**) in the aerobic oxidation of alcohols.[2]

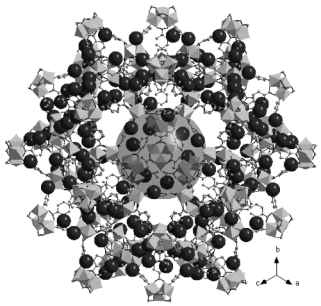

Figure 2. Palladium nanoparticles inside functionalized MIL-101(Cr).

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Flash-41

Nuevos Complejos de Ru(II): Metalosurfactantes Luminiscentes y "Cassettes" Polipiridinas-BODIPY

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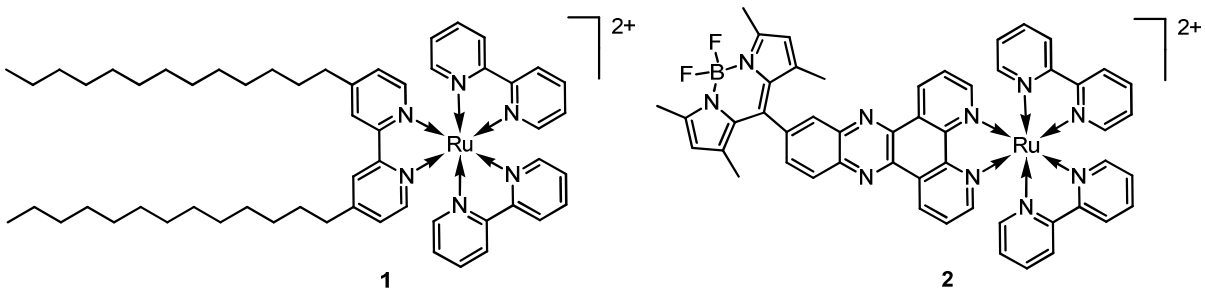
El diseño de estructuras moleculares capaces de responder a un estimulo externo son la base para construir dispositivos moleculares. Cables moleculares, diodos y transistores son algunos ejemplos, con aplicaciones en campos tales como medicina, biotecnología, electrónica, y optoelectrónica. De particular importancia son los sistemas supramoleculares donde los procesos fotoinducidos de transferencia de carga y energía se puedan dar a largas distancias y en direcciones predeterminadas. El diseño de una estructura supramolecular, con el espaciado adecuado entre niveles electrónicos, que posibiliten procesos fotoinducidos de transferencia de carga con alta eficiencia, es el primer paso para realizar una verdadera conversión fotoquímica de energía solar.

Metalosurfactantes lumininiscentes,[1] con distintos grupos dadores o aceptores, capaces de formar agregados mixtos y que formen agregados coloidales, útiles en procesos de transferencia de carga y/o energía, así como especies multicromofóricas han recibido una gran atención en los últimos años debido a las favorables propiedades fotoquímicas y fotofísicas que presentan para su aplicación como sistemas sintéticos de conversión y almacenamiento de energía solar y en dispositivos optoelectrónicos. Entre estos últimos sistemas se encuentran los formados por uno o más cromóforos BODIPYs (emisor singlete) y complejos de polipiridina-Ru(II) (emisor triplete).[2]

En esta comunicación se describe la síntesis de metalosurfactantes y complejos derivados de tris-bipiridina o bis-terpiridina-Ru(II) unidos covalentemente a BODIPYs. Un ejemplo de cada tipo de sistemas se muestra en la Figura 1.



1 **2**

Se están estudiando las propiedades fotofísicas de estos sistemas, incluyendo las duraciones de los tiempos de vida de los diferentes estados involucrados. Los resultados que se están obteniendo muestran efectos muy prometedores.

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Hierarchical Organization of Supramolecular Materials for C_{60}-Based Photoactive Devices

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The objective of nanotechnology is to handle matter at the molecular level thus creating new materials with unique biological and physical properties.[1] In this sense, the "bottom-up" approach to nanotechnology deals with the controlled hierarchical assembly of organized and linked molecules in order to obtain nanoscale structures. Thermodynamic control of the molecular self-assembly can be achieved by non-covalent interactions such as hydrogen bonds, electrostatic interactions, π-π stacking, metal-ligand coordination or van der Waals forces. The presence of different non-covalent binding motifs in the same molecule can give rise to hierarchically organized super-structures with outstanding properties.[2]

One of the most realistic applications of the "bottom-up" approach is the creation of optoelectronic devices as well as artificial photosynthetic systems. For such a system, it is crucial the presence of redox- and photo-active centers in the molecules able to act as n and p-type materials, therefore producing photoinduced electron and/or energy transfer events.[3]

With their extended and delocalized π-electron system, good electron acceptor features and low reorganization energy, fullerenes represent a paradigmatic example of n-type and have been successfully used in the preparation of optoelectronic devices such as solar cells or field effect transistors.[4] As p-type materials, efficient electron-donor molecules, like for instance porphyrins[5] and extended tetrathiafulvalene derivatives (exTTFs)[6] are being widely used.

In our labs, we have prepared new families of supramolecular C_{60} derivatives endowed with different donor moieties, which allow photoinduced electron and/or energy transfer events. The well-defined nanometric structure together with the electronic and optical properties of the assemblies thus obtained, make them very appealing candidates for the preparation of photoactive devices such as organic solar cells or field effect transistors (OFETs).

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Flash-43

C_{60} dumbbells-type molecular wires

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Organic electronics is one of the most known fields in which the use of fullerene C_{60} has been mentioned.[1] Due to its opto-electronic properties, C_{60} has been widely used in photo-induced electron transfer studies to measure the conductivity along Donor-Bridge-Acceptor system. On the other hand, the good affinity, revealed recently, for gold or graphite electrodes envisages the fullerenes as suitable anchor groups in molecular junction approach.[2]
In this regard, we have already synthesized dumbbell type molecules in which the pyrrolidine ring acts as a spacer between C_{60} and the bridge.[3]
Recently, the results of the difluorene dumbbell-type molecule have been reported[4] using STM technique in a singular way. Fullerenes, in fact, could be considered as *"beacons"* to be detected onto surface.

Herein, we report our strategy to obtain dumbbell molecules using fluorene as π bridge core linked to C_{60} by different spacers (X in figure 1).
Preliminary results obtained by STM or MCBJ will be shown.

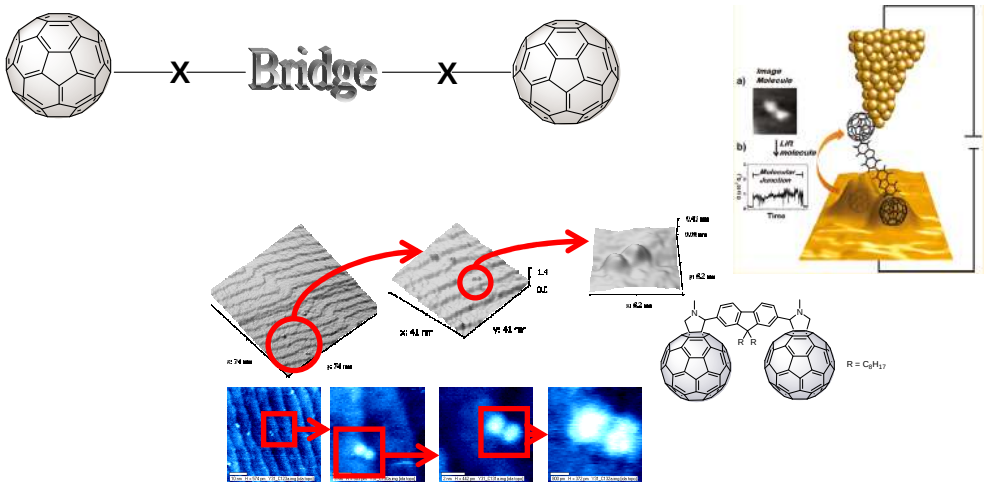

Figure 1. STM studies onto dumbbell molecules

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Lipophilic cavitands based on Calix[4]pyrrole scaffolds

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Cavitands are macrocyclic compounds with enforced cavities[1]. The concave surface provided by the large aromatic cavity build-in the structure of these compounds make them interesting species for the inclusion of other molecules or ions (molecular containers). In this presentation, we will describe the synthesis and structural characterization of a novel series of lipophilic cavitands based on calix[4]pyrrole scaffolds. The elaboration of the upper rim of the calix[4]pyrrole-resorcinarene hybrid[2] through nucleophilic aromatic substitution with electron-poor aromatic systems afforded deeper cavitands in moderate yields. Deep cavitands, as the ones presented here, can adopt two conformations, kite or vase, depending on the arrangement of the aromatic rings installed in the upper rim. In both conformers, the calix[4]pyrrole core is probably locked in a cone conformation by inclusion of solvent molecules. *N*-oxides and other electron rich molecules or ions can displace the included solvent molecule and become encapsulated. The control of the switching process between the two conformers[3] of the cavitands is under current investigation. We expect that the inclusion of suitable guests stabilizes the vase conformer by establishing intermolecular interactions with the aromatic flaps of the cavitand.

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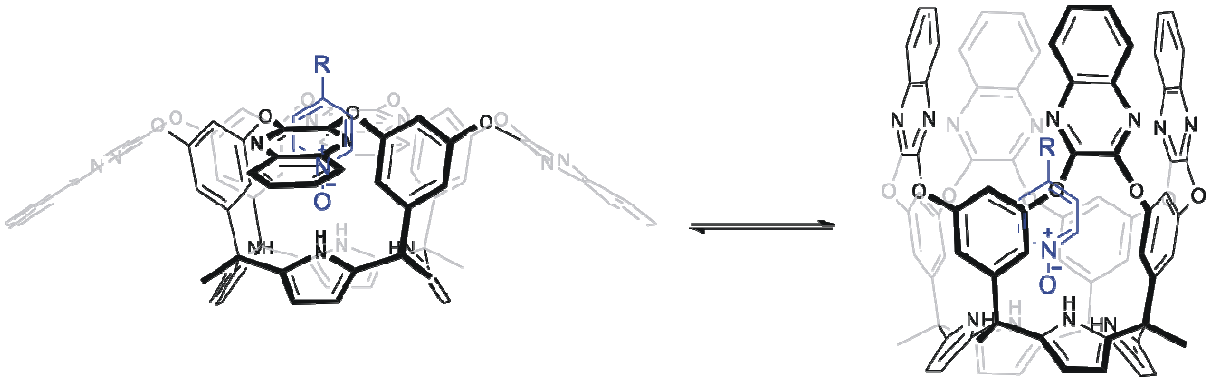

Figure. Molecular structure of the tetraquinoxaline calix[4]pyrrole deep cavitand with an included N-oxide pyridyl derivative showing the equilibrium that exist between the kite and the vase conformers.

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Flash-45

Toward Cyclic α,γ-Glycopeptides Derivatives

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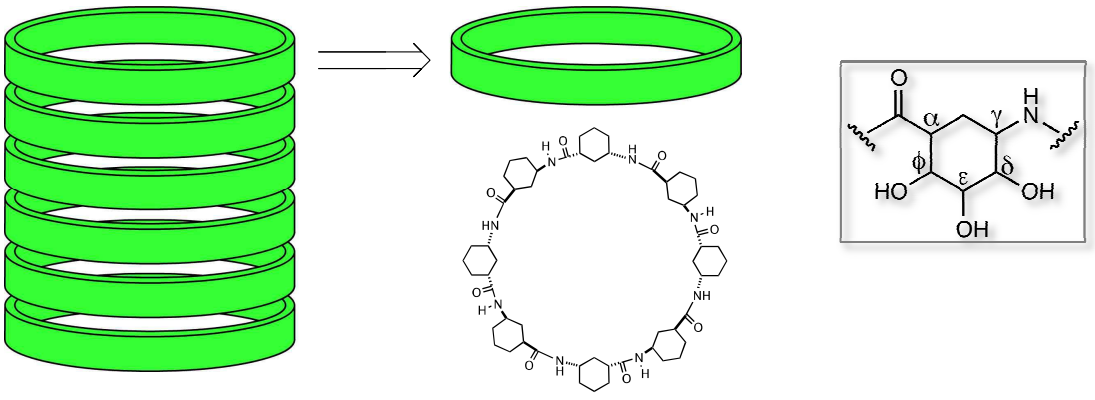
Over the last years many groups have been working in the self-assembling peptide nanotubes (SPN) field, for their technological and biological applications.[1] Our group is a pioneer in this field and we have focused on the design, synthesis and properties of cyclic peptides (CPs) made of alpha and gamma amino acids.[2] The γ-Aminocycloalkanecarboxylic acids (γ-Acas) might include different functional groups on their methylene groups that allow the modification of the inner or outer surface of the ensemble without disrupting their self-assembling properties.

The structural elucidation in 2002 of the natural cyclic glycopeptides antibiotics named mannopeptimycins[3] has focus attention in the design of CPs for their potential biological applications.[4]

In this communication, we will present our design, synthesis and structural results from CP constituted by γ-Acas derived from monosaccharides that contains hydroxy groups on the δ, ε, and/or ϕ position; with the idea to expand these designs to α,γ-SPN with antimicrobial properties.



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Nuevos Derivados de BODIPY: Láseres Altamente Eficientes y Fotoestables

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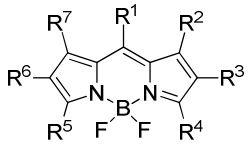
Entre los colorantes orgánicos, los 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenos, conocidos comúnmente con el nombre comercial de BODIPY, se consideran hoy como unos de los colorantes más útiles y versátiles, con numerosas aplicaciones entre las que cabe destacar su utilidad como colorantes láser. Presentan alta eficiencia láser, buena fotoestabilidad, altos rendimientos cuánticos de fluorescencia, bajo cruce intersistema y elevados coeficientes de absorción molar.[1] Uno de los principales problemas relacionados con el uso de estos colorantes como fuente de radiación láser es su exposición a elevadas irradiaciones de bombeo y temperatura, lo que limita significativamente su fotoestabilidad, disminuyendo la vida útil de los colorantes, por lo que se hace necesaria la búsqueda de nuevos BODIPYs con estabilidad y eficiencia superiores a los actualmente conocidos. En esta área nuestro grupo de investigación ha descrito recientemente colorantes láser de esta familia con emisión en diferentes regiones del espectro visible (naranja-rojo).[2]

En esta comunicación se describen unos nuevos colorantes con estructura de BODIPY **1** caracterizados por presentar en su estructura al menos un átomo de cloro covalentemente unido al sistema carbonado de boradiazaindaceno. Para la síntesis de los nuevos compuestos se han seguido tres estrategias generales previamente descritas para otros halo-BODIPYs via reacciones de sustitución electrófila.



1

R^1 = Alquilo, arilo; R^2, R^7, R^3, R^6 = H, alquilo, Cl; R^4, R^5 = H, alquilo, arilo, Cl

Se ha observado que los nuevos colorantes permiten mejorar la fotoestabilidad y la eficiencia láser respecto a sus análogos no clorados. Estos compuestos pueden ser especialmente útiles como medio activo en láseres de colorante tanto en fase líquida como en estado sólido, aumentando la vida útil de éstos y también en todas aquellas aplicaciones ópticas y analíticas propias de los colorantes.

1. (a) Loudet, A.; Burgess, K. *Chem. Rev*. **2007**, *107*, 4891-4932. (b) Ziessel, R.; Ulrich; G.; Harriman, A. *New J. Chem.* **2007**, *31*, 496-501. (c) Ulrich, G.; Ziessel, R.; Harriman, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 1184-1201. (d) Arbeloa, F. L.; Banuelos, J.; Martinez, V.; Arbeloa T.; Arbeloa, I. L. *Trends in Physical Chemistry* **2008**, *13*, 101-122. (e) Benniston, A. C.; Copley, G. *Phys. Chem. Chem. Phys*. **2009**, *11*, 4124-4131. (f) Benstead, M.; Mehl, G. H.; Boyle, R. W. *Tetrahedron* **2011**, *67*, 3573-3601. (g) Boens, N.; Leen V.; Dehaen, W. *Chem. Soc. Rev*. **2012**, *41*, 1130-1172.
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Flash-47

Boradiazaindacenos (BODIPYs) como Generadores de Oxígeno Singlete

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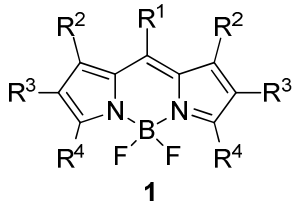
La terapia fotodinámica (*PhotoDynamic Therapy*, PDT) es un nuevo tratamiento de determinados tipos de cáncer y otras enfermedades para alguna de las cuales casi no existen tratamientos alternativos. Está basada en la aplicación de un fotosensibilizador sobre el tejido canceroso que cuando se irradia con luz visible provoca la generación de especies citotóxicas, siendo la más importante el oxígeno singlete, que da lugar a la muerte de las células cancerosas por apoptosis. Los fotosensibilizadores más utilizados son derivados de las porfirinas pero se ha observado que otros compuestos, como por ejemplo los 4-bora-3a,4a-diaza-*s*-indacenos o BODIPYs[1] adecuadamente sustituidos pueden también emplearse.

Entre ellos, los bromo y yodo-derivados pueden actuar como fotosensibilizadores en PDT ya que dan lugar a la generación eficiente de oxígeno singlete por un aumento del cruce intersistema debido a la presencia del átomo pesado.[2] Recientemente, nuestro grupo de investigación ha realizado un estudio sobre la reacción de yodación selectiva de BODIPYs con distinto grado de sustitución, observando que alguno de los derivados obtenidos son excelentes generadores de oxígeno singlete.[3]

En esta comunicación se describe el diseño y síntesis de una serie de BODIPYs bromados y yodados **1** en distintas posiciones del esqueleto de BODIPY y se estudia la influencia que ejerce la posición de estos halógenos en la generación de oxígeno singlete.

Los resultados obtenidos muestran que la posición en la que se encuentra el halógeno tiene un marcado efecto sobre las propiedades fotofísicas y modula la capacidad fluorescente del BODIPY resultante. En general, la sustitución en las posiciones 3 y/o 5 favorece la fluorescencia mientras que el resto de posiciones la disminuye, y se activa el proceso de cruce intersistema.



1

R^1 = Alquilo, arilo; R_2 = H, Br, I; R_3 = Br, I; R_4 = Br, I, $CH(COOCH_3)_2$, $NHC_6H_4OCH_3$

1. (a) Loudet, A.; Burgess, K. *Chem. Rev*. **2007**, *107*, 4891-4932. (b) Ziessel, R.; Ulrich; G.; Harriman, A. *New J. Chem.* **2007**, *31*, 496-501. (c) Ulrich, G.; Ziessel, R.; Harriman, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 1184-1201. (d) Boens, N.; Leen V.; Dehaen, W. *Chem. Soc. Rev.* **2012**, *41*, 1130-1172.
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Flash-48

Amphiphilic Bent-Core Based Molecules And Their Supramolecular Organizations

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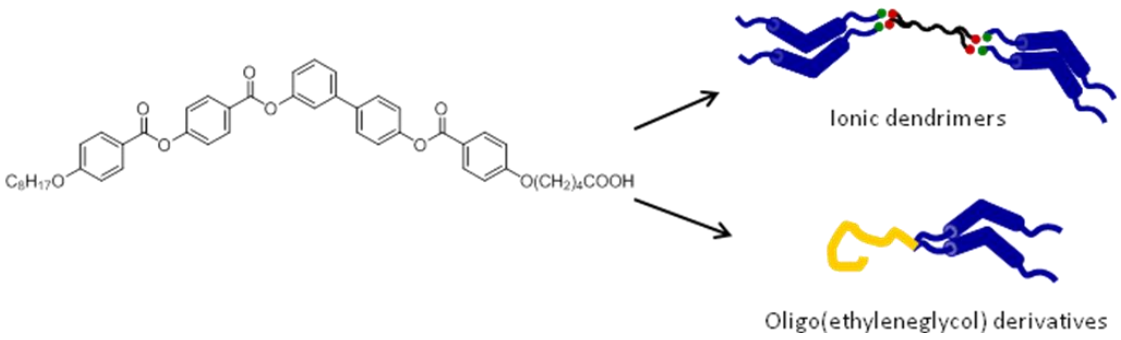
The combination of polar and nonpolar structures in classical calamitic or discotic liquid crystalline molecules have been used to modulate the melting and the stability of mesophases, specially if highly flexible oligo(ethylene oxide) units are used. Likewise complex self-assembled supramolecuar architectures can also be generated by the segregation of the incompatible polar/nonpolar moieties of the material spontaneously, either in bulk or promoted by the presence of a solvent.

Herein, we report synthesis and characterization of two different types on bent-shaped structures combining polar and nonpolar units. Besides, supramolecular organizations of these oligo(ethylene oxide) or ionic dendrimeric bent-core based molecules have been study in bulk and in the presence of water.



Most of the materials form liquid crystals providing lamellar and columnar organizations depending on the system studied. Interestingly, many of them have also the ability to induce lamellar arrangements in water, affording different morphologies, as they have been observed by TEM and SEM techniques.

Acknowledgments. Financial support from the Spanish Government (CICYT-FEDER MAT2009-14636-C03-01), Aragon Government and CSIC are gratefully acknowledged.

Flash-49

Novel cyclobutane based chiral surfactants: synthesis, physico-chemical behavior and applications

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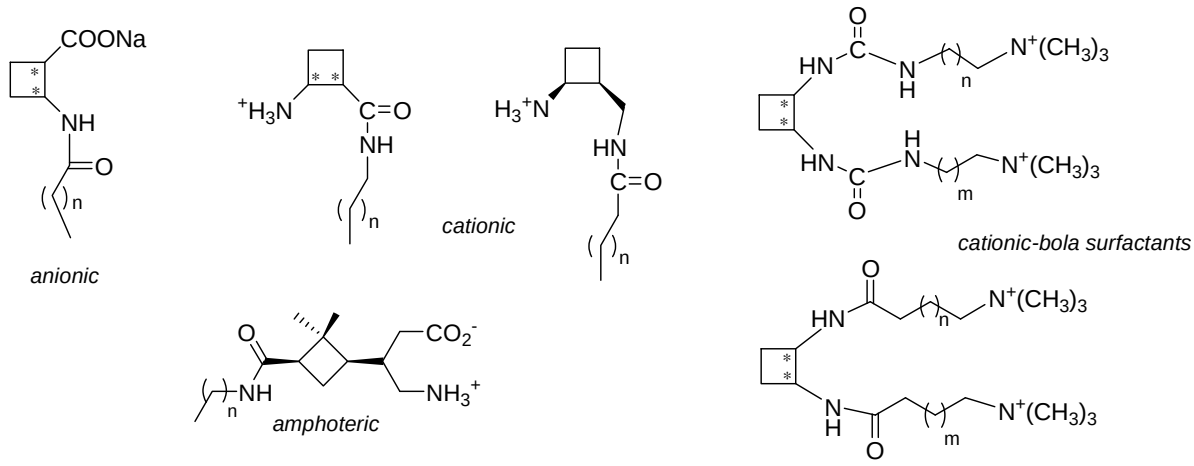
Alicyclic homo and hetero disubstituted compounds, such as β- and γ-amino acids and 1,2-cyclic diamines are extremely versatile building blocks in organic chemistry. They are used as scaffolds for the preparation of various derivatives ranging from foldamers[1] to gelators[2] and self-assembling molecules (used as templates for inorganic nanostructures),[3] thanks to the possibility to control, exploit and modulate their stereochemistry, steric demand and rigidity.

Herein we report on the stereoselective synthesis of new chiral single head-single tail and bola surfactants derived from β- and γ,ε-cyclobutane amino acids and 1,2-diaminocyclobutane building blocks (Scheme), on the investigation of their aggregation properties and on their potential applications. We also report on the investigation of chirality and chiral recognition of their aggregates.



Aggregates formed by chiral amphiphiles, have been largely investigated as media for enantioselective reactions, enantioselective separations and as suitable models for investigating the role of chirality in biological membranes.[4] However, to the best of our knowledge there are no reports concerning chiral surfactants derived from unnatural cyclobutane amino acids and 1,2- diamine so our aim is to investigate how the conformational constraints imposed by the rigid four-membered ring will affect their properties, aggregation behavior and the hierarchical transfer of chirality from the monomers to the assembly.

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[2] (a) De Loos, M.; *et al. Org. Biomol. Chem.* **2005**, *3*, 1631-1639; (b) Zweep, N.; *et al. Langmuir* **2009**, *25*, 8802-8809.
[3] (a) Jung, J. H.; *et al. J. Am. Chem. Soc.* **2000**, *122,* 5008-5009; (b) Kobayashi, S. *et al. J. Am. Chem. Soc.* **2002**, *124,* 6550-6551.
[4](a) Bombelli, C.; *et al. J. Am. Chem. Soc.* **2008**, *130,* 27-32-2733; (b) Borocci, S.; *et al. Synlett.* **2009**, *7*, 1023-1033; (c) Sorrenti, A.; *et al. Tetrahedron: Asymmetry*, **2009**, *20*, 2737-2741.

Flash-50

Carbon Nanotubes as Nanometric Support: Application to Catalysts Recycling

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The immobilization of homogeneous catalysts on solid support is very attractive to facilitate their recycling and reuse.[1] However, the "heterogenized" catalysts developed so far, suffer from decreased catalytic activities and enantioselectivities due to restriction by the solid matrix, which limits mobility and accessibility of the active sites. Herein, we present a possible solution to overcome these limitations by applying a new concept for the recycling based on the non-covalent interaction of the active catalyst and the solid support. The approximation which uses carbon nanotubes as molecular jig,[2] is based on the adsorption of our recently developped chiral catayst **1**,[3] onto the carbon nanotube surface through π–π interaction,[4] Figure 1.

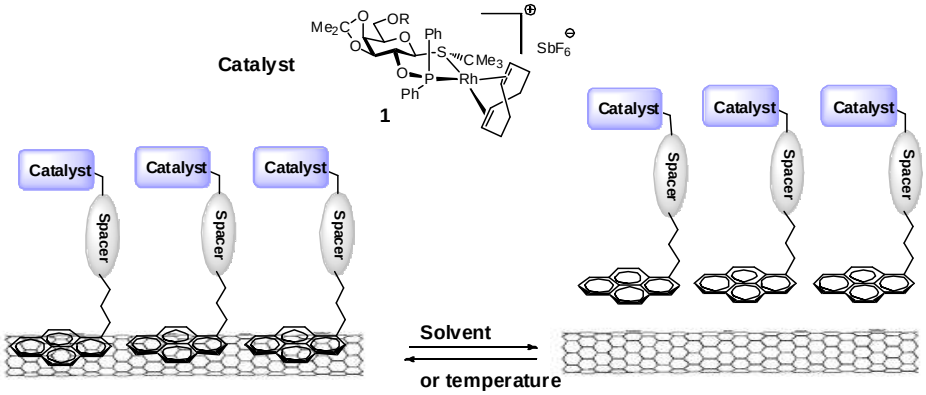

Figure 1

The new nanosystem perform catalysis in a homogeneous manner in the solvents and at temperature where the π–π interaction is weak (Figure 1B), and allow the recycling of the chiral catalyst through solid/liquid separation by simply changing the solvent to those solvents where the π–π interaction is strong, Figure 1.

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Flash-51

Catálisis sostenible en la síntesis de azepanos a través de la ciclación de Prins

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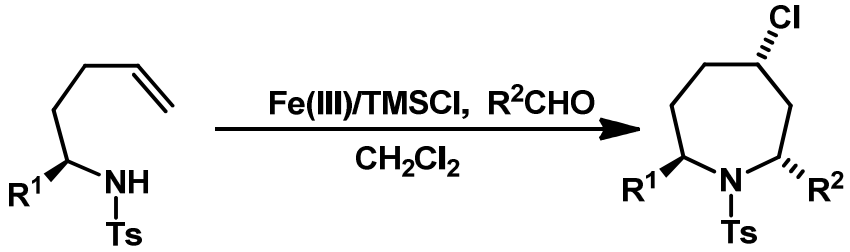
La ciclación de Prins es una de las metodologías más potentes para la generación de heterociclos (tanto oxigenados como nitrogenados), mediante la formación de enlaces carbono-carbono, lo que la convierte en una gran herramienta en la síntesis orgánica. La ciclación de Prins en su versión nitrogenada permite un acceso rápido y directo a distintos aza-ciclos presentes en múltiples productos tanto de origen sintético como natural, pero aun así ha recibido menos atención que la versión oxigenada de dicha ciclación.[1]

En nuestro grupo de investigación tenemos experiencia en la síntesis de azaciclos de seis miembros a través de la ciclación de Prins y en un contexto de catálisis sostenible,[2] por lo que decidimos extender dicha metodología a la síntesis de azepanos diferentemente sustituidos. Esta nueva metodología posee además numerosas ventajas: bajo coste, respetuosa con el medio ambiente, obtención sencilla de los productos de partida y en un solo paso de reacción se forma un enlace C-C, C-N y C-Cl con control de la estereoquímica.



Esquema 1: Síntesis de azepanos mediante catálisis sostenible con Fe(III).

En este trabajo presentaremos los resultados de nuestra metodología en la obtención de aza-ciclos de siete miembros y mostraremos su alcance y limitaciones.

Agradecimientos: Este trabajo ha sido financiado por el Ministerio de Economía y Competitividad (MINECO), cofinanciado con fondos FEDER (CTQ2011-28417-C02-01). M. P. agradece a la ULL por la concesión de una beca SEGAI. SJP agradece al MINECO una beca F.P.U.

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Flash-52

Síntesis de pirrolidinas quirales altamente funcionalizadas

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La construcción de una manera estereoselectiva de heterociclos nitrogenados altamente funcionalizados es un objetivo importante para la química de los productos naturales y la química medica. La nitronas son herramientas sintéticas de gran utilidad en la química orgánica, especialmente, en el campo de los alcaloides y de los productos naturales.

La nitrona[1] 1 fue elegida como material de partida, ya que es un compuesto ampliamente utilizado en la síntesis de compuestos activos biológicamente como pirrolidinas o pirrolizidinas polihidroxiladas.[2] En este sentido hemos sido capaces de ampliar la enorme versatilidad de este sintón para la construcción de pirrolidinas altamente funcionarizadas (Figura 1) y sistemas bicíclicos de una forma sencilla y en pocos pasos. La enorme variedad de compuestos obtenidos y funcionalizaciones abre la puerta para la obtención de análogos de pirrolizidinas e indolizidinas con funcionalización extra.

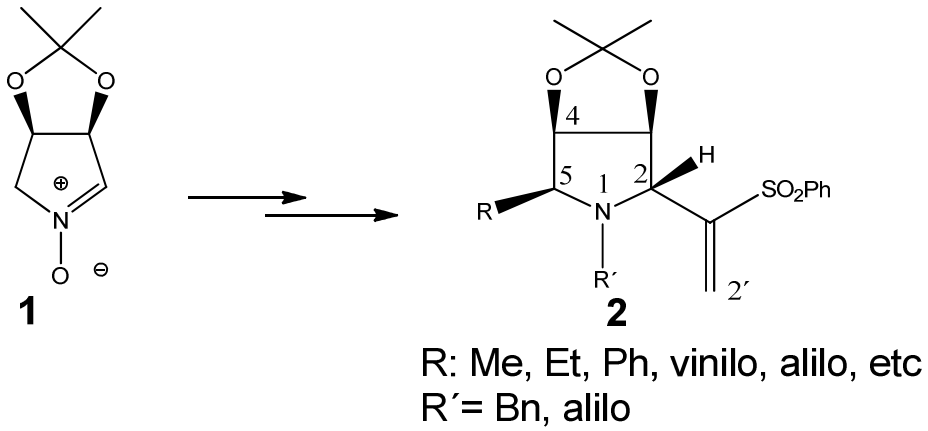

Figura 1

[1] (a) Flores, M. F.; García, P.; Garrido, N. M.; Sanz, F.; Diez, D. *Acta Cryst*. **2011**, *E67*, o1115. ; (b) Flores, M. F.; Garcia, P.; Garrido, N.M.;Nieto, C.; Basabe, P.; Marcos, I. S.; Sanz, F.; Goddman, J.N.; Diez, D. *Tetrahedron*: *Asymmetry*, **2012,** 23, 76–85.

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Flash-53

Sulfinyl-Mediated Stereoselective Overman Rearrangements and Diels-Alder Cycloaddition

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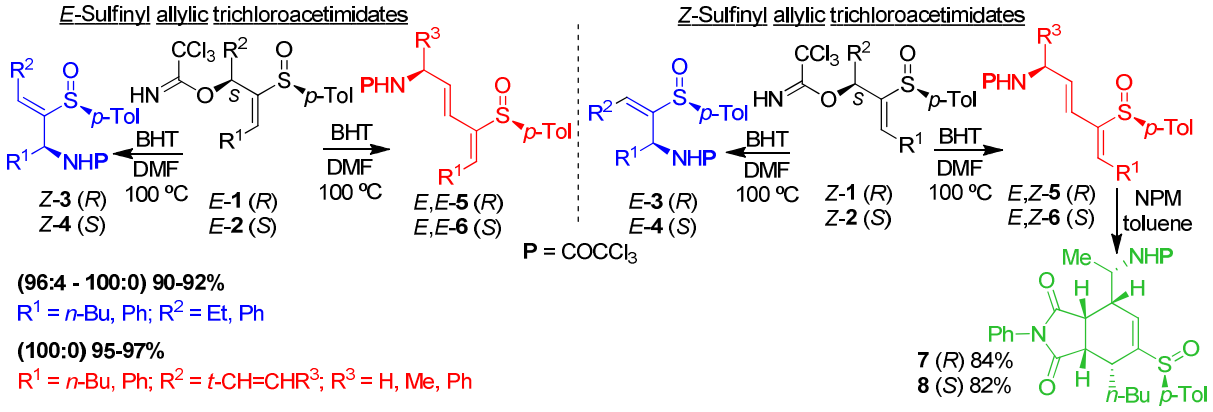
The synthesis of chiral allylic amines is a problem of current interest in synthetic methodology, medicinal chemistry, and synthesis of natural products. The [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates (Overman Rearrangement),[1] is one of the most general routes to allylic amine derivatives.
E-Sulfinyl allylic trichloroacetimidates *E*-**1** (*R*) and diastereoisomers *E*-**2** (*S*) with representative R^1 and R^2 have been studied, obtaining allylic trichloroacetamides *Z*-**3** and *Z*-**4** respectively, with *Z* geometry[2] in excellent yields and selectivities especially for isomers **2**, complementing our previous synthesis of allylic sulfinyl amines.[3] The influence of vinyl sulfoxide geometry was tested and *Z* substrates *Z*-**1** (*R*) and *Z*-**2** (*S*) were used to produce *E* trichloroacetamides *E*-**3** and *E*-**4** respectively as single isomers and in excellent yields.



We examined bis-allylic substrates and to our delight, the rearrangement took place with complete stereo and chemoselectivity, often elusive in the known examples,[4] to produce dienes **5** and **6** in excellent yields, with the apropiate stereochemistry and double bond geometry.
Exploratory experiments on the behavior of our sulfinyl amido dienes *E*,*Z*-**5** and *E*,*Z*-**6** in diastereoselective Diels-Alder[5] with *N*-phenylmaleimide (NPM) afforded excellent yields of α-endo cycloadducts **7** and **8** respectively as single isomers.[6]

[1] (a) Overman, L. E.; Carpenter, N. E. *Organic Reactions* **2005**, *66*, 1–107. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218-224.
[2] In sharp contrast with: Lee, S. I.; Moon, S. Y.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 3234-3237.
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[4] Chemoselective Overman rearrangement on bis-allylic trichloroacetimidates continues to be a challenge, since poor selectivity (60:40) has been achieved. See ref. 1.
[5] (a) Fernández de la Pradilla, R.; Montero, C.; Viso, A. *Chem. Commun.* **1998**, 409-410. (b) Fernández de la Pradilla, R.; Montero, C.; Tortosa, M.; Viso, A. *Chem. Eur. J.* **2005**, *11*, 5136-5145.
[6] Cycloaddition with the amido sulfonyl diene gave a 66:34 mixture of sulfone adducts, establishing that the stereochemical outcome of the Diels-Alder cycloaddition is primarily controlled by the chiral sulfur atom.

Preparación de heterociclos ópticamente actives mediante procesos biocatalíticos

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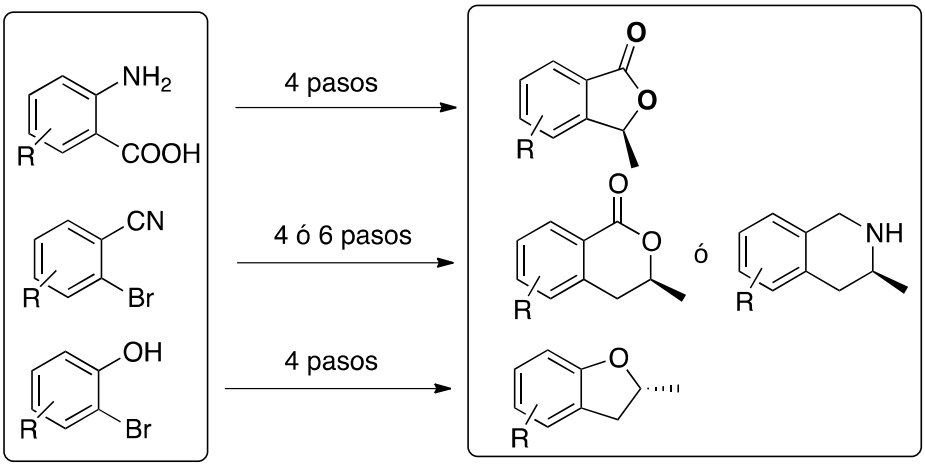
El desarrollo de estrategias sintéticas estereoselectivas para la preparación de heterociclos ópticamente activos, ha adquirido una gran importancia en síntesis orgánica en los últimos años. En particular, el desarrollo de metodologías sintéticas para la preparación de dihidrobenzofuranos, tetrahidroisoquinolinas, benzofuranonas e isocromanonas, posee un especial interés debido a que estas estructuras se encuentran presentes en una gran variedad de productos naturales con destacadas actividades biológicas.[1] Aunque los procesos organocatalíticos o empleando metales de transición han sido ampliamente desarrollados, las síntesis quimioenzimáticas han sido escasamente empleadas hasta la fecha.

La Biocatálisis ofrece un amplio intervalo de posibilidades sintéticas basándose en la resolución cinética (dinámica) de los heterocíclos finales, o bien permitiendo el acceso a precursores ópticamente activos, siendo las hidrolasas y oxidorreductasas clases de enzimas que actúan en condiciones suaves de reacción y con elevadas selectividades.[2] Por este motivo, en esta presentación se describe la preparación de diferentes tipos de heterociclos en forma enantiopura (Esquema 1) a través de diferentes rutas quimioenzimáticas, en las cuales la etapa clave es una transformación asimétrica, como por ejemplo la resolución de alcoholes racémicos empleando lipasas, o la biorreducción de cetonas proquirales catalizadas por alcohol deshidrogenasas. [3]



Esquema 1. Síntesis quimioenzimática de heterociclos ópticamente activos.

[1] *Targets in Heterocyclic Systems. Chemistry and Properties*, Vol. 10; Eds. Attanasi, O. A., Spinelli, D.; Societá Chimica Italiana:Roma, 2010.
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Flash-55

Aryne Cycloaddition Approach to Sterically Congested Large PAHs

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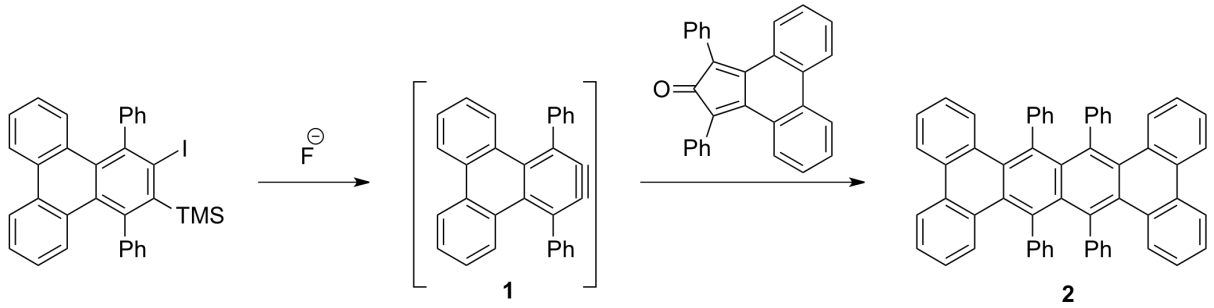
Polycyclic Aromatic Hydrocarbons (PAHs), and in particular acenes and acene derivatives, are considered privileged species as molecular materials.[1] Using a recently described methodology to prepare *o*-iodoaryl(trimethyl)silanes[2] as efficient aryne precursors, we have generated 1,4-diphenyl-2-triphenylyne **1.** Cycloaddition reactions of this polycyclic aryne afford large, sterically congested PAHs such as tetrabenzotetracene **2**.



Scheme 1

X-ray diffraction analysis of **2** confirms the twisted conformation previoulsy calculated by Pascal[3] for this longitudinally distorted acene. In particular, the end-to-end twist turns out to be 104.6º.

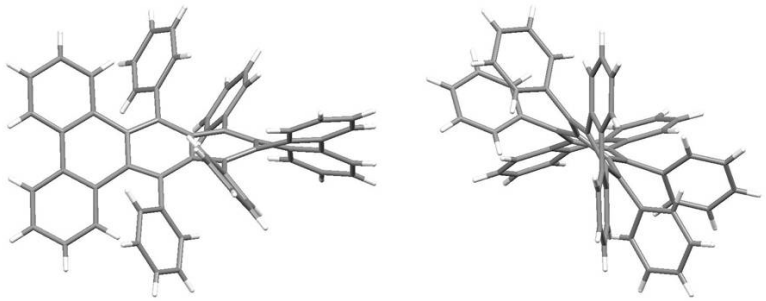


Figure 1. X-ray structure of **2** (top and lateral views).

[1] (a) J. E. Anthony, *Angew. Chem. Int. Ed.* **2008**, *47*, 452. (b) M. Bendikov, F. Wudl, F. Perepichka, *Chem. Rev.* **2004**, *104*, 4891.
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Olefination of Carbonyl Compounds through Reductive Coupling of Alkenylboronic Acids and Tosylhydrazones.

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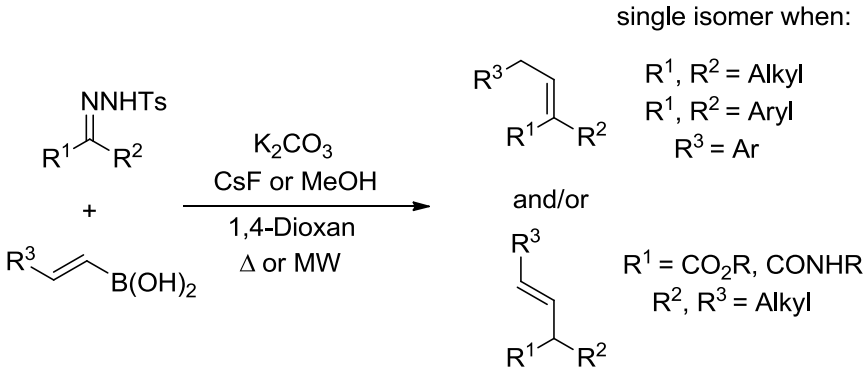
The selective creation of carbon-carbon bonds is a fundamental transformation of organic chemistry. In the recent years, among the metal-catalyzed cross-coupling, the development of efficient processes in terms of selectivity, availability of starting materials, operational simplicity, environmental sustainability that do not require a metal catalyst have attracted increasing attention. This methodology, called cross-coupling metal-free, has been employed to form C-C, C-O,[1] C-N,[2] C-S[3] and C-B[4] bonds between tosyhydrazones and different available coupling partners. Particularly, boronics acids are versatile reagents owing to their high stability and low toxicity. For example, we have recently reported a extremely simple and new metal-free C-C bond-forming between tosylhydrazones and boronic acids.[5]

In this context, a very general and efficient reductive cross-coupling of alkenylboronic acids and tosylhydrazones to form C-C bonds is shown. This transformation is very simple and takes place without the need of metal catalyst or inert atmosphere and tolerates a variety of functional groups. In addition, depending on the nature of the substituents, and in a predictable manner, the reaction gives rise to different isomers that differ in the position of the double bond (Scheme 1). Moreover, it is not necessary to isolate the tosylhydrazone and the reaction can be conducted in one pot directly from the carbonyl compound. Finally, this methodology could be envisioned as a new type of olefination of carbonyl compounds through tosylhydrazones.



Scheme 1

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Flash-57

Síntesis de nuevas moléculas binaftalénicas con simetría C_2 y con quiralidad central y axial

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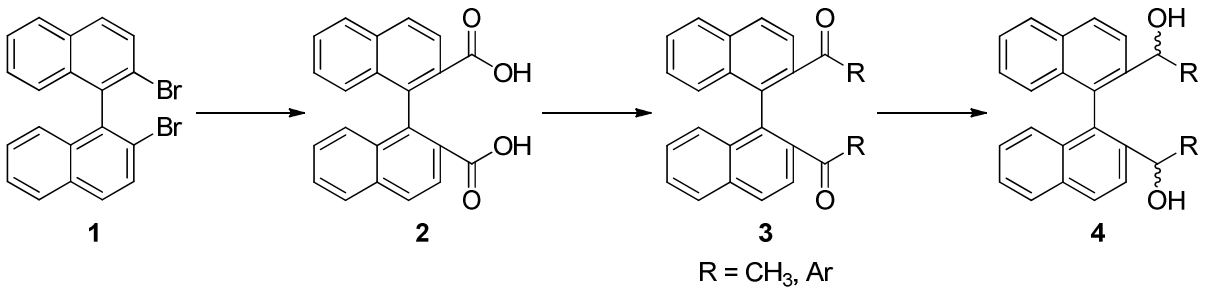
La línea principal de investigación de nuestro grupo se basa en la síntesis y el estudio de nuevos compuestos enantiopuros con una posible aplicación como agentes de solvatación quiral (CSA) y como auxiliares quirales.[1] El objetivo es introducir variaciones estructurales que mejoren el enantioreconocimiento de los CSA más usados actualmente y así poder mejorar la determinación de los excesos enantioméricos mediante la Resonancia Magnética Nuclear (RMN).

Actualmente, en nuestro grupo se está investigando en la síntesis de nuevos compuestos con estructura binaftalénica. Este esqueleto resulta muy interesante ya que introduce en estos compuestos un eje estereogénico además de los otros posibles centros quirales que la molécula presente, generando así una simetría axial C_2, característica muy interesante en estas aplicaciones por simplificar los espectros de RMN y reducir el número de posibles estados de transición.

Así, partiendo del compuesto 2,2'-dibromo-1,1'-binaftaleno, **1**, en su forma racémica, se ha obtenido el diácido racémico **2**,[2] que es el precursor en la síntesis de un conjunto de cetonas **3**. Se ha estudiado la diferente reactividad de estas cetonas en reacciones de reducción usando tanto hidruros metálicos aquirales como diversos métodos de reducción enantioselectivos. De esta manera se han sintetizado los diferentes diastereoisómeros de los dioles **4** de forma enantiopura con unos excesos enantioméricos muy buenos. Además, se ha conseguido determinar la configuración absoluta de los dioles **4** sintetizados mediante resolución del diácido **2**, difracción de rayos X y CHPLC.

Estos últimos compuestos son los interesantes en el campo de los agentes de solvatación quiral y de los auxiliares quirales y en alguno de ellos ha sido estudiada esta aplicación como CSA mediante ensayos de solvatación quiral.



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Formation of vinyl oxetanes catalyzed by chloride ammonium salts

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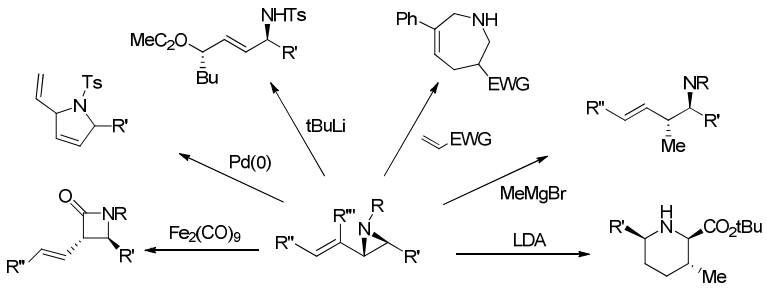
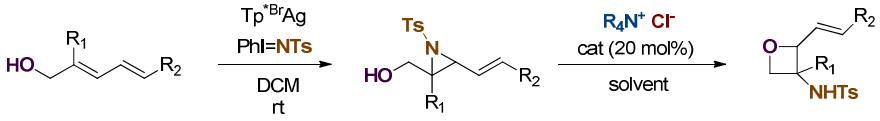
Vinylaziridines are versatile building blocks for stereoselective synthesis of biologically and synthetically important compounds, due to their high reactivity and ability to act as carbon electrophiles.[1] In particular, vinylaziridines can be regio- and stereoselectively opened by various carbon and heteroatom nucleophiles making them very useful precursors for the synthesis of functionalized amines. Moreover, appropriately functionalized vinylaziridines give an easy access to a wide range of interesting products such as allyl amines,[2] homoallyl amines,[3] β-lactams,[4] pyrrolidines,[5] pyperidines[6] and azepines[7] (Scheme 1).



Scheme 1

We have recently developed a regio- and stereoselective procedure for the preparation of hydroxymethyl vinyl aziridines,[8] which offer new synthetic possibilities through reactions at the hydroxylic oxygen. In this communication, we will also present a new method for the synthesis of vinyl oxetanes promoted by ammonium chloride (Scheme 2). The scope of the reaction and the mechanism of this new organocatalytic reaction will be described.



Scheme 2

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Flash-59

Microwave-Assisted Domino Access to C_2-Chain Functionalized Furans from Tertiary Propargyl Vinyl Ethers

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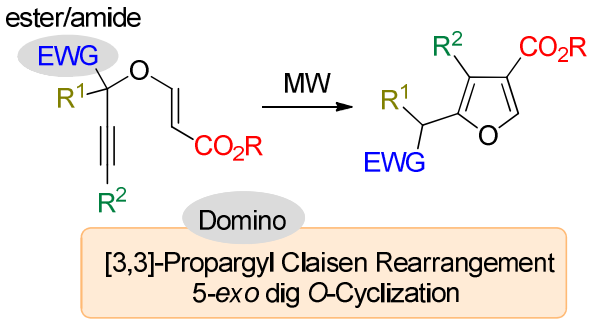
Furans are very attractive structures because they are part of many natural products and they are part of pharmacologically active compounds, such as ranitidine, zandac and other compounds with great impact in medicine. Furthermore, they are versatile synthetic intermediates in organic synthesis. Among all the strategies described in the bibliography for the synthesis of these heterocycles, the reactions of cyclo-isomerization of alkynyl and allenyl ketones catalyzed by transition metals are prominent[1], and provide access to a variety of di- and tri-substituted furan derivatives. Recently, Kirsch and collaborators[2] have developed a new cascade methodology from propargyl vinyl ether (PVE) units. The reaction is initiated by a propargyl [3.3]-sigmatropic rearrangement, which forms an allenic carbonyl compound intermediate that generates the furan ring in the presence of a gold catalyst.
Our research group has recently published[3] a domino methodology that provides a new efficient regioselective construction of tri-substituted furan units, bearing a functionalized side chain at position C_2 of the ring. The methodology is developed in a single stage format ("one-pot") by the coupling of two sequential domino processes, taking place in absence of metals. The furan unit is constructed from readily available starting materials (1,2- ketoesters, 1,2-ketoamides, alkynes and methyl propiolate).



Acknowledgment. This research was supported by the Spanish and European MICINN RDF (CTQ2008-06806-C02-02 and CTQ2011-28417-C02-02), and FUNCIS (REDESFAC PI01/06). L. C. thanks Spanish MEC for a FPI grant.

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Flash-60

Microwave-Assisted, Solvent- and Catalyst-Free Amination of π-defficient Nitrogen Heterocycles

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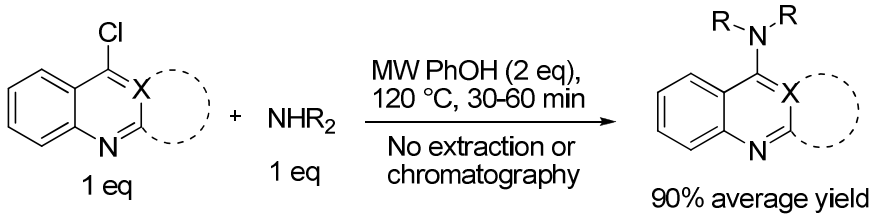
Many π-defficient nitrogen heterocycles bearing amino or polyamino side chains, including acridine, quinoline and quinazoline derivatives, are key structural fragments of antimalarial, anti-prion[1] and anti-cancer compounds. The key reaction in the construction of these compounds is a nucleophilic aromatic substitution between aryl halides and nitrogen nucleophiles. Under conventional conditions, this reaction requires the use of very high temperatures and long reaction times (5-24 h)[2] or toxic transition metal catalysts,[3] and the yields obtained are only moderate. Some microwave-mediated protocols also exist, which involve carrying out the reaction in high-boiling organic solvents and a large excess of amine, or the use of transition metals as catalysts.[4] The metal- and solvent-free amination of aryl halides under microwave irradiation is an attractive goal that has not been achieved.

In this communication we describe a new, efficient and eco-friendly microwave-assisted method for the reaction between chloro-substituted *N*-heterocycles, requiring only one equivalent of amine and giving the required products in excellent yields. The reaction was carried out using 2 equivalents of phenol as the catalyst and reaction medium and, workup did not require the use of organic solvents, as it was carried out by simple filtration after addition of aqueous NaOH.



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Flash-61

Oxetane Ring Enlargement by Generation of Radical Cations and Nucleophilic Trapping with Acetonitrile

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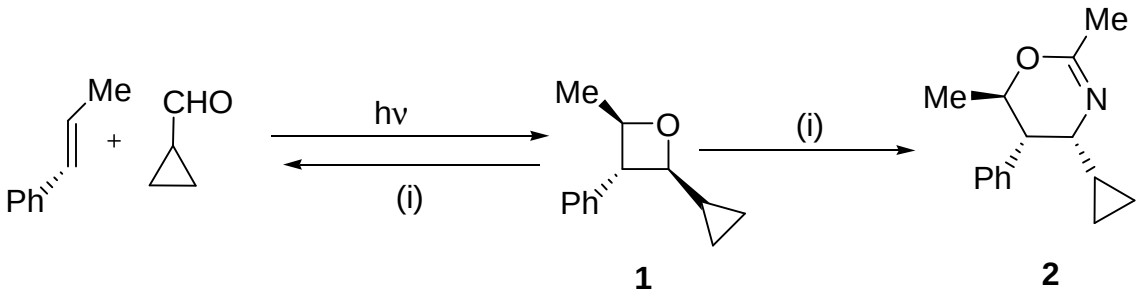
Photocycloaddition of carbonyl compounds to alkenes (Paterno-Büchi photoreaction) is an efficient way to afford oxetanes. These versatile building blocks[1] can undergo cycloreversion to yield either the starting materials or the formal metathesis products.[2,3] Cycloreversion can be promoted by photosensitized electron transfer processes.

Hence, photolysis of oxetane **1** has been achieved in acetonitrile/N_2, in the presence of triphenyl(thia)pyrylium perchlorate (TPTP) as photosensitizer. The obtained products are *trans*-β-methylstyrene and cyclopropanecarboxaldehyde (arising from cycloreversion) together with oxazine **2** (resulting from the intermolecular nucleophilic trapping of an oxetane-derived radical cation by acetonitrile).

Theoretical calculations on the course of the reaction at the UB3LYP/6-31+G(d) level of theory support the radical cation mechanism.



1 **2**

(i): hν, λ_{exc} > 350 nm, MeCN, TPTP, N_2

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Flash-62

First Total Synthesis of the Pyrrolizidine Alkaloid Amphorogynine C

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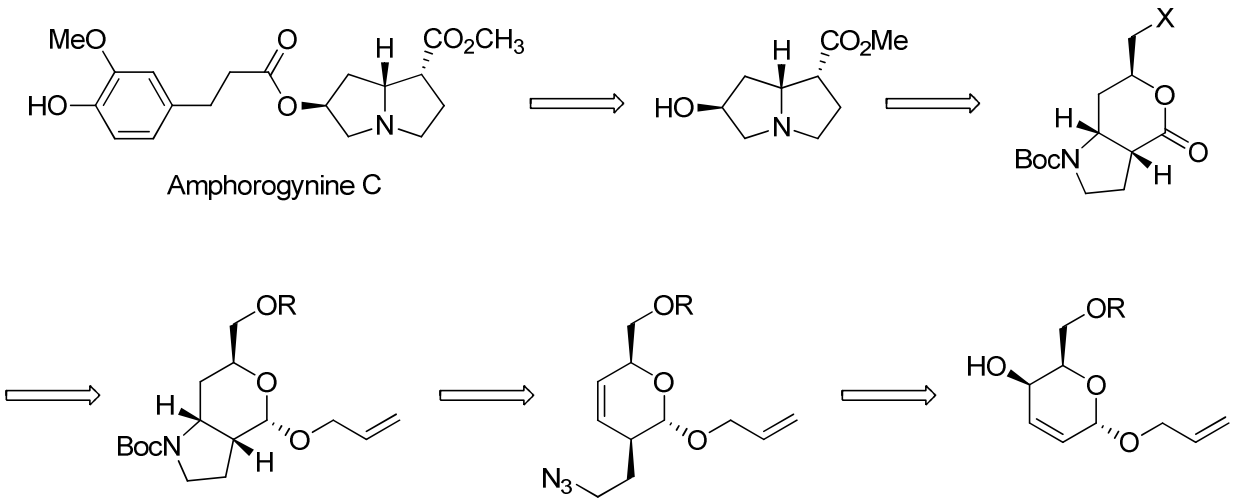
In 1998, four new pyrrolizidine alkaloids were isolated from the New Caledonian plant Amphorogynine Spicata by Païs and co-workers[1]. This class of compounds, named amphorogyinines A, B, C, and D are characterized by a double substitution pattern at positions C(1) and C(6) of the bicyclic pyrrolizidine core.

We present here the first total synthesis of Amphorogynine C following the retrosynthetic analysis shown in the scheme. Key steps include a Claisen-Johnson rearrangement and an intramolecular azide-olefin cycloaddition. Finally, the proposed structure of Amphorogynine C was confirmed by single-crystal X-ray diffraction analysis.



Retrosynthesis of Amphorogynine C

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Flash-63

Sesterterpenos de esqueleto salmahyrtisano

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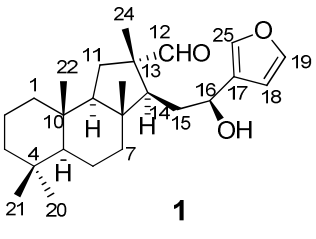
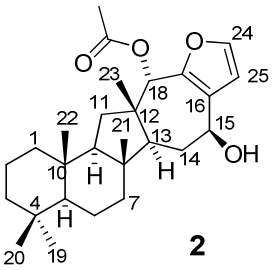
Las esponjas del genero *Hyrtios* son ricas en diversos metabolitos bioactivos. Entre ellos se encuentran sesterterpenos con nuevos esqueletos carbonados como hyrtiosal (**1**) y salmahyrtisol A (**2**). Ambos se aíslan de la esponja *Hyrtios erectus*. [1-2]



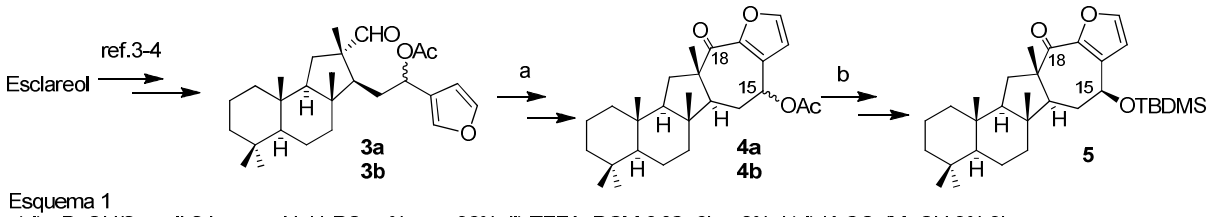
1



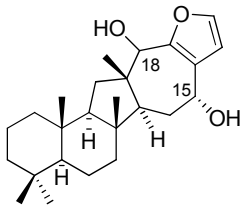
2

Hyrtiosal inhibe la proliferación in vitro de las células KB y salmahyrtisol A presenta una significativa actividad frente a células de leucemia murina (P-388), carcinoma humano de pulmón (A-549) y carcinoma de colon (HT-29). Ambos se aíslan de la fuente natural en poca proporción, por lo que la escasez de su disponibilidad así como las interesantes actividades biológicas las transforman en moléculas que constituyen un interesante objetivo sintético.

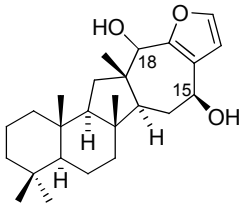
En trabajos anteriores[3-4] hemos llevado a cabo la síntesis de hyrtiosal a partir de un compuesto asequible como esclareol. En este trabajo se pretende optimizar la síntesis de la cicloheptenona **5** a partir de la mezcla de acetylhyrtiosal y 16-epiacetil hyrtiosal (**3a/3b**) obtenidos de esclareol. (Esquema 1)



Esquema 1
a) i) t-BuOH/2-metil-2-buteno, NaH_2PO_4 5%, t.a., 96%; ii) TFFA, DCM,0 ºC, 6h, 50%; b) i) K_2CO_3/MeOH 3%,3h, t.a. 82%; ii) MnO_2, DCM,1h, t.a. 75 %; iii) $NaBH_4$,EtOH,0 ºC - t.a.,3h, 94%; iv) TBDMSTf, 2,6 lutidina, DCM, 1h, 0 ºC - t.a., 37 %;v) TPAP, NMO, DCM, t.a. 62%.



6 18(*S*)
7 18(*R*)



8 18(*S*)
9 18(*R*)

La cicloheptenona **5** es el intermedio clave para la síntesis de salmahyrtisol A, lo que requiere poner a punto la reducción estereoselectiva del carbonilo en C-18. El disponer de hyrtiosal y su epímero en C-16 permitirá obtener los sarmahyrtisanos **6-9** con el fin de llevar a cabo estudios de SAR.

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Germacone, an exceptional source of structural diversity: Radical versus cationic transannular cyclizations of epoxides

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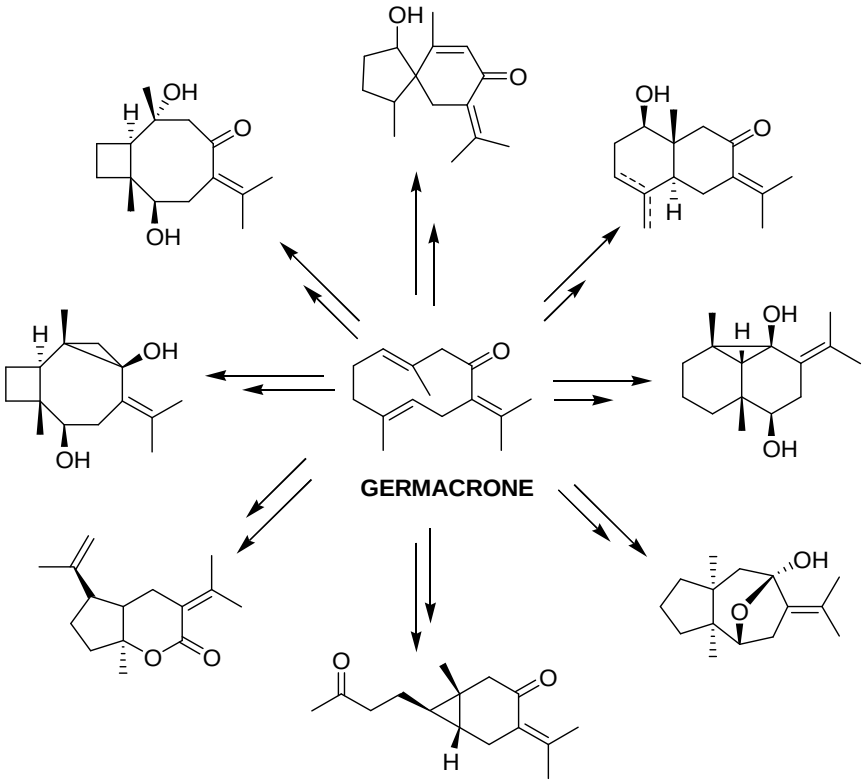
Germacrone is a natural sesquiterpene isolated in multigram scale from the essential oil of *Geranium macrorrhizum* or *Baccharis latifolia*[1]. This molecule has a potential use in natural material-related diversity-oriented synthesis[2]. We report herein the results obtained in the Lewis-acid and /or Ti(III)-mediated radical cyclization of epoxides of germacrone and isogermacrone. We decide to treat the epoxides with Lewis acid. The results obtained confirmed our hypothesis of germacrone being an incomparable source of structural diversity. Mechanistical studies rationalizing the generation of the different skeletons obtained will be presented.



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Acknowledgements: Ministerio de Ciencia y Tecnología (CTQ 2010-16818, BQU) and Junta de Andalucía (P08-FQM-3596)

Flash-65

Síntesis y estudio estructural de un nuevo complejo Cloroquina-Plata(I)

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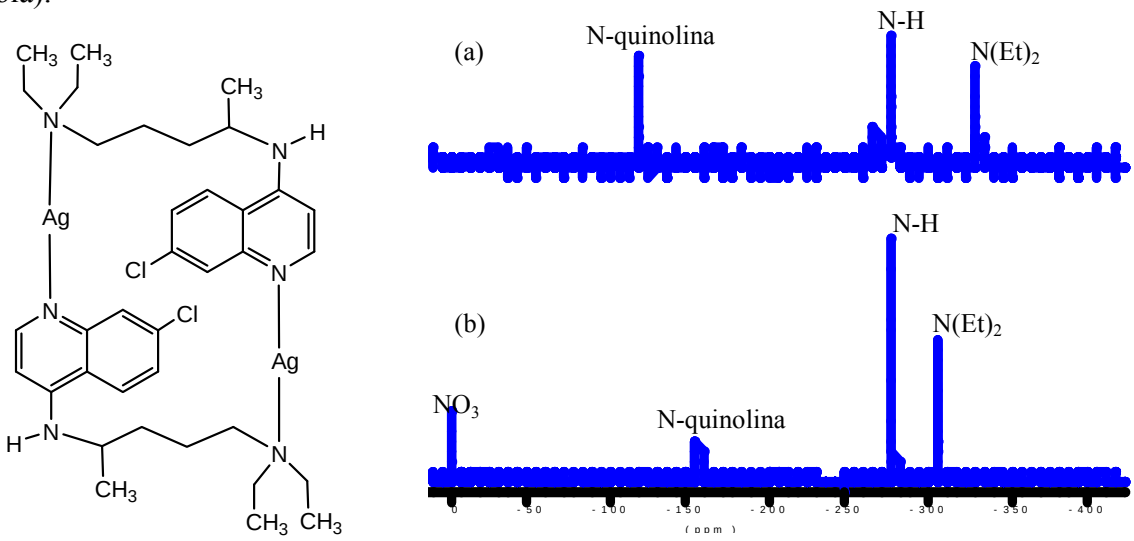
La cloroquina (CQ) ha sido uno de los fármacos más potentes utilizados contra la malaria, enfermedad todavía hoy causante de numerosas muertes al año (655.000 en 2010).[1] Aunque se sigue usando, debido a la resistencia adquirida por diferentes cepas del parásito (*Plasmodium falciparum*) a la misma, en la actualidad se propone como una alternativa el uso de complejos metálicos de cloroquina.[2-5] En esta comunicación se presenta el estudio estructural de un nuevo complejo de cloroquina–$AgNO_3$ (CQ–$AgNO_3$) por espectrometría de masas utilizando un espectrómetro ESI 7T FT-ICR (Fourier Transform Ion Cyclotron Resonance Spectrometry) así como por RMN de ^{13}C y ^{15}N tanto en disolución como en estado sólido. Asimismo, se han llevado a cabo cálculos GIAO (B3LYP/6-311++G(d,p)/LANL2DZ) para la determinación de los desplazamientos químicos teóricos de ^{15}N. Los resultados obtenidos indican la existencia de dímeros $CQ_2Ag_2^{2+}$ o catémeros (cabeza-cabeza o cabeza-cola).



Espectros ^{15}N-RMN CPMAS de la cloroquina (a) y del complejo CQ–$AgNO_3$ (b)

Agradecemos la financiación económica del MCINN (Proyecto CTQ2010-16122).

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Flash-66

Bencimidazoles Fluorados como Inhibidores de la Sintasa del Óxido Nítrico (NOS)

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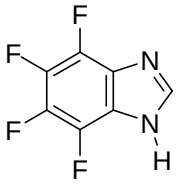
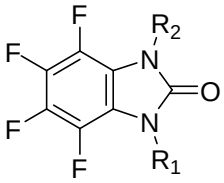
Continuando con nuestra investigación en la búsqueda de nuevos compuestos con actividad inhibidora frente a la Sintasa del Óxido Nítrico (NOS),[1,2] se han sintetizado los bencimidazoles fluorados **1-5**. Estos compuestos aportarán nuevos datos sobre la influencia de la perfluoración en el anillo bencénico del bencimidazol y sus consecuencias sobre la interacción con la enzima.

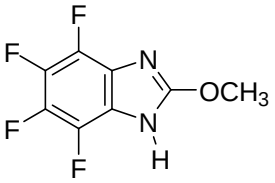
El 4,5,6,7-tetrafluoro-1*H*-bencimidazol (**1**) se ha preparado por reacción de ácido 2-amino-3,4,5,6-tetrafluorobenzoico y azida amónica.[3] Los compuestos **3** y **4**, se han sintetizado a partir de la 4,5,6,7-tetrafluoro-1*H*-bencimidazol-2(3*H*)-ona (**2**) obtenida de la reacción del 1,2-diamino-3,4,5,6-tetrafluorobenceno y urea.[4] Por otro lado, en la primera etapa de reacción para la obtención de 4,5,6,7-tetrafluoro-2-metoxi-1*H*-bencimidazol (**5**), se aísla la 6,7,8,9-tetrafluoro-4-metil-2,3-dihidro-1*H*-1,5-benzodiazepin-2-ona (**6**) como producto mayoritario.



1



2, R_1=R_2=H
3, R_1=R_2=CH_3
4, R_1=CH_3,R_2=H



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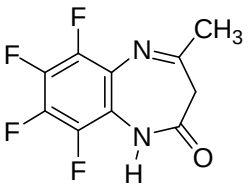

6

En esta comunicación se describe además el estudio estructural realizado, por espectroscopia de RMN en disolución (^{1}H, ^{13}C, ^{15}N, ^{19}F) y en estado sólido de (^{13}C, ^{15}N), y por análisis de difracción de rayos-X (**1**,**3**,**4**,**6**). Todos los compuestos sintetizados están siendo ensayados frente a las tres isoformas de la NOS.

Agradecimientos: Este trabajo está siendo financiado por el Ministerio de Ciencia e Innovación (MICINN), proyecto CTQ2010-16122

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Flash-67

Towards a Structural Basis for the Relationship Between Blood Group and the Severity of E1 Tor Cholera

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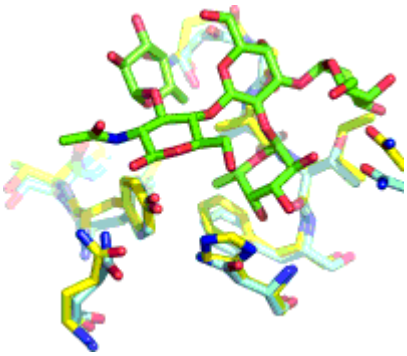
It has long been known that people with blood group O are more severely affected by El Tor cholera than those with blood groups A or B. In this communication it will be shown how microcalorimetry and STD-NMR spectroscopy are used to evaluate the ability of the B-subunits of cholera toxin and *E. coli* heat-labile toxin to bind to selected blood group oligosaccharides.[1]



[1] *Angewandte Chemie Internantional Edition*, **2012**, 51, 5143-5146.

Flash-68

A Very Expedient Route Toward Seco Nor-abietane Diterpenes: First Synthesis of Taxodal

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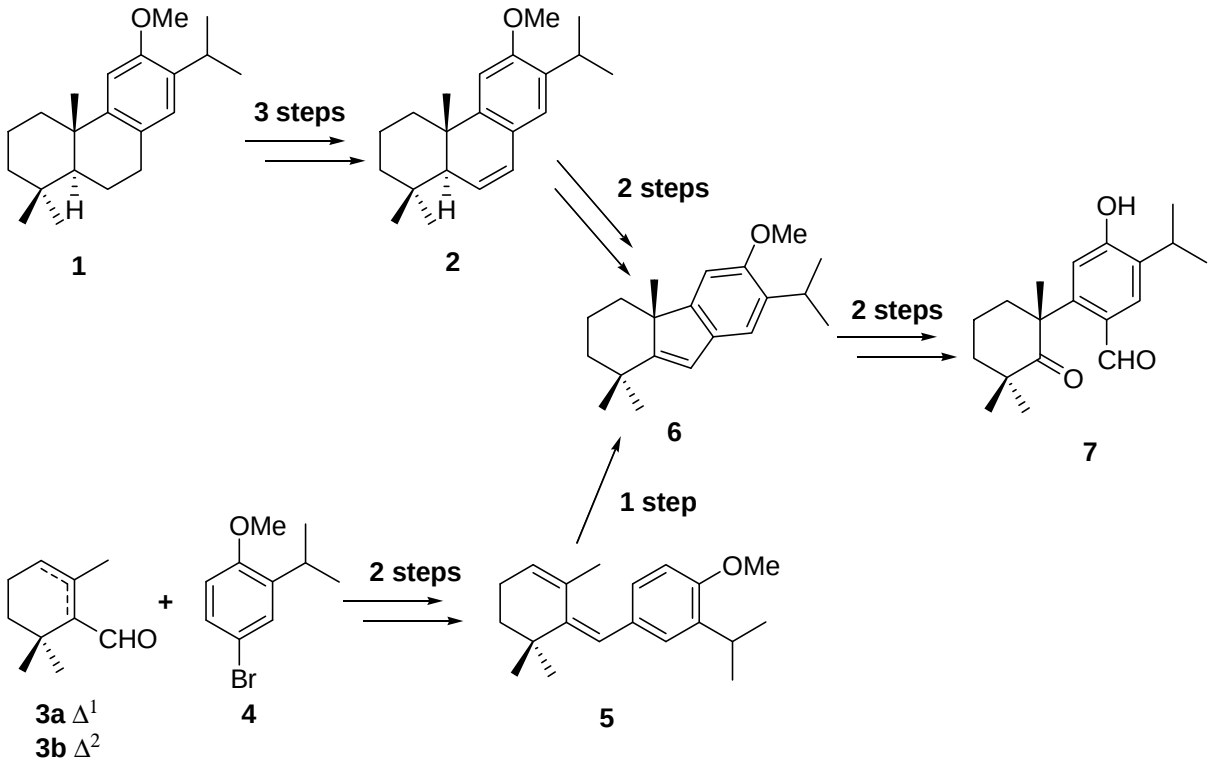
Taxodium distichum Rich. (Taxodiaceae) is a deciduous conifer native from Mexico. A variety of abietane-type diterpenes with cytotoxic activities, such as taxodistine A and B[1], have been isolated from their cones.

Recently, taxodal (**7**)[2], a new nor-abietane-type diterpene, has been found in *T. distichum,* in the study of self-defense bioactivity.

We have achieved the first synthesis of (±)-taxodal (**7**) from *α*-(**3a**) or *β*-cyclocitral (**3b**) and the first enantiospecific synthesis of (-)-taxodal (**7**) from *O*-methyl ferruginol (**1**), to confirm its absolute stereochemistry and evaluate its biological activity.



1 **2** **6** **7**

3a Δ^1 **3b** Δ^2 **4** **5**

1 Hirasawa, Y; Izawa, E; Matsuno, Y; Kawahara, N; Goda, Y; Morita, H *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(21), 5868-5871.

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Flash-69

Síntesis de Moléculas Híbridas como Potenciales Antivirales contra la Gripe A (H1N1).

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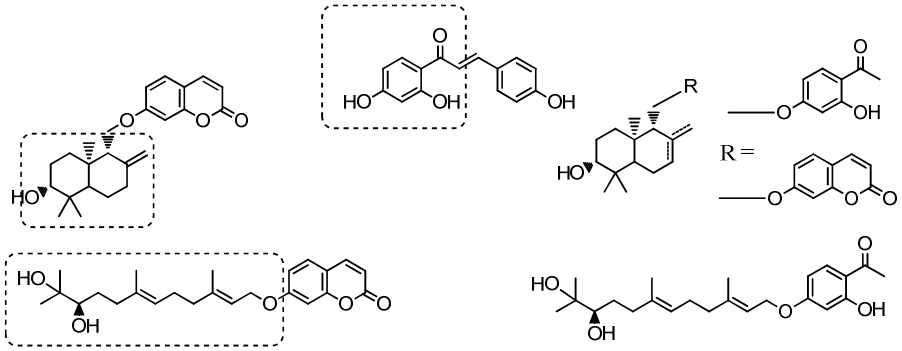
Las pandemias de gripe son producto de la aparición de nuevas cepas del virus de la gripe, las cuales se originan a partir de virus provenientes de otros organismos que, a causa de una mutación o adquisición de genes, traspasan la barrera interespecie y contagian al ser humano.[1] En el año 2009, la organización mundial de la salud alerto acerca de una posible pandemia provocada por un nuevo tipo de virus de la gripe A, el virus H1N1. Este virus presenta genes provenientes de cuatro tipos de virus. Su capacidad de infección y las sucesivas recombinaciones que ha sufrido en los últimos años lo han convertido en una seria amenaza. Los productos naturales y sus derivados son una importante fuente de agentes terapéuticos. Recientemente se han obtenido una serie de compuestos, aislados de extractos vegetales provenientes de *Ferula assa-foetida*, con estructuras híbridas que mostraron una importante actividad contra el virus H1N1.[2]

Una de las líneas de investigación de nuestro grupo se centra en la síntesis de moléculas hibridas, con el fin de estudiar procesos biológicos relevantes, orientadas al diseño de nuevos fármacos y moléculas bioactivas en general. Las moléculas híbridas están constituidas por al menos dos farmacóforos, integrados en una sola molécula mediante la unión por un "linker" con la capacidad de interaccionar simultáneamente con más de una diana.[3]

En esta comunicación presentamos la síntesis de moléculas mixtas análogas[4] a esas que han presentado actividad contra el virus (H1N1)



Compuestos con actividad antivírica y análogos

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Enantioselective Access to Pentacyclic Yohimbine-type Alkaloids

Mercedes Amat, Maria Pérez, Federica Arioli, and Joan Bosch

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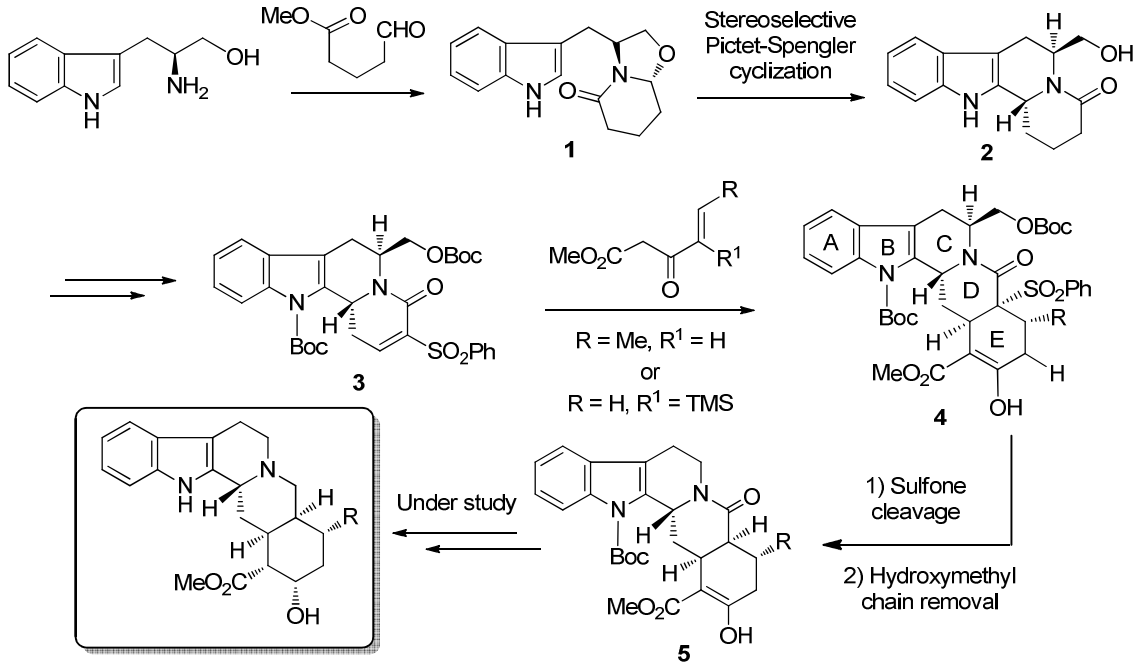
Tryptophanol-derived oxazolopiperidone lactams have proven to be versatile building blocks for the enantioselective synthesis of indole alkaloids and related bioactive compounds.[1] These lactams are easily accessible by a stereoselective cyclocondensation reaction between a *δ*-oxoacid derivative and (*S*)-tryptophanol, which not only acts as a chiral inductor but can also be used to assemble complex polycyclic targets by cyclization on the indole ring.

We will present our studies on the synthesis of pentacyclic yohimbine-type alkaloids. Our approach involves, as a key step, the generation of the E ring of these alkaloids by a double Michael reaction of a suitable Nazarov reagent to a tetracyclic unsaturated lactam **3**. The conversion of **4** into the target yohimbine-type derivatives requires the removal of the hydroxymethyl and sulfone substituents and, finally, the chemoselective reduction of the lactam and ketone functions.



Acknowledgements: Financial support from the MICINN, Spain (project CTQ2009-07021/BQU), and the DURSI, Generalitat de Catalunya (grant 2009-SGR-1111).

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Flash-71

Total Synthesis of Vitamin E and Analogues - A Catalytic Enantioselective Approach to Chiral Chromans

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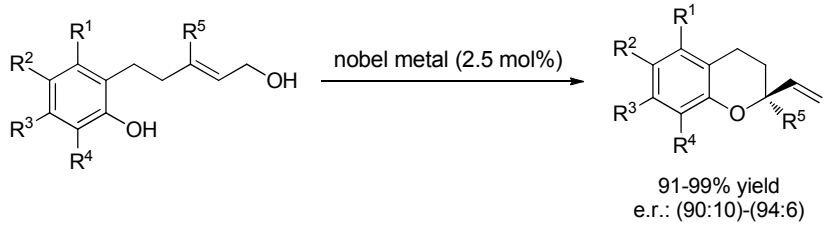
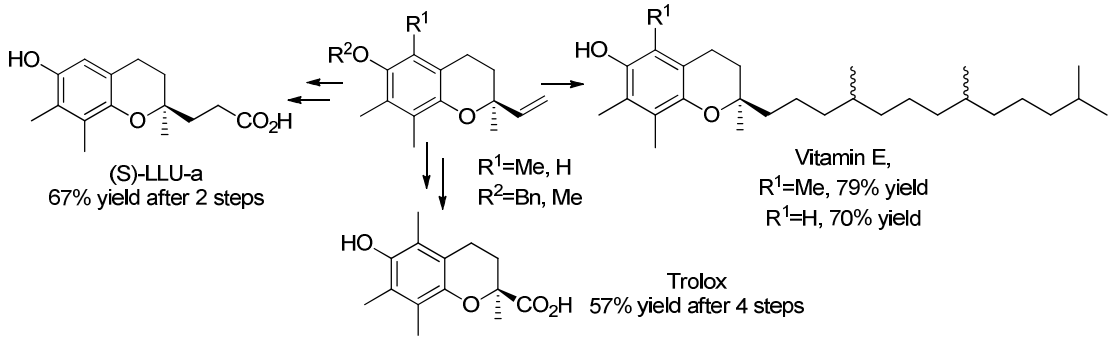
Chiral chromans constitute a privileged framework which is present in many biologically active natural products such as Vitamin E, Trolox, (*S*)-LLU-α or MDL-73404. Although a variety of enantioselective approaches have been described for their synthesis (Sharpless bishydroxylation,[1] palladium catalysis,[2] ruthenium catalysis,[3] organocatalysis[4]) easier and more efficient methods are still required. Here, we describe the development of a catalytic intramolecular enantioselective allylic alkylation reaction employing noble metals which provides a wide range of chromans in excellent yields and good enantioselectivities.



After having established an optimal and general protocol for the synthesis of enantioenriched chromans, we have demonstrated their high ability to undergo chemical modifications. Thus, readily available biologically active α- and γ- tocopherol (most active compounds of Vitamin E), (S)-LLU-α as well as Trolox were prepared by simple and straightforward procedures.



1. Selected examples: (a) Takano, S.; Sugihara, T.; Ogasawara, K. *Synlett* **1990**, 451-452. (b) Tietze, L. F.; Görlitzer, J. *Synlett* **1996**, 1041-1042. (c) Tietze, L. F.; Görlitzer, J. ; Schuffenhauer, A.; Hübner, M. *Eur. J. Org. Chem.* **1999**, 1075-1084.
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Synthesis and Structural Analysis of Tetraponerines T-1 to T-4

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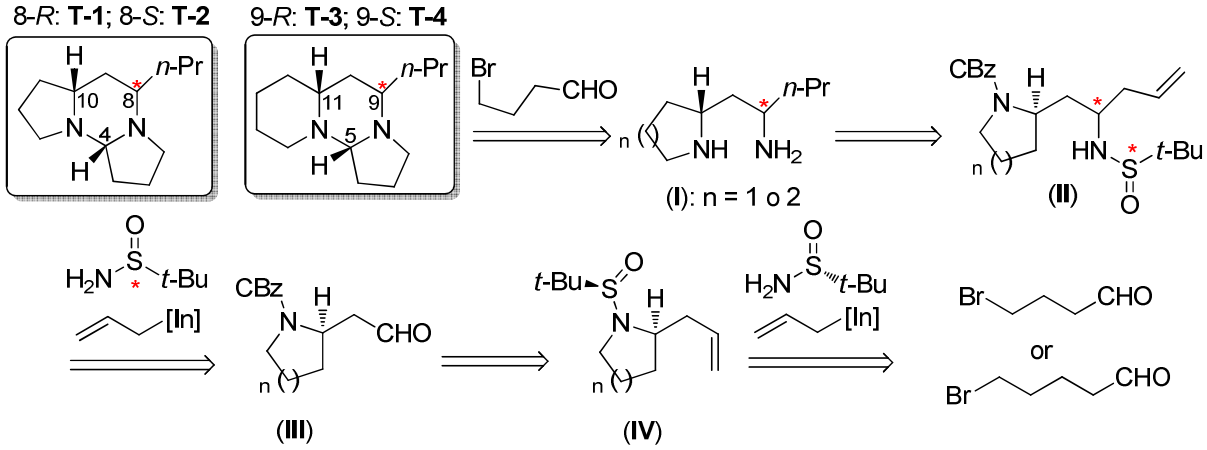
Tetraponerines are alkaloids with two unprecedented tricyclic structures that were originally detected in the venom of a pseudomyrmecine ant, *Tetraponera sp.*, from Papua New Guinea.[1] The eight tetraponerines from this species of ant have been named tetraponerine-1 (**T-1**) to tetraponerine-8 (**T-8**). Four have a C-8 n-propyl or n-pentyl substituent and a 5-6-5 fused ring system; four have a C-9 n-propyl or n-pentyl substituent and a 6-6-5 system.

In this communication we present a general synthesis for tetraponerines **T-1** to **T-4**. Reasoning that the aminal core of natural tetraponerines are the most stable of all possible, our approach to these compounds implies the formation of the aminal moiety at the latest stage, from the corresponding diamines **I** and 4-bromobutanal. The required diamines **I** were prepared using our indium mediated protocol of α-aminoallylation[2] with aldehyde **III**, followed by conventional functional group manipulation. In this key step, the stereochemistry at the carbon center was efficiently controlled by the chiral *tert*-butylsulfinamide used, allowing the access to both configuration at C-8 (**T-1** and **T-2**) or C-9 (**T-3** and **T-4**) of the final compounds. Formation of intermediates **III** was performed by oxidative cleavage of homoallylic amines **IV**, which were prepared by stereoselective α-aminoallylation of 4-bromobutanal or 5-bromopentanal.[3]



To our knowledge, a detailed study of the stereochemical structure of these alkaloids has not been reported. Our results on the geometry optimization of these tetraponerines using DFT calculations will also be presented here in, providing insightful information that match with the Bohlmann band pattern observed in their infrared spectrum (C-H stretching vibrations at 2800-2700 cm^{-1}).

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Flash-73

Mimicking Nature: Simple Access to Halimane-type Terpenoids through Multistep Cationic Cyclization and Rearrangements.

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Biomimetic strategies allow the construction of complex natural products in a minimum of steps which is in accordance with the ‘‘atom economy’’ principle of green chemistry and, in addition, simple reagents can be used to access the targets. The pursuit of biomimetic syntheses also promotes the development of new reactions to prove or disprove a biosynthetic proposal or to unravel mechanistic implications of a proposed biosynthesis and can lead to the identification of new natural products.[1] In this sense, careful design of tandem, cascade or multi-component processes provides an innovative solution to the problem of complex molecule synthesis.[2]

Herein we present the development of a Lewis acid-catalyzed biomimetic cyclization–rearrangement of epoxypolyenes. This process encompasses the construction of two new rings (cationic cyclization), three stereogenic centers (triple Wagner–Meerwein rearrangement) and a new double bond (regioselective proton elimination) in a single chemical operation between multitudes of different carbocationic pathways. Based on this cascade transformation, we achieved a unified strategy toward the stereoselective total syntheses of interesting bioactive halimane type terpenoids[3] and analogues as a proof–of–concept study.

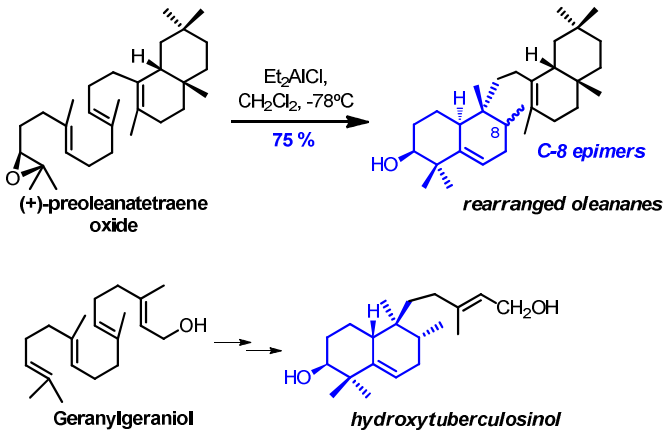

Fig.1 Initial findings and a viable target molecule

This research was supported by the Spanish Ministry of Science and Technology, Project No. CTQ2010-16818 (BQU). V.D. thanks the Spanish Ministry of Science and Technology for a predoctoral grant enabling him to pursue these studies.

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Flash-74

Multicomponent Bicyclization of Fischer Carbene Complexes, Alkynyl Ketone Lithium Enolates, and Grignard Reagents Leading to 5-5 Bicyclic 2-Butenolides

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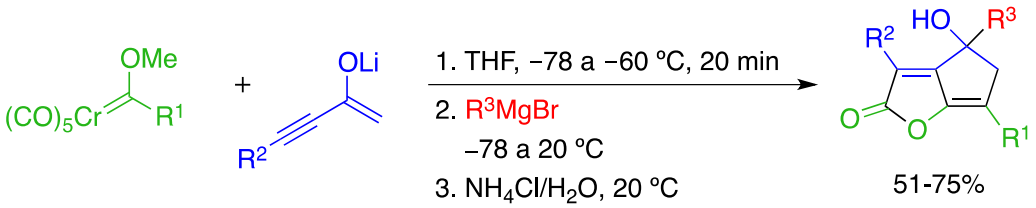
Heteroatom stabilized Fischer carbene complexes (FCCs) are valuable reagents in synthetic organic chemistry that present the ability to participate in multicomponent reactions allowing the construction of a large variety of highly functionalized structures through several patterns of reactivity.[1] A multicomponent strategy for the enantioselective synthesis of fused 6-5 bicyclic 2-butenolides, which involves the reaction of an alkoxycarbene complex of chromium, a chiral imide lithium enolate, and an organocerium reagent, has been reported recently.[2] In this context, we have developed the coupling reaction between a Fischer carbene complex, an alkynyl methyl ketone enolate anion and different organomagnesium compounds. This multicomponent reaction provides bicyclic γ-alkylidene-2-butenolides through a double cyclization process that combines the carbene ligand, two CO ligands, the enolate framework, and one unit of organomagnesium reagent in a process where five new carbon-carbon bonds and one C-O bond are formed (see Scheme). These fused bicyclic butenolides with a highly unsaturated core exhibit strong blue fluorescence in solution.



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Flash-75

Síntesis de nuevos α-*O*-glicoaminoácidos mediante metátesis cruzada

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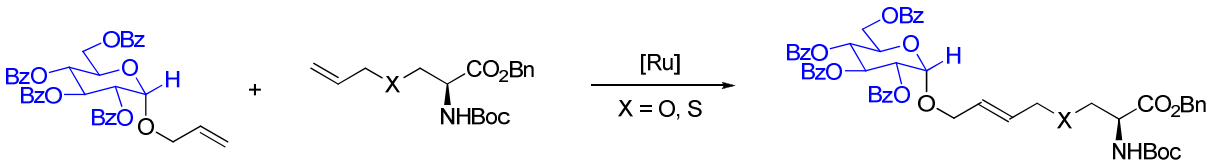
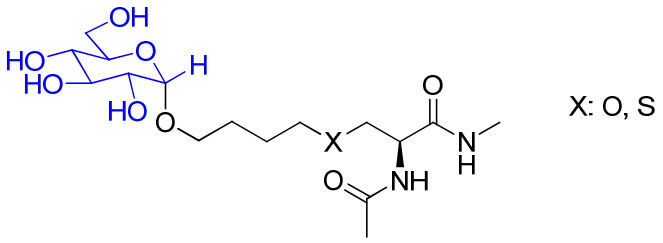
Nuestro grupo de investigación lleva desarrollando durante los últimos años líneas de trabajo centradas tanto en la reactividad en procesos de metátesis como en el estudio sintético y conformacional de *O*-glicoaminoácidos y *O*-glicopéptidos que incorporan aminoácidos no naturales.[1] Nuestros estudios demostraron que la presentación del carbohidrato ante las diferentes dianas biológicas depende de la naturaleza del aminoácido al que está unido. Por tanto, en este trabajo se pretende elongar la cadena que une carbohidrato y aminoácido, empleando para ello reacciones de metátesis. De este modo, el actual objetivo consiste en la preparación de *O*-glicoaminoácidos, con elongación en la cadena a través de linkers, mediante la preparación de alil-α-D-glucopiranosa y derivados de *O*-alil-serina/*S*-alil-cisteína ortogonalmente protegidos, seguido de una posterior reacción de metátesis cruzada (CM).



Así se accedió a interesantes compuestos intermedios mediante la desprotección ortogonal e hidrogenación de los mismos, para obtener finalmente los glicosilaminoácidos, con sus extremos en forma de diamida para simular péptidos, sobre los cuales se realizaron estudios conformacionales.



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Flash-76

Asymmetric Allylation / RCM: A Facile Entry to the Sertraline Core

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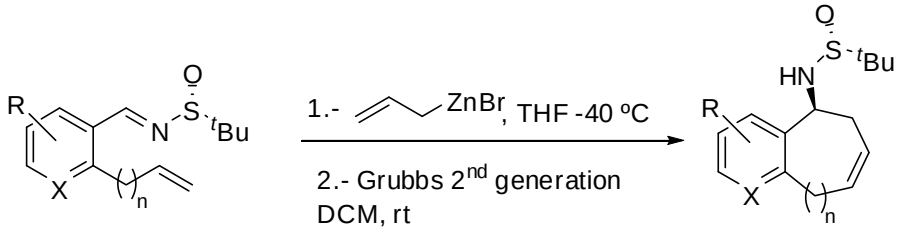
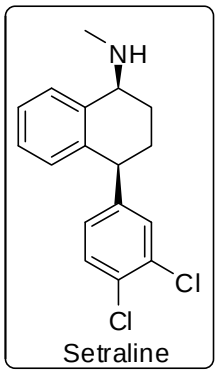
Arguably, the asymmetric allylation of imines is the most important method for the synthesis of homoallylic amines which are versatile building blocks in organic synthesis. Among the existing methods, the diastereoselective addition of allylizinc bromide to Ellman's *tert*-butilimines presents a number of advantages: high degree of diastereocontrol and chemical yields, reliability, functional group compatibility, among others.[1] On the other hand, ring closing metathesis lies among the most reliable methods for the construction of medium-sized rings.[2] The combination of both strategies allows for the rapid construction of cyclic benzo-fused homoallylic amines (scheme). Sertraline,[3] an important antidepressant, displays a core tetrahydronaphtalene amine structure which can be conveniently achieved by our methodology; therefore a project towards its synthesis has been started in our laboratories. Moreover, this new strategy allows for the synthesis of a number of analogs bearing several substitution patterns on the aromatic ring as well as heteroaromatic ones.





Setraline

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Flash-77

Theoretical and experimental study of the regioselective orthopalladation of α-amino acids through C-H bond activation and its synthetic applications

Esteban P. Urriolabeitia, F. Javier Sayago, Salvador Moncho, Ángel García Montero, Carlos Cativiela and Eduardo Laga

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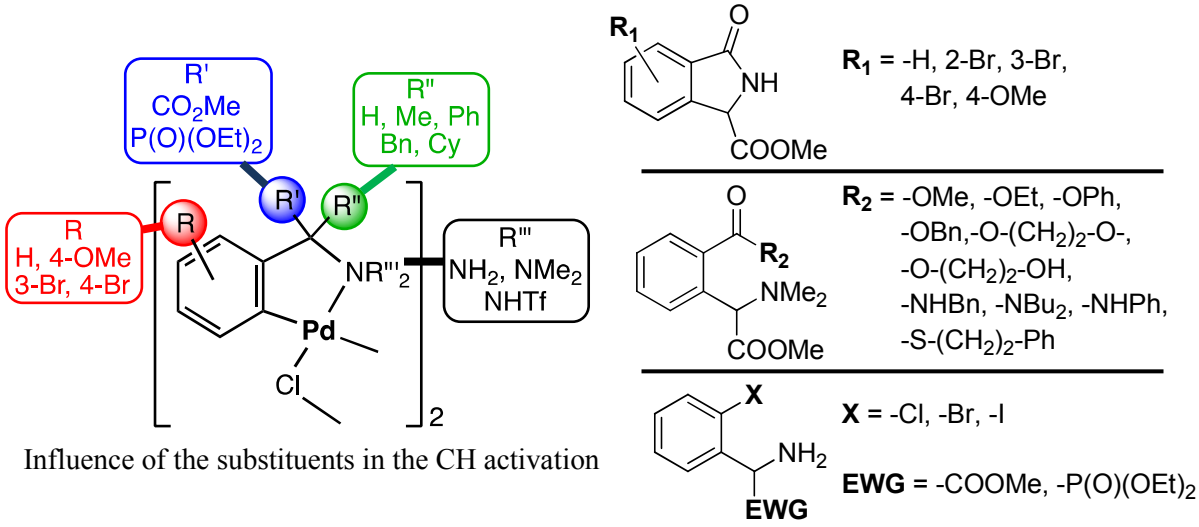
The synthesis of phenylglycines modified in the ortho position of the phenyl ring is still a difficult task, since conventional organic routes lack of generality, are multistep and generate toxic residues. We have recently shown that the use of orthopalladated complexes derived from phenylglycine allows its regioselective functionalization and affords a vast family of new compounds, keeping the C_α configuration in most of the cases.[1]

This contribution reports the results obtained on the theoretical and experimental study of the C-H bond activation promoted by Pd-complexes on a variety of substituted phenylglycines. The influence of different functional groups at the N atom (NH_2, NMe_2, NHTf), at the Cα (H, Me, Ph, Bn), and at the aromatic ring (H, 4-OMe, 2-Br, 3-Br, 4-Br, 4-NO_2), and the nature of the electron-withdrawing group at the Cα (CO_2Me, $P(O)(OEt)_2$) has been tested. For representative examples, a kinetico-mechanistic study has been performed, and the intimate mechanism of the C-H bond activation has been elucidated by DFT methods.

Furthermore, the reactivity of the orthopalladated phenylglycine derivatives has been tested. Their reaction with halogens or halo-iodonium salts let us to obtain ortho-halogenated phenylglycines (-Cl, -Br, -I), while carbonylation afford the corresponding isoindolinones,[2] glutamates or glutamines, as a function of the precursor and the reaction solvent, providing access to different arrays of biologically actives molecules.



Influence of the substituents in the CH activation

Acknowledgment. The authors thank the MINECO (Project CTQ2011-22589) for financial support.

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"Sulfolefins": Highly Modular Sulfinamidoolefin Ligands for Enantioselective Conjugate Addition in Micellar Medium.

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[1] Instituto de Investigaciones Químicas, CSIC-Universidad de Sevilla, c/ Américo Vespucio, 49. Isla de la Cartuja, 41092- Sevilla. [2]Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, 41012-Sevilla, c/ Profesor García González, 2, 41012-Sevilla.

In the last decades, chiral sulfinyl derivatives have been used with success in a plethora of asymmetric chiral C-C and C-X bond formation.[1] Surprisingly, despite their interesting metal-coordinating abilities, the great efforts devoted to their application in asymmetric catalysis have met with little success. Within our interest toward the synthesis of chiral sulfinyl derivatives,[2] and their application in organic and organometallic asymmetric catalysis,[3,4] in the present work we report our preliminary results on the synthesis of modular sulfinamide / olefin mixed ligands and their application in highly enantioselective 1,4-addition of boronic acids to cyclic and acyclic α,β-unsaturated ketones in micellar medium. The designed "sulfolefins" ligands, Figure 1, with a chiral sulfur atom as the sole chiral center are obtained in a single step from allylamines and diastereomerically pure DAG-sulfinate esters.

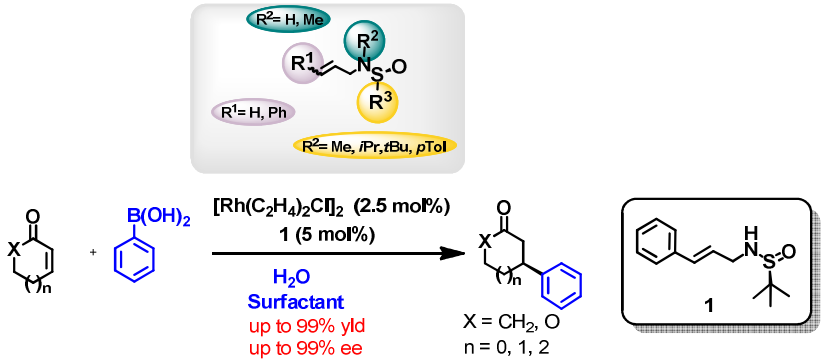

***Figure 1**. Sulfolefin-catalyzed enantioselective conjugate addition in micellar medium*

The screening of this new family of ligands in the model reaction of 2-cyclohexanone and phenyl boronic acid, reveals that "sulfolefin" **1** derived from cinnamylamine and bearing a highly sterically-demanding group at the sulfur is the optimal ligand. Indeed, ligand **1** exhibits an excellent behavior and general electrophile scope, such as cyclic enones, lactones and what is more interesting, the challenging acyclic substrates.[4] These and others investigations directed toward the determination of the scope and limitation of the "sulfolefins" ligands will be discussed in this communication.

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Flash-79

Rhodium-Catalyzed Amidation of C—H Bonds with Nonafluorobutanesulfonyl Azide

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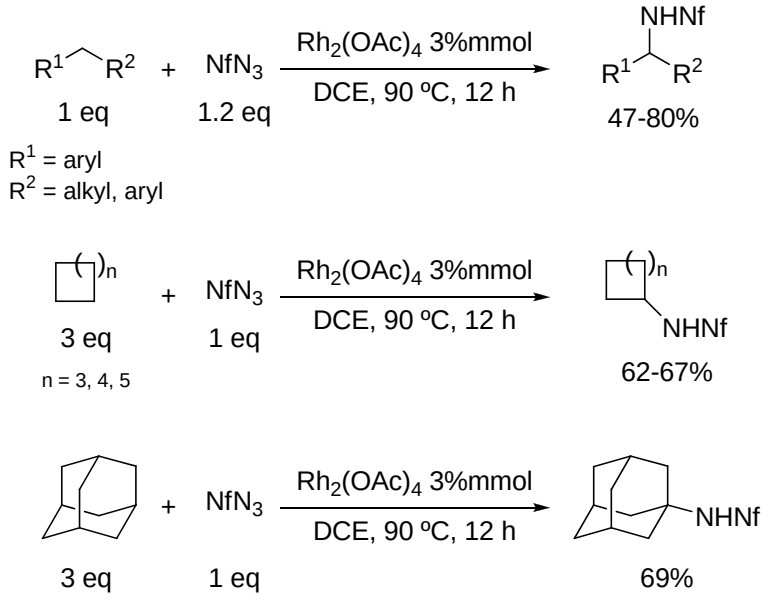
The selective oxidation of C–H to C–N bonds has been very actively investigated in the last decade. In spite of recent progress, the direct amination of unactivated C–H bonds with acceptable product yields and selectivities using mild reaction conditions remains a difficult challenge.[1] Sulfonyl azides are particularly appealing nitrogen sources for this endeavor due to the very favorable thermodynamic driving force of the reaction with formation of nitrogen gas as the only by-product.[2] We will describe our studies on the use of nonafluorobutanesulfonyl azide (NfN_3)[3] as an efficient and shelf-stable nitrogen-transfer reagent for the selective sulfamidation of unactivated and benzylic C–H bonds catalyzed by $Rh_2(OAc)_4$ under mild thermal conditions (Scheme).



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Flash-80

1,7-Octadiene-assisted Tandem Multicomponent CEYM-Diels-Alder Reaction. A Useful Alternative to Mori´s Conditions

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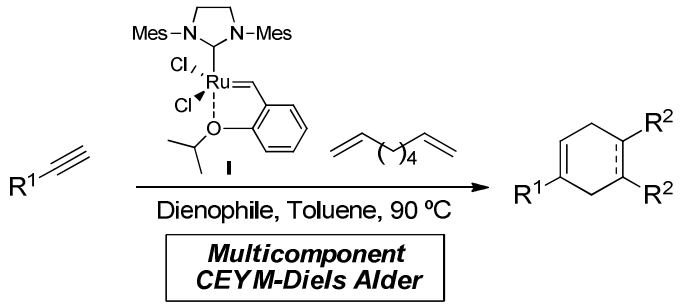
Enyne metathesis is a powerful synthetic tool for generating 1,3-dienes by redistributing unsaturated functionalities between an alkene and an alkyne via vinylalkylidene intermediates. In addition, a number of enyne metathesis processes have been designed and applied in a tandem fashion.[1] This metathesis cascade chemistry is therefore, a powerful tool for the synthesis of skeletally diverse small molecules, converting the diene created through enyne metathesis into other useful functionalities and increasing the molecular complexity with minimal added cost or waste.[2]

The discovery of the beneficial effect of ethylene has changed the difficulties encountered in cross metathesis processes involving enynes (CEYM). In this context, we found that 1,7-octadiene can act as a in situ source of ethylene by a ring closing metathesis reaction (RCM), allowing the formation of dienes by the combination of RCM-CEYM. This finding led us to identify suitable conditions to perform a tandem CEYM-Diels Alder reaction in a multicomponent fashion avoiding the use of ethylene. The process was evaluated with a wide variety of alkynes being particularly efficient with aromatic substituents. Subsequently the tandem protocol was extended to fluorinated alkynes.[3]



R^1=aryl, alkyl, hereroaryl, TIPS, CF_2COR, EtO_2C

in situ ethylene source by RCM

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New non-metathetic processes catalysed by ruthenium complexes

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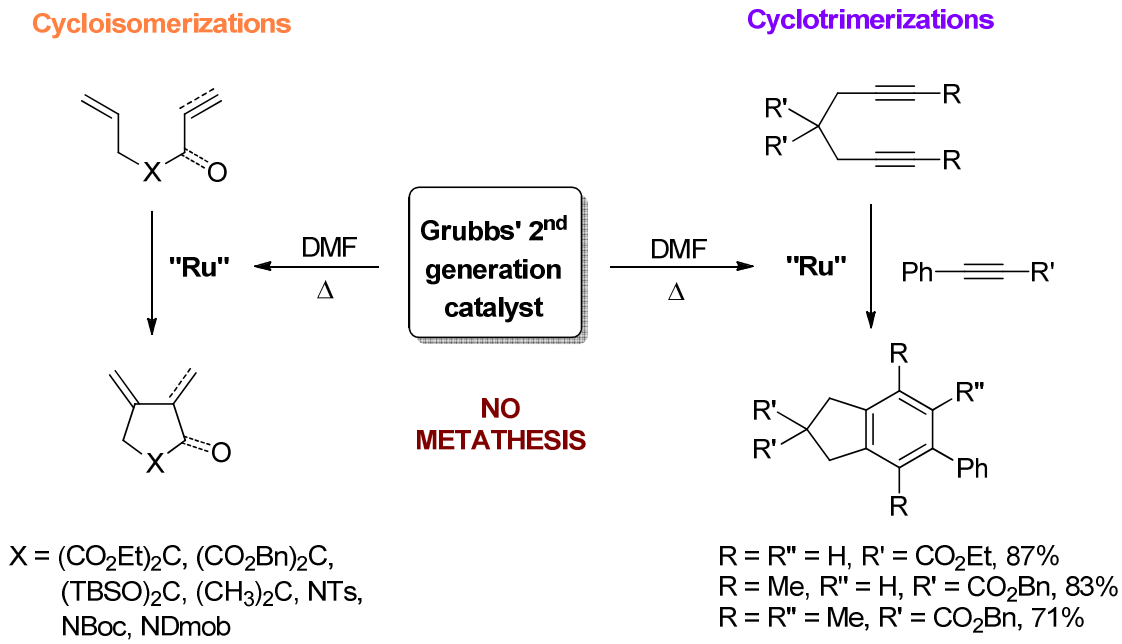
Non-metathetic transformations[1] are side reactions observed frequently when developing metathesis reactions catalysed by ruthenium alkylidene catalysts.[2] However, these alternative reactions, if optimized, may be useful transformations. Examples include oxidations, hydrosilylations of alkynes, hydrogenation of olefins, cyclopropanations, cycloaddition reactions and olefin isomerizations.

Many times the key issue in directing a particular process either to a metathesis or to a different transformation is to modify the ruthenium species before or during the reaction. We have shown recently the ability of both Grubbs' and Hoveyda-Grubbs' catalysts to promote a concurrent tandem catalysed triple process including RCM-isomerization-cyclopropanation,[3] as well as [2+2+2] cyclotrimerization reactions.[4]

Herein we present the ability of a new ruthenium species coming from the thermal modification of Grubbs' 2nd generation catalyst in DMF to promote both cycloisomerization and cyclotrimerization reactions in good yields and selectivity. No metathesis reaction has been observed. Studies devoted to identify the catalytic species are currently underway.



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Flash-82

Síntesis de Indolo[2,3-*a*]quinolizinio por Reacción de Metátesis

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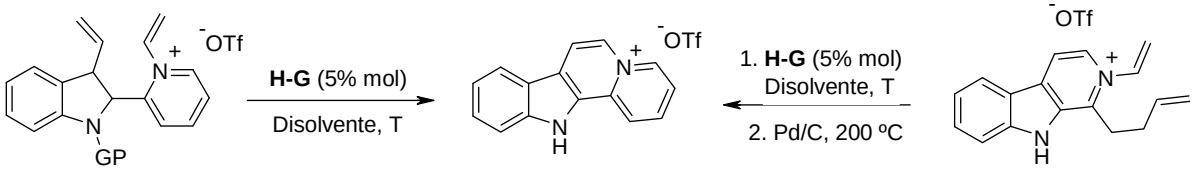
El quinolizinio[1] y los sistemas relacionados han demostrado gran utilidad como tintes y compuestos altamente fluorescentes usados como sondas para la detección de biomoléculas. Estos compuestos también muestran algunas actividades biológicas relevantes y el sistema de quinolizinio está presente en una variedad de alcaloides naturales tales como la coralina y la familia de las berberinas.

Como una parte de nuestros estudios en cationes tipo quinolizinio, recientemente se ha desarrollado una nueva metodología de síntesis de sistemas de quinolizinio[2] y benzoquinolizinio[3] empleando la reacción de metátesis de cierre de anillo (RCM) sobre la correspondiente sal de azinio usando los catalizadores de Grubbs y Hoveyda.

En base a estos resultados, nos propusimos la aplicación de la RCM para la obtención del indolo[2,3-*a*]quinolizinio que forma parte de una familia de alcaloides biológicamente activos como la flavopereirina, sempervirina, vicarpina y otros, que presentan actividad como analgésicos, antitusígenos y antidiarreicos.[4]



(65-70%)

Indolo[2,3-a]quinolizinio

Agradecimientos: Los autores agradecen al Ministerio de Economía y Competitividad (proyecto CTQ2011/24715) y al Instituto de Salud Carlos III (Red de Investigación Renal, REDinREN, RD06/0016/0016) por la financiación y a la universidad de Alcalá por la concesión de una beca predoctoral (B. A.).

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Flash-83

Synthesis of Novel Chiral Room Temperature Ionic Liquids (RTCILs). Application as Chiral Media in Organocatalytic Aldol Reaction

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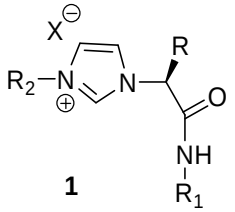
Ionic liquids (ILs) are attracting considerable attention as green reaction solvents, extraction liquids, electrolyte materials as well as structured media for other technological applications such as their use for enhancing the sensitivity of thermal lens measurements.[1]
On the other hand, chirality plays a key role in organic chemistry. Therefore, the design and synthesis of enantiopure ionic liquids with the possibility of easy structural tuneability is highly attractive. Within this context, our group has been involved in the preparation and study of chiral ionic liquids (CILs).[2] Here we were interested on the preparation of a new family of CILs using natural amino acids as the source of chirality and containing an amide group as an essential structural feature (**1)**. We describe the synthetic approach for the synthesis of these chiral imidazolium salts as potential room temperature ionic liquids that leads to a large variety of configurationally and structurally diverse CILs (see Figure 1), and the studies of the supramolecular structure in the solid state (X-Ray) and in solution (^{1}H NMR) of **1** (R = Ph, R_1 = Bn, R_2 = nBut).[3]



1

Also, in this work we present the efficiency tested for the aldol condensation reaction shown below, when the CILs were used as solvent or aditive in this reaction.[4]

Acknowledgements
Financial support from the Spanish M.C.I. (CTQ2011-28903-C02-01) and Fundació Bancaixa-UJI (P1-1B-2009-58) is acknowledged.

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Enantioselective Allylboration / RCM: Concurrent Tandem Catalysis for the Synthesis of Benzo-fused Cyclic Homoallylic Alcohols

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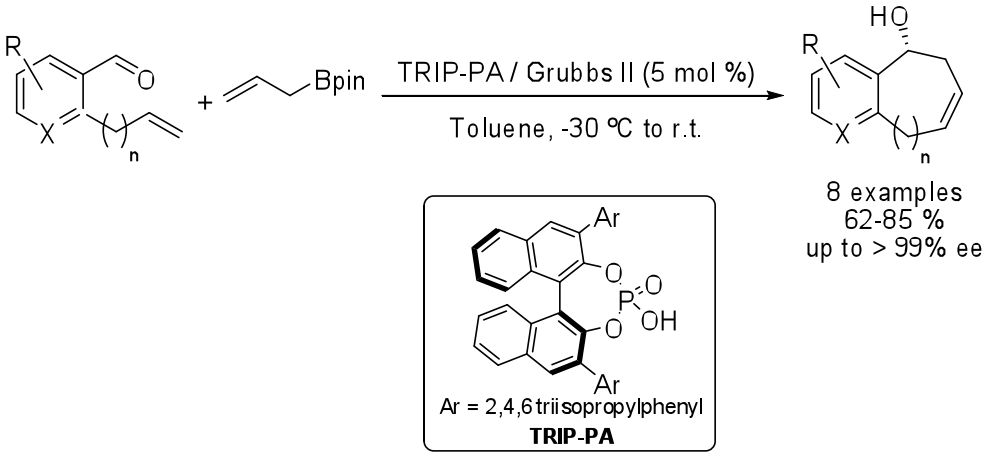
Asymmetric allylboration of aldehydes has been an invaluable tool for the formation of carbon-carbon bonds with control over relative and absolute stereochemistry.[1] Over the past three decades, additional methodologies that have relied upon stoichiometric chiral reagents or mediators have emerged.[2] Catalytic methods have also been reported and have opened new doors for the synthesis of homoallylic alcohols an important class of versatile intermediates used in the synthesis of pharmaceuticals and natural products.[3] On the other hand, ring closing metathesis (RCM) lies among the most reliable methods for the construction of medium-sized rings.[4] Combining a chiral phosphoric acid with the 2nd generation Grubbs catalyst renders a concurrent tandem catalyzed (CTC)[5] enatioselective allylboration / RCM process (scheme).



Scheme. Tandem enantioselective allylboration / RCM

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Flash-85

Sales de guanidinio: Nuevos aditivos para la prolina en reacciones aldólicas organocatalizadas

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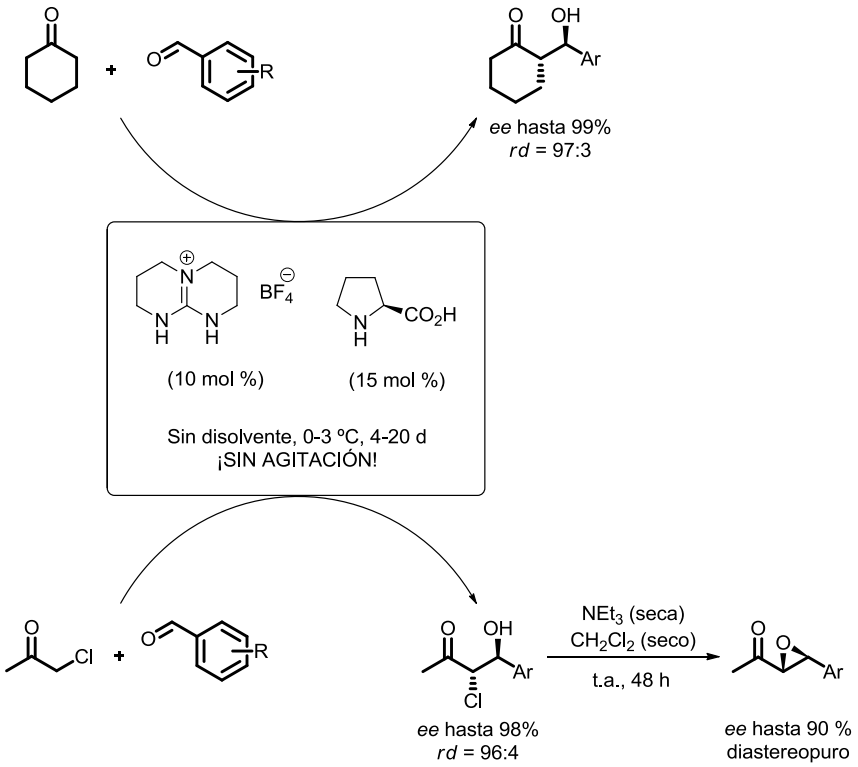
El descubrimiento de la primera reacción aldólica catalizada por prolina, junto con el desarrollo de las reacciones asimétricas organocatalizadas, han hecho que este sea un campo de especial interés en la actualidad. Nuestro objetivo consiste en el empleo de aditivos simples y fácilmente disponibles en reacciones aldólicas directas entre cetonas y aldehídos aromáticos catalizadas por (*S*)-prolina, para intentar mejorar los resultados que se obtienen cuando se emplea este catalizador por sí solo.
La actividad combinada de la (*S*)-prolina y un cocatalizador aquiral (una sal de guanidinio derivada del 1,5,7-triazabiciclo[4.4.0]dec-5-eno) permite llevar a cabo reacciones aldólicas con elevada diastereo- y enantioselectividad,[1] en ausencia de disolvente y sin necesidad de ningún tipo de agitación.
Esta metodología también ha permitido llevar a cabo por primera vez la reacción aldólica entre cloroacetona y aldehídos aromáticos, obteniéndose las correspondientes clorhidrinas con alta regio-, diastereo- y enantioselectividad.[2]



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Adición Nucleofílica "Sobre Agua" de *N,N*-Dialquilhidrazonas del Formaldehído a α-Cetoésteres.

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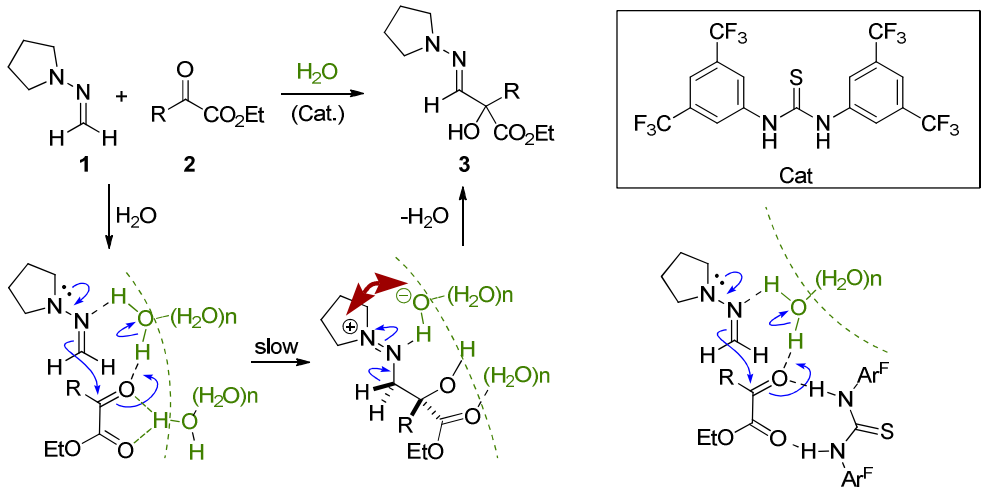
La necesidad de desarrollar una química sostenible ha estimulado en los últimos tiempos la investigación de nuevas aproximaciones que provoquen el menor impacto medioambiental posible, destacando entre ellas la reducción o sustitución de disolventes orgánicos. En este campo, el empleo del agua aparece como una de las posibilidades más atractivas, a lo que contribuye la gran ventaja de su bajo coste.[1]

Por otro lado, nuestro grupo de investigación ha conseguido demostrar la eficacia de las *N,N*-dialquilhidrazonas del formaldehído (DAHF) como nucleófilos frente a una variada gama de electrófilos de utilidad sintética, así como sus posibilidades como equivalentes neutros del ión formilo o cianuro tras desprotección de la función *N,N*-dialquilhidrazona.[2] En esta comunicación presentamos los resultados obtenidos para la adición de 1-metilenaminopirrolidina (**1**) a α-cetoésteres (**2**), en la que el agua es el medio de reacción clave que permite obtener carbinoles altamente funcionalizados (**3**) con excelentes rendimientos. La necesidad de condiciones heterogéneas y el efecto isotópico cinético observado para el disolvente apoyan una propuesta de activación "sobre agua".[3]



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Flash-87

Brønsted acid catalyzed enantioselective intra- and intermolecular α-amidoalkylation reactions in the synthesis of the isoquinoline framework.

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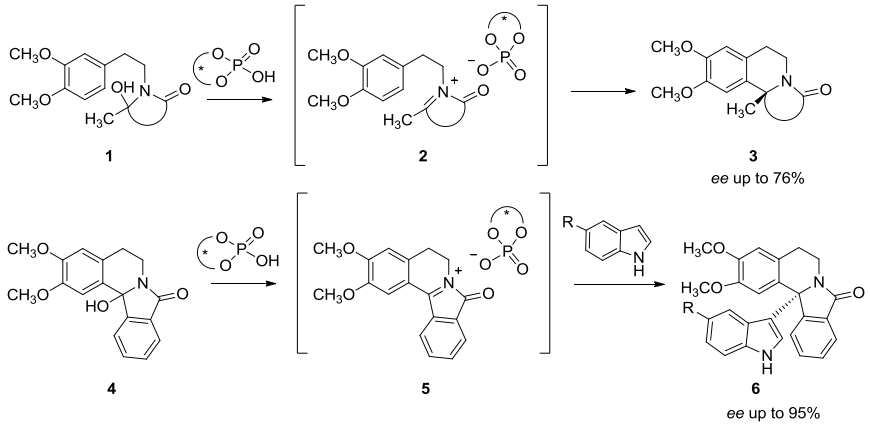
Enantiomerically pure nitrogen heterocycles are ubiquitous structures in natural products and pharmaceuticals. In this context, the enantioselective construction of the isoquinoline unit continues to be an intensely investigated field.[1] The α-amidoalkylation reaction of aromatic systems using *N*-acyliminium ions as electrophiles is one of the most attractive methods for C-C bond formation in heterocyclic chemistry and has found widespread application in natural products synthesis.[2] A significant progress in the application of enantioselective versions of α-amidoalkylation reactions has been marked by the development of chiral Brønsted acids (mainly BINOL derived phosphoric acids)[3] and hydrogen bond donors (mainly ureas and thioureas).[4] However, the intramolecular α-amidoalkylation reactions are still limited to a few examples and specifically with electron-rich heteroaromatic rings.[5] In this context, we have shown that BINOL-derived chiral Brønsted acids are capable of carrying out the the intramolecular α-amidoalkylation of a tertiary *N*-acyliminium ions **2**, obtained from hydroxylactams **2**, when a methoxylated benzene ring is used as the internal π nucleophile, though with moderate yield an enantioselectvities.[6] The Parham cyclization – intermolecular α-amidoalkylation sequence offers an efficient alternative, resulting in the facile enantioselective synthesis of 12b-substituted isoindoloisoquinolines **6** (*ee* up to 95 %).[7]



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Flash-88

Diastereodivergent Asymmetric Sulfa-Michael Additions of α-Branched Enones using a Single Chiral Organic Catalyst

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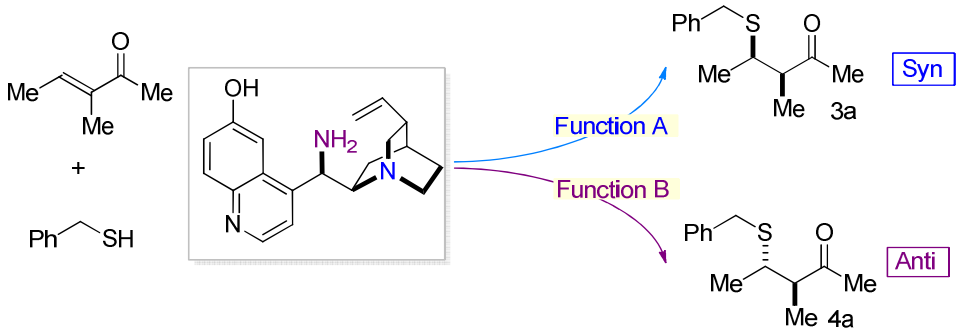
Chemists have created many different catalytic systems with the aim of synthesizing molecules bearing more than one stereogenic center in a diastereo- and enantiopure fashion. While it is usually straightforward to prepare either enantiomer of a given diastereoisomer by using the appropriate enantiomer of the catalyst, there is no obvious means of modifying a catalyst to modulate the relative sense of the stereocenters. Accessing the full matrix of all the possible diastereoisomers using a single chiral catalyst remains an unmet challenge. We describe herein an organocatalytic system based on the use of a cinchona alkaloid-based primary amine that is able to induce diastereodivergent pathways upon fairly simple modifications to the reaction conditions. Depending on the solvent and acid co-catalyst, the aminocatalyst can fully control the stereochemical outcome of the asymmetric conjugate addition of alkyl thiols to a challenging class of Michael acceptors (α-substituted α,β-unsaturated ketones), thus leading at will to the selective synthesis of all possible stereoisomers. [1]



Distinct Catalytic Functions Powered by a Chemical Stimulus

[1] Xu Tian, Carlo Cassani, Yankai Liu, Antonio Moran, Atsushi Urakawa, Patrizia Galzerano, Elena Arceo, and Paolo Melchiorre *J.Am.Chem.Soc* **2011**, *133*, 17934-17941.

Asymmetric catalysis of Diels-Alder reactions with *in situ* generated heterocyclic *ortho*-quinodimethanes

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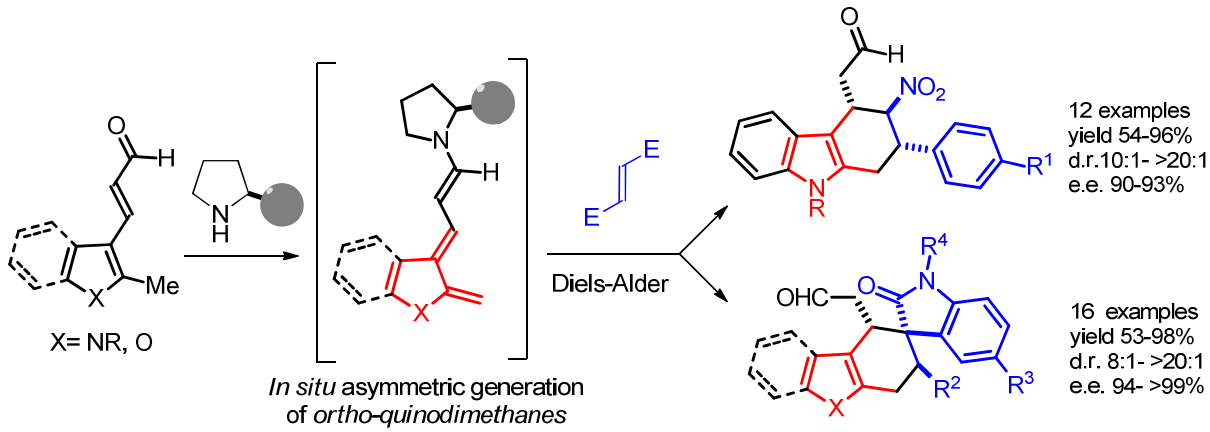
The Diels-Alder reaction[1] is considered to be one of the most powerful synthetic strategies for achieving structural and stereochemical complexity. The synthetic ability of this pericyclic transformation has greatly increased with the emergence of asymmetric catalytic variants, and research aimed at further expanding its potential is still important for the chemical community. Although the scope of the asymmetric Diels-Alder reaction has greatly expanded, one highly useful class of dienes, *ortho*-quinodimethanes (*o*QDMs), has never been used for a catalytic enantioselective approach. This communication documents the first asymmetric catalytic Diels-Alder reaction of *in situ* generated heterocyclic *ortho*-quinodimethanes (*o*QDMs)[2].

Asymmetric aminocatalysis, that uses chiral amines as catalysts, is the enabling strategy to induce the generation of indole-based *o*QDMs from simple starting materials, while directing the pericyclic reactions with nitroolefins and methyleneindolinones towards a highly stereoselective pathway. The indole-2,3-quinodimethane strategy, originally conceived for the straightforward synthesis of indole alkaloids more than 30 years ago[3], can now be made catalytic with a chiral amine. This strategy can then be used to synthesise a structurally diverse range of complex nitrogen and spirooxindole-containing tetrahydrocarbazoles with high chemical yield and excellent stereoselectivity. This new strategy can be easily extended to access complex pyrrole- and furan-based heterocyclic compounds while using mild and simple reaction conditions and may provide for the rapid application of this chemistry in synthetic and medicinal arenas.



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Flash-90

Three component Nitro-Manich Reaction operating "on water". A convenient access to 1,2-diamins.

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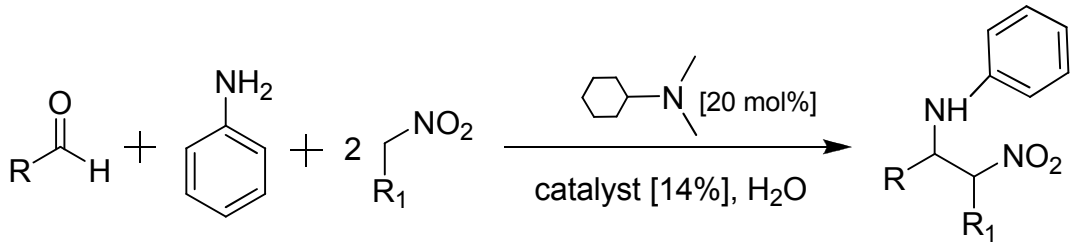
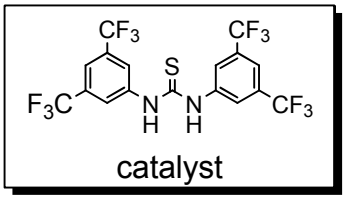
Herein we present an efficient multicomponent Nitro-Manich[1] reaction with a wide scope in the aldehyde component. The manifold operates under "on water" conditions[2] and involves the three-component reaction of aniline, an aldehyde and a nitroalkane in the presence of catalytic amounts of cyclohexyldimethylamine (Lewis base) and a thiourea-derivatived (catalyst). The presence of water and thiourea is essential for the reaction; whereas the water catalyzes the formation of the intermediate imine, the thiourea activates[3] the nitro-anion via H-bonding formation. In this communication we will show the most recent advances in our laboratory on this reaction.





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Flash-91

p-Nitrophenyl as Activating Group in Enantioselective Organocatalysis *via* Iminio. Synthetic Applications and Mechanistic Insights.

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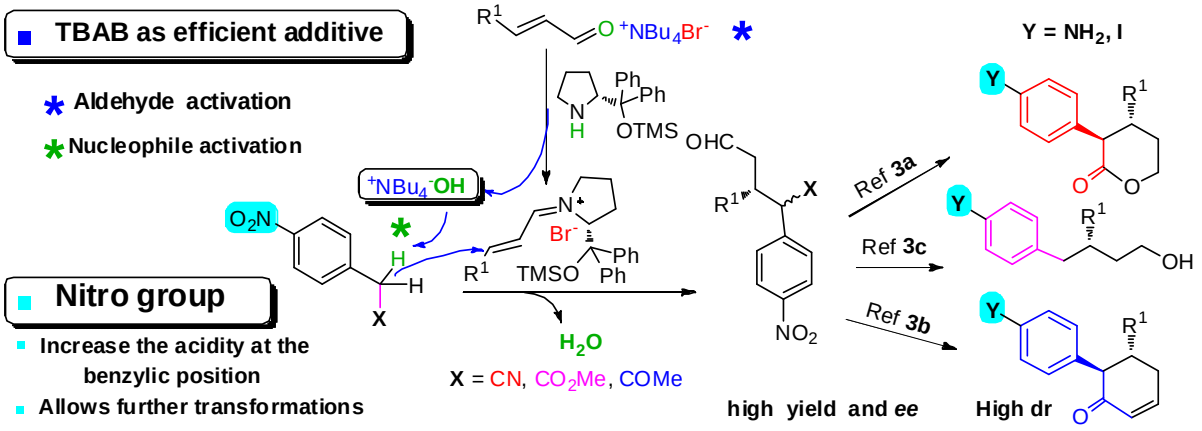
During the past few years, the research area of asymmetric organocatalysis has grown rapidly to become one of the most exciting and modern tools for the synthesis of optically active compounds without using any metal.[1] In particular, iminium catalysis using chiral secondary amines as catalysts, is an effective method to introduce nucleophiles at the β position of α,β-unsaturated aldehydes *via* enantioselective Michael addition.[2] Nevertheless, some challenges remain unsolved, such as some mechanistic aspects and the structural limitation of the nucleophile.

With the exception of the nitro derivatives, the pro-nucleophilic species require the presence of two geminal electronwithdrawing groups to get the appropriate acidity of the methylenic protons for being able to intervene in organocatalytic processes. In order to avoid this handicap we thought of a long distance activation of the methylene. The incorporation of a nitro group at the *para* position of an aromatic ring confers high acidity to benzylic protons and in this way, arylacetic acid derivatives can act as nucleophiles in organocatalytic reactions through an iminium intermediate in high yield and enantioselectivity. The resulting Michael adducts could be transformed into interesting synthetic substrates in high diastereoselectivity.[3]



In this context, we have also established that quaternary ammonium salts are efficient neutral additives in organocatalyzed Michael additions to enals, promoting sequential iminium / enolate formation.[3c] Our studies provide the mechanistic basis for understanding their role in these reactions, as well as that of other basic additives like LiOAc.

[1] For a recent review on organocatalysis see: Catalytic Asymmetric Conjugate Reactions, Vicario, J.L.; Reyes, E.; Badia, D. and Carrillo, L. Cordova, A. Wiley-VCH,Weinheim, Germany, 2010, chapter 6, p. 619.
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Flash-92

New sulphonic acid-based organocatalysts for triglycerides transesterification

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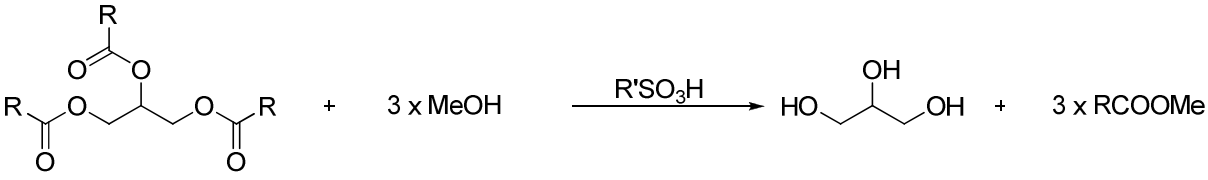
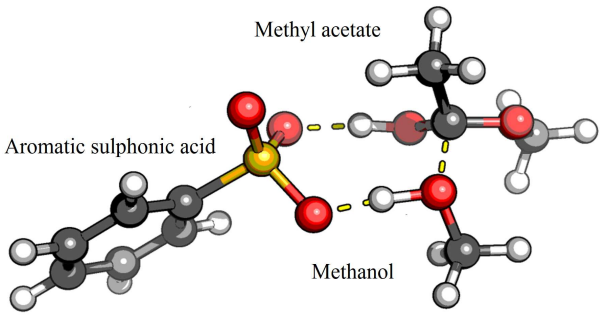
Oil-price rising and increasing greenhouse effect are making more attractive the use of alternative and renewable sources for fuel obtaining. One possibility is triglycerides transesterification, which is usually catalyzed with NaOH on industrial scale. However, this reagent has several drawbacks. To overcome these disadvantages it is fundamental to understand the reaction procedure and how the catalyst can be improved. In this work, a detailed kinetic study of the transesterification reaction is presented, process which may show different properties depending on the medium polarity.

With this knowledge, we tried to use some enzyme strategies like hydrophobic effect and/or molecular recognition, to design several sulphonic acid-based organocatalysts[1] which had shown a great catalytic activity in the transesterification of low-cost oils which could be used for the preparation of biofuels.





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Synthesis of aminophosphonic acids based on the structure of proline

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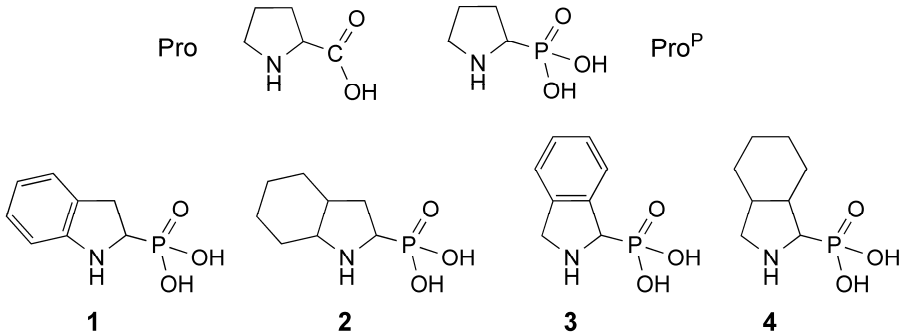
α-Aminophosphonic acids are surrogates of α-amino acids in which the planar carboxylic acid (CO_2H) has been replaced by a tetrahedral phosphonic acid [$P(O)(OH)_2$]. The phosphonate moiety mimics the tetrahedral intermediate formed during the enzymatic hydrolysis of a peptide bond. As a consequence, α-aminophosphonic acid derivatives act as inhibitors of numerous enzymes involved in the metabolism of peptides.

In particular, dipeptides containing the phosphonic counterpart of proline, phosphoproline (Pro^P, Figure 1) have been shown to be potent irreversible inhibitors of several serine proteases that are involved in the regulation of crucial physiological events and are considered primary targets for drug development. Effective inhibitors of these enzymes could be useful in the treatment of autoimmune and neurodegenerative diseases, cancer or diabetes, as well as to prevent the rejection of transplanted tissue.

Modification of the phosphoproline skeleton could be of great help in the development of inhibitors that are not only highly potent but also, and most importantly, selective for one specific serine protease. Actually, as often observed for proline in the carboxylic acid series, the attachment of additional hydrophobic groups to the pyrrolidine ring of phosphoproline can be foreseen as a powerful tool to tune the properties of peptides based on this α-aminophosphonic acid. We have developed an efficient route for the synthesis of phosphoproline and successfully extended this methodology to the production of the surrogates that incorporate a benzene or a cyclohexane ring fused to the [c] or [d] faces of the pyrrolidine moiety[1] (**1**−**4** in Figure 1). For the latter derivatives, both the *cis* and *trans* configurations of the cyclohexane unit and the phosphonic acid have been considered. Efficient methods for the synthesis of all these phosphoproline derivatives in racemic form have been developed. Access to enantiopure amino acids is underway.



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Flash-94

Ruptura Oxidante de 5-Heteroarilpirrolidinas. Síntesis asimétrica de derivados del ácido piroglutámico.

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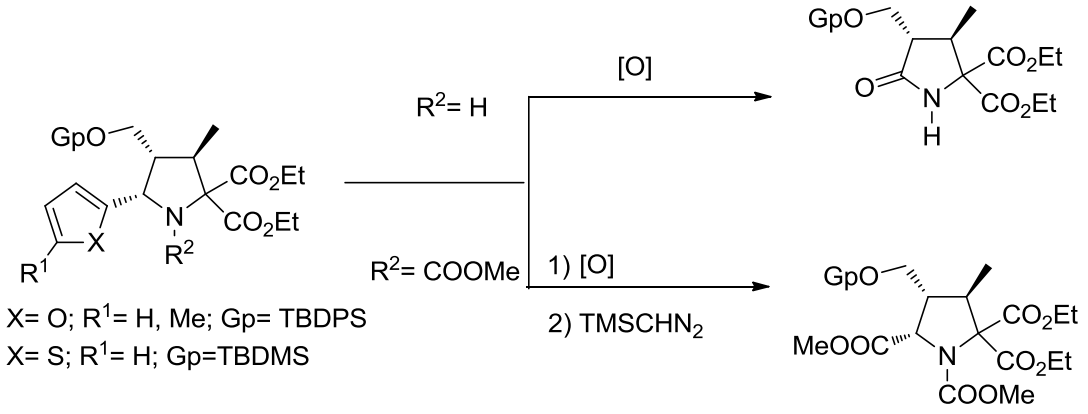
Las reacciones de oxidación de heteroarilos han demostrado ser de gran interés en etapas intermedias de numerosos procesos sintéticos. La oxidación completa de sistemas heteroarílicos al correspondiente ácido carboxílico se lleva a cabo, típicamente, con ozono,[1] tetróxido de rutenio[2] o $KMnO_4$[3] como agentes oxidantes siendo el anillo de furano el sistema heterocíclico más utilizado para este fin.

En nuestro grupo de investigación se ha puesto a punto un procedimiento para la síntesis de pirrolidinas densamente funcionalizadas mediante cicloadición [3+2] organocatalítica enantioselectiva.[4] Sobre las pirrolidinas 5-heteroaril sustituidas preparadas mediante esta metodología se han evaluado diferentes sistemas oxidantes con el fin de transformar el sistema heteroarílico en posición 5, proporcionando un acceso directo a las correspondientes γ-lactamas o derivados del ácido piroglutámico, o bien a α-aminoésteres derivados de prolina, todos ellos versátiles *buiding blocks* quirales en síntesis de numerosos productos de interés.



Agradecimientos: Los autores agradecen al MICINN (CTQ2011-22790), al Gobierno Vasco (IT328-10) y a la Universidad del País Vasco (UPV/EHU) por el soporte económico. I. Ugarriza y A. Iza agradecen a la UPV/EHU la Beca para Formación y Perfeccionamiento de Personal Investigador, y I. U. la ayuda económica (UFI QOSYC 11/22).

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Flash-95

The Chameleonic Chemical Behavior of Optically Pure Dicyclohexylidene-D-glucose Phosphinates.

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The development of efficient methods for the synthesis of chiral phosphinyl derivatives in the last years has broadened their applications in various actively developing fields including bioorganic chemistry, asymmetric synthesis and asymmetric catalysis.[1] In this sense, we have developed a cheap and very simple methodology for the synthesis of both diastereomers of phosphinate esters, epimer at phosphorous, using the sugar derived secondary carbinol dicyclohexylidene-D-glucose (DCG) as unique inductor of chirality, by choosing the adequate base (Py or Et_3N),[2] Figure 1.

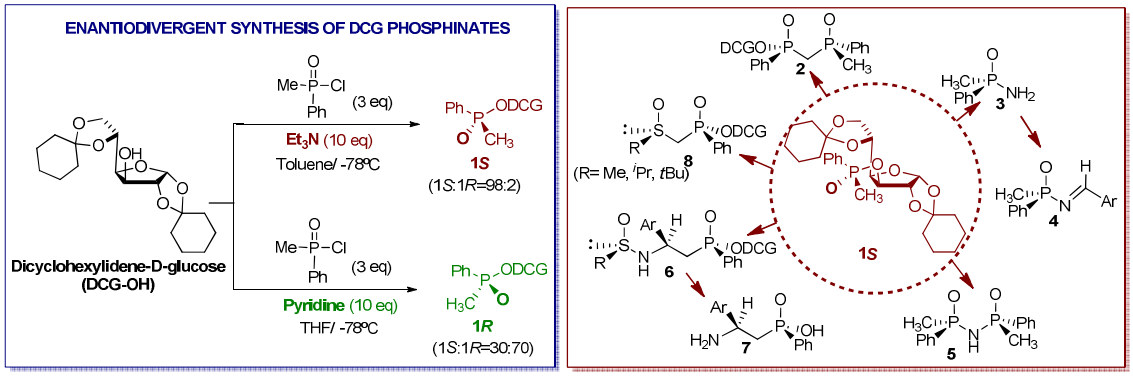

Figure 1

This method has been optimized for the large scale (20 g) synthesis of (*S*)-DCG methylphenylphosphinate, **1*S***, as precursor of a plethora of optically pure chiral phosphinyl derivatives of biological or synthetic interests (figure 1). In this communication it will be discussed the different chemical behaviour of this phosphinate **1*S***, as nucleophile or electrophile, depending on the nature of the nitrogenated base used as reagent (LHMDS, $NaNH_2$ or $LiNH_2$).

Acknowledgements: We thank the Dirección General de Investigación Científica y Técnica (Grant No.CTQ2010-21755-CO2-02) and the Ministerio de Asuntos Exteriores for a predoctoral MAEC-AECID Grant for A. Chelouan.

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Enantioselective Cycloaddtion of N-Metalated Azomethine Ylides onto Fullerenes

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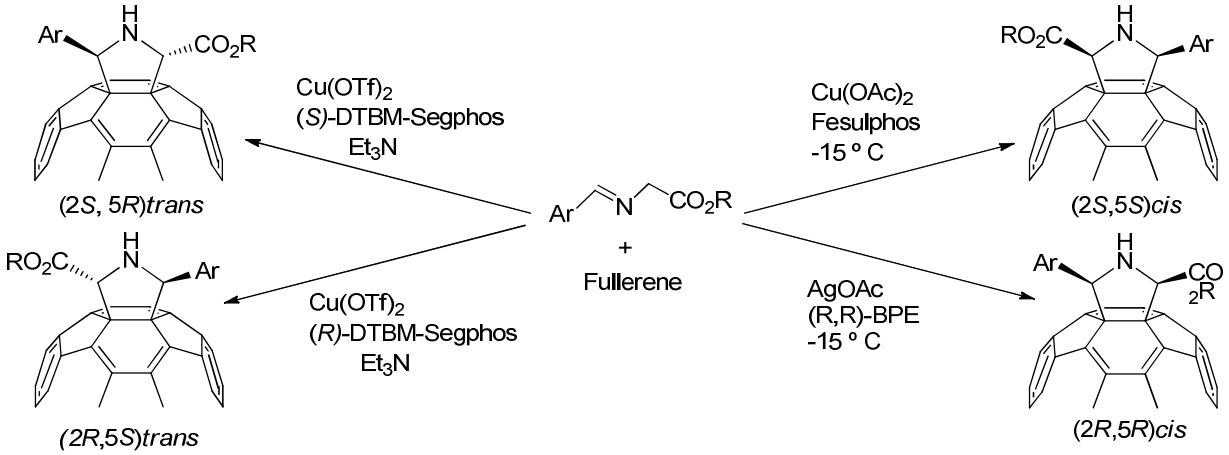
The refined control of some fundamental aspects, such as the regio- and the stereo-selectivity in the fullerene functionalization, are important issues still to be properly addressed. Indeed, the lack of a general enantioselective methodology has limited the use of enantiopure fullerene derivatives, which have been usually obtained just after HPLC isolation on a chiral column or prepared from chiral starting materials.[1]

In this communication, we report on the first catalytic enantioselective synthesis in fullerene science affording enantiomerically pure fullerenes with a total control of the stereochemical result. The suitable choice of the chiral metal catalyst ([Cu(II) or Ag(I)] in combination with a variety of different chiral ligands) directs the 1,3-dipolar cycloaddition of N-metalated azomethyne ylides on C_{60} (*Nature Chem.*,**2009**)[2] and on C_{70}(*Angew. Chem. Int. Ed.*,**2011**)[3] with high levels of site-,regio-, diastereo- and enantio-selectivity allowing a switching in selectivity.



The use of the curved double bond of fullerene cages as 2π component in cycloaddition reactions is a challenging goal considering its no ligand properties and it represents a unique scenario to shed light onto mechanistic aspects

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Flash-97

Síntesis "*one-pot*" estereoselectiva de 1,2,3-triazoles homoquirales derivados de dioles: combinación de la biocatálisis junto con la *"click chemistry"*

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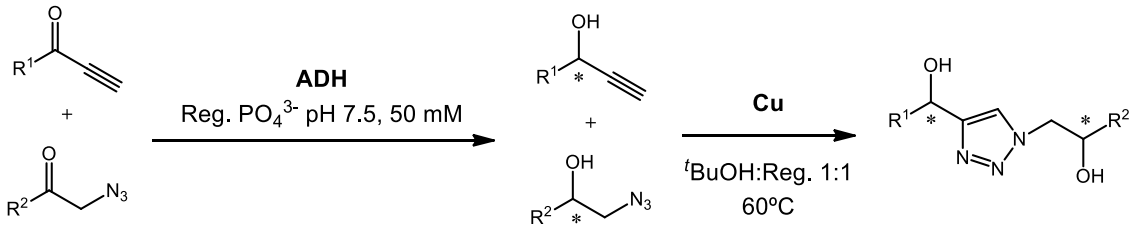
Debido a su alta regio-, quimio- y enantioselectividad, su carácter benigno para el medioambiente, y su disponibilidad cada vez mayor como consecuencia del rápido progreso en los campos de la ingeniería genética y la biología molecular, los enzimas juegan cada vez un papel más importante aplicados a la síntesis de compuestos orgánicos de interés.[1] Dentro de los biocatalizadores más empleados en los últimos años, las alcohol deshidrogenasas (ADHs) han sido utilizadas para relalizar la reducción asimétrica de, por ejemplo, alquinil cetonas[2] y azido cetonas[3] obteniéndose los alcoholes derivados con excelentes conversiones y estereoselectividades.



Esquema 1. Obtención de los dioles enantiopuros tras bioreducción y posterior cicloadición.

La cicloadición de Huisgen entre azidas orgánicas y alquinos se ha convertido en una versátil herramienta para la síntesis de heterociclos del tipo 1,2,3-triazol.[4] Durante los últimos años diversos derivados con anillos de triazol en su estructura han demostrado ser compuestos de potencial interés debido a su actividad farmacologica.[5] En este caso mostramos un proceso por etapas centrándonos en la bioreducción simultanea de dos derivados de cetonas utilizando ADHs y la posterior cicloadición de los derivados de alcohol enantiopuros obtenidos catalizada por Cu dando lugar a los dioles homoquirales enantioenriquecidos con buenos rendimientos.

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Visible-light Photoredox Catalysis for the α-Functionalization of Tertiary Amines

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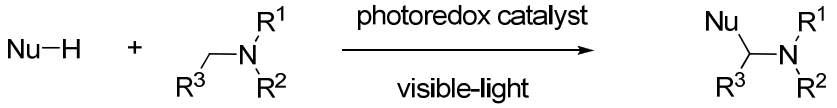
The application of visible light photoredox catalysis has emerged as a growing field in organic chemistry.[1] In this context ruthenium and iridium based polybipyridyl complexes which have well-known properties and long-living excited states are generated by irradiation with visible light.[2] These complexes have been used in a variety of organic transformations. In particular, the oxidation of sp^3 C-H bonds adjacent to nitrogen atoms using photoredox catalysis has attracted enormous attention.[3]

In this communication, we report the use of visible light photoredox catalysis in the α-functionalization of tertiary amines with different nucleophiles using visible-light.4 The reaction proceed under mild reaction condition and provide a series of different amines in good yields.



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Flash-99

Synthetic applications of allylsilanes: synthesis of oxacycles

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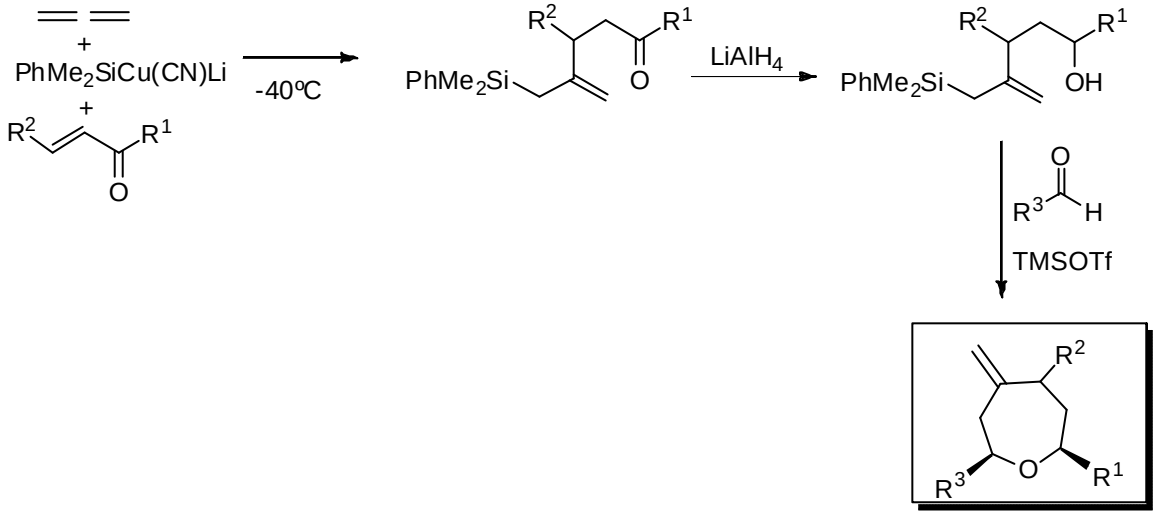
The stereoselective synthesis of substituted tetrahydropyran and oxepane scaffolds has attracted considerable attention, due to the presence of these units in a wide range of natural products exhibiting important biological activities.[1] Among the many available methods for the construction of these cyclic ethers, Prins cyclization has shown to be one of the most effectives.[2] Moreover, the silyl-Prins modification has provided very satisfactory results.

On the other hand, our research group has been involved for the past years in the synthesis of different sized carbocyles starting from functionalized allylsilanes.[3] In this communication we now present our recent results on the extension of this methodology to the synthesis of oxacycles.



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Access to the pyrrolo[3,4,5-*de*]quinoline framework based on the Bartoli indole synthesis

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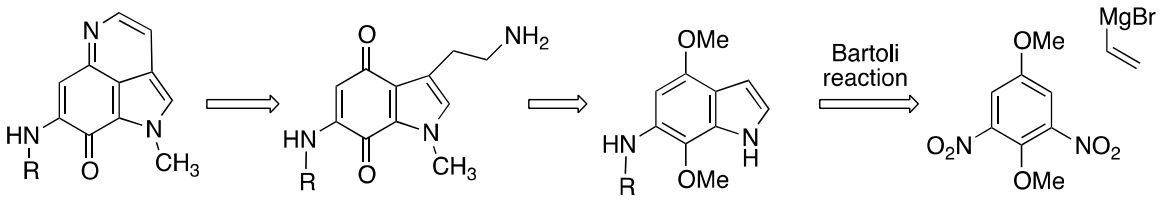
Marine organisms provide a valuable source of natural products. Pyrroloiminoquinone alkaloids including the makaluvamines, isobatzellines, tsitsikammamines and wakayin have emerged as an important class of marine metabolites due to their prominent biological activities and unusual structures.[1] In this communication we described a rapid route for the preparation of the pyrrolo[3,4,5-*de*]quinoline core of these alkaloids and its application to the synthesis of the makaluvamine B scaffold.

Our route is based on the Bartoli indole synthesis,[2] and starts from a dinitronitroarene having already in place the two nitrogen atoms of the 6-aminopyrrole core inherent to makaluvamine. Installation of the C-3 chain was followed by oxidative demethylation to generate a quinone and a final one-pot cyclization-dehydrogenation process.



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Flash-101

Nueva reactividad de TosMIC: síntesis de 2-vinilbenzonitrilos mediante doble funcionalización de bromuros de 2-bromobencilo

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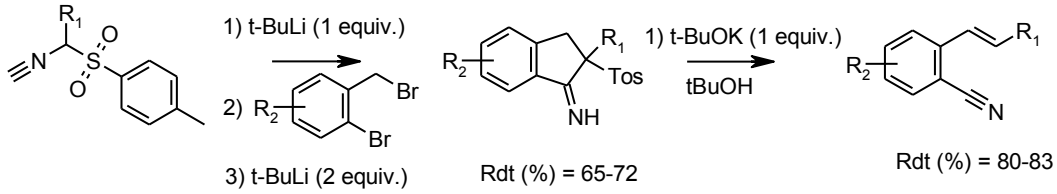
Dentro del amplio grupo que constituye la familia de los isonitrilos, el tosilmetil isonitrilo (TosMIC) ha sido objeto de especial atención debido a sus particulares características que lo han hecho particularmente útil en síntesis para construir sistemas heterocíclicos nitrogenados de cinco miembros.[1]

La molécula de TosMIC contiene tres puntos de posible reacción química: el grupo isocianuro, los protones ácidos en posición α a este grupo y el tosilo, que es un buen grupo saliente; esto confiere a la molécula una gran versatilidad sintética y la convierte en una candidata idónea para sufrir distintos tipos de reacción en cascada.

Nuestro grupo ha estudiado la reacción entre diversos derivados α-alquilados de TosMIC y bromuros de 2-bromobencilo, utilizando ^{t}BuLi como base, y ha obtenido 2-iminoindanos como únicos productos de la reacción en cascada que se produce. Este resultado se explica a través de una ruta en la que inicialmente se formaría una isoquinolina que, posteriormente, sufriría una reorganización molecular con contracción de anillo. El posterior tratamiento de los 2-iminoindanos obtenidos con *t*-BuOK conduce a diversos 2-vinilbenzonitrilos con buen rendimiento, en lo que representa una eficaz doble funcionalización de los bromuros de 2-bromobencilo iniciales.



Esta doble funcionalización es una alternativa a la reacción de cianación catalizada por paladio, metodología que se ha demostrado útil pero que también presenta importantes inconvenientes, como la toxicidad de los reactivos necesarios para este proceso.[2]

Agradecimientos. Los autores agradecen la financiación del Ministerio de Economía y Competitividad (proyecto CTQ2011-24715) y a la Universidad de Alcalá por una Beca predoctoral (A.C.).

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Application of the PIFA-Mediated Alkyne Amidation Reaction to the Construction of C-10 Substituted Pyrrolo[1,2-*b*]isoquinolines.

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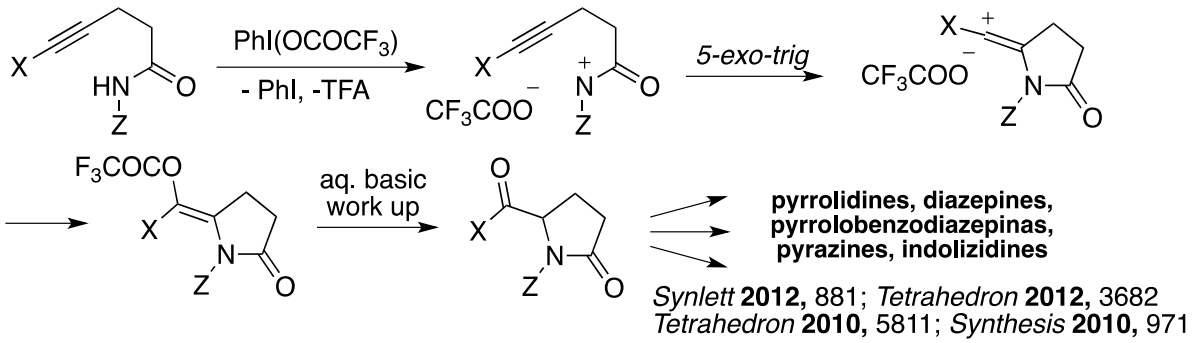
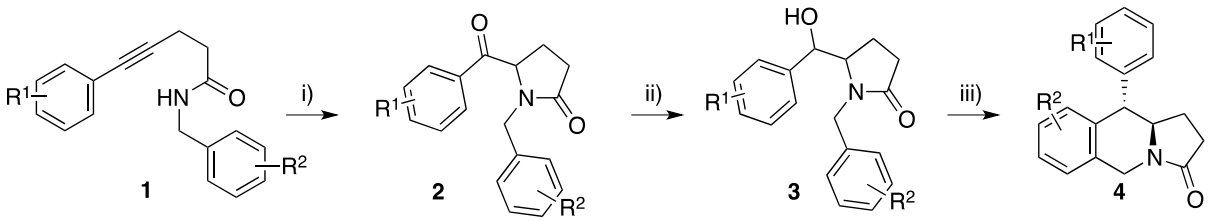
Our group discovered that properly substituted alkynylamides can be transformed into highly functionalized pyrrolidinone derivatives by the action of the hypervalent iodine reagent PIFA [*bis*(trifluoroacetoxy)iodo]benzene].[1] This strategy involves the generation of a N-acylnitrenium intermediate that is trapped by the alkyne moiety. The adequate selection of the carbon skeleton, the substitution at the triple bond (X), and the nature of the amidic substituent (Z) will determine the outcome of the reaction and the type of heterocycle that, eventually, will be formed.



In this communication it will be shown that this strategy can be also applied to the construction of pyrroloisoquinolines following the procedure described below. Thus, I(III)-promoted heterocyclization of **1** yields aroylpyrrolidinones **2**, whose keto-carbonyl group is then stereoselectively reduced (relative configuration not determined). Finally, treatment of **3** in acidic conditions leaves heterocycles **4** with high diastereocontrol (dr>85%).



Scheme 1. i) PIFA, TFEA, 0 ºC (32-79%); ii) L-selectride, THF, -78 ºC (74-90%); iii) H_2SO_4/AcOH or H_2SO_4/TFA (detailed conditions to be optimized).

Acknowledgements

Financial support from the University of the Basque Country (UPV/EHU), the Basque Government (GIU IT 370-10 and SAIOTEK S-PE11UN006), and the Spanish Ministry of Education and Science (CTQ2010-20703) is gratefully acknowledged. L. M. Pardo thanks UPV/EHU (UFI QOSYC 11/22) for financial support.

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Flash-103

Síntesis de los fragmentos C19-C25 y C1-C6 de las Anfidinolidas B y D

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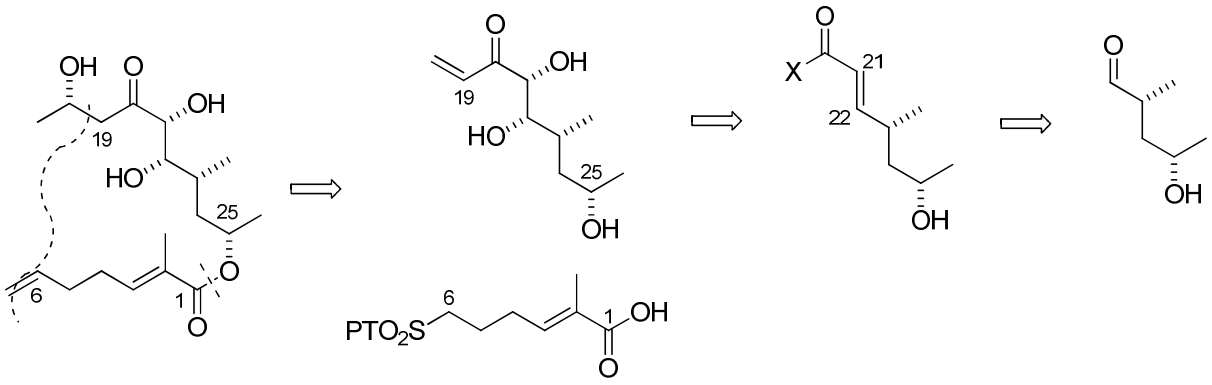
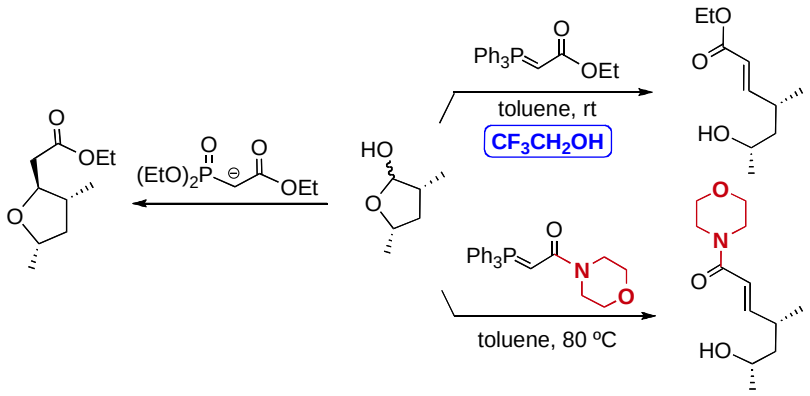
La retrosíntesis diseñada para la parte Este (Fragmentos C19-C25 y C1-C26) de las Anfidinolidas B y D, es la siguiente:



En la síntesis del Fragmento C19-C25, se obtuvieron resultados erráticos en la reacción de Horner−Wadsworth−Emmons de formación del doble enlace C21-C22. Con este trabajo se presenta una solución práctica. La reacción de HWE, para este caso particular, tiene gran tendencia a formar oxolanos, mientras que con los reactivos estabilizados de Wittig obtenemos los derivados carbonílicos insaturados de configuración *E* deseados:[1]



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Flash-104

Chemically modified ELRs to obtain biomaterials of potential biomedical applications via click chemistry

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J. C. Rodríguez-Cabello and M. Santos
Bioforge Group, University of Valladolid, Pº Belén 1
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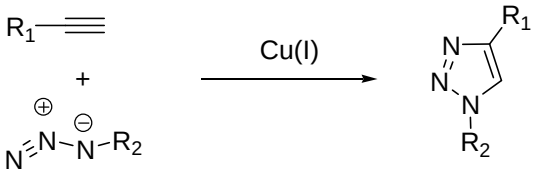
The bottom line of Click Chemistry Methodology encompass those near-perfect reactions that combines high efficiency and biocompatiblity with a high tolerance of functional groups and solvents, simple reaction conditions, fast reaction times, moderate reaction temperatures as well as high selectivity; what make this methodology to be an important key to biomedical applications. The most well-known and widely spread click reaction is copper catalyzed Hüisgen 1,3-dipolar cycloaddition between an azide and an alkynyl group. This click reaction takes place at room temperature in aqueous medium or at physiological conditions, and in an orthogonal, efficient and fast way.[1]



Elastin-like polymers, ELPs, are a new class of synthetic polypeptides whose composition has been inspired by repeating sequences found in natural elastin. The use of recombinant DNA technologies has revolutionized the design and production of novel ELPs. These techniques provide a tool for recombinant polymers, recombinamers, tailoring with an absolute control of the architecture, lack of randomness in amino acid stereochemistry and sequence and with unmatched degree of complexity and control. Elastin like recombinamers, ELRs, have been attracting interest because of the excellent biocompatibility and bioactivity and of their intrinsic "smart" stimuli-responsive nature.[2]

We present herein the chemical modifications of bioactive ELRs which once adequately functionalized along their chains have been crosslinked via click reaction allowing us to obtain, under mild and physiological conditions, 3D hydrogels suitable for biomedical applications. In addition, these hydrogels with selected patterns have been obtained by replica molding from polydimethylsiloxane (PDMS) stamps. Also smart thermoresponsive surfaces has been obtained by click reaction between ELRs functionalized with several azide groups at the end of their chains and surfaces previously chemically functionalized with alkynyl groups. The surfaces with ELRs covalently bonded as brushes provide a useful and efficient method for cell harvesting with potential biomedical application because of the intact maintenance of cell-cell and cell-extracellular matrix interactions.

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Flash-105

Síntesis y Resolución de carbenos *N*-heterocíclicos quirales en sistemas de biarilo

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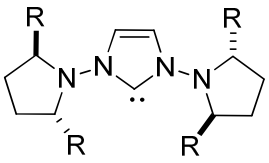
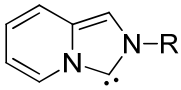
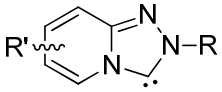
Los carbenos *N*-heterocíclicos (CNHs) han demostrado en los últimos años un enorme potencial, no sólo como versátiles ligandos de metales de transición,[1] sino también como organocatalizadores nucleofílicos en diversos procesos,[2] constituyéndose como una alternativa interesante a los ligandos tipo fosfina. En los últimos años, la investigación de nuestro grupo se ha dirigido al diseño de nuevas estructuras de CNHs intentando mejorar dos aspectos esenciales: la modulación de la capacidad donadora σ y la generación de entornos quirales eficientes alrededor del carbono carbénico. Entre las nuevas familias de CNHs desarrolladas se encuentran los 1,3-bis-(*N*,*N*-dialquilamino)imidazolin-2-ilidenos quirales **I**[3a] y carbenos *N*-heterocíclicos condensados en sistemas bicíclicos como imidazo[1,5-*a*]piridin-3-ilidenos **II**[3b] y [1,2,4]triazolo[4,3-*a*]piridin-3-ilidenos **III**.[3c] En este trabajo presentaremos la síntesis, resolución y química de coordinación de una nueva familia de CNHs **IV**, que incorpora estructuras de imidazo[1,5-*a*]isoquinolin-2-ilideno o [1,2,4]triazolo[4,3-*b*]isoquinolin-3-ilidenos en un sistema biarílico. El diseño de este nuevo tipo de ligandos presenta una importante novedad estructural: incorporan, por primera vez, una combinación de un biarilo con un eje axial quiral y configuracionalmente estable con un ligando excepcionalmente donador, como un carbeno *N*-heterocíclico *incluido en el sistema aromático de uno de los arilos*. Aunque existen ejemplos de CNHs enlazados a sistemas con quiralidad axial, esta nueva familia de ligandos incluye el carbeno *N*-heterocíclico en el sistema policíclico, lo que orientará necesariamente el par de electrones del ligando (y el enlace C-metal en el correspondiente complejo) en la proximidad del eje quiral. De esta forma, el sistema proporciona una atractiva combinación de protección estérica y excelente capacidad donadora σ que será estudiada en catálisis asimétrica.



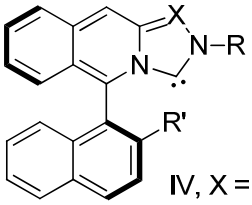
I



II



III



IV, X = CH, N

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Flash-106

Interacciones débiles entre 1,2,3-triazoles C-sustituidos y el benceno: Un análisis estructural

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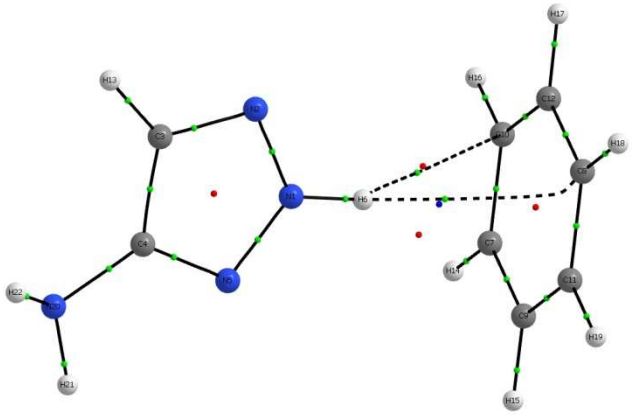
El amplio rango de actividad biológica desplegado por los 1,2,3-triazoles, específicamente por aquellos sistemas que disponen de las posiciones nitrogenadas libres[1], justifica un amplio estudio teórico sobre los mismos. Presentamos aquí un análisis sobre las interacciones débiles existentes entre estos heterociclos y el benceno en los mínimos energéticos detectados en la superficie de energía potencial, tomando en consideración las tres formas tautoméricas básicas presentes en los mismos.

Los análisis de la densidad electrónica llevados a cabo por la metodología AIM ("Atom in Molecules")[2] y los procedimientos de localización del método NBO[3] ("Natural Bond Orbital") nos permiten una mejor comprensión de la naturaleza de estas interacciones.



Agradecimientos: Este trabajo ha sido financiado por el Ministerio de Economía y Competitividad (MINECO), cofinanciado con fondos FEDER (CTQ2011-28417-C02-01).

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Ring Splitting of Azetidin-2-ones via Radical Anions

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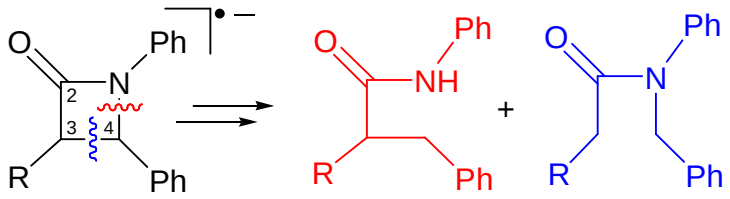
The chemistry of azetidin-2-ones has attracted considerable interest over the last decades,[1] mainly because compounds of this family (*β*-lactams) are associated with important biological activities, noteworthy their widespread clinical application as antibacterial agents.[2]

Azetidin-2-ones can be used as building blocks in organic synthesis by exploiting the possibilities of cleavage at any of the single bonds of the four-membered ring. In this context, reductive cleavage has been achieved by palladium-catalyzed hydrogenolysis, whereas oxidative ring opening has been performed by treatment with ozone.[3] By contrast, the photoreactivity of azetidin-2-ones has received much less attention,[4] and in fact these compounds are generally considered nearly photostable.

The behavior of radical anions of azetidin-2-ones remains unexplored, in spite of their potential to exhibit new chemistry; in fact, injection of one electron to the ring system constitutes a different (and complementary) activation strategy. With this background, the aim of the present work is to use triethylamine as donor for the generation of the radical anions of azetidin-2-ones upon UV-excitation. Phenyl substitution at N, C3 and/or C4 has been chosen for convenience, in order to introduce light absorbing chromophore(s) and to contribute to the stabilization of the radical and anionic centers developed during a possible ring splitting process.

Product studies show that the most general result is β-cleavage (Scheme 1), leading to open-chain amides. This reactivity diverges from that found for the neutral excited states, which is characterized by α-cleavage. The experimental results are fully supported by DFT calculations on the course of the reaction at the UB3LYP/6-31+G(d) level of theory.

Scheme 1



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.Push-Pull Cromophores based on Triphenylamine as photosensitizers and electron donor for molecular solar cells

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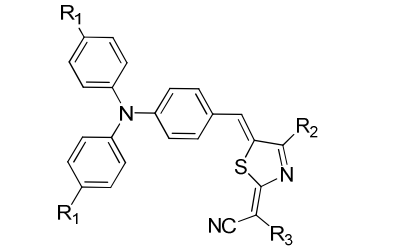
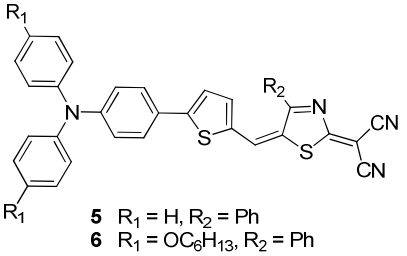
Organic photovoltaic cells offer the advantage with respect to analogous devices based on semiconductors of the possibility to use organic synthesis to prepare a wide array of molecules having the same core structure but different substituents. [1] In this way the energy levels and the absorption spectra of the organic molecules can be fine the tuned to optimize the efficiency of the devices.[2] In the area of organic solar cells there is much current interest in studying the performance of push–pull molecules having triphenylamine as electron donor moiety and electron pull alkenes as acceptors.

Here, we communicate the synthesis and properties of several new push-pull cromophores based on triphenylamine as donor and methylenethiazole as acceptor unit (Scheme 1).[3] These molecules show panchromatic absorption in the visible and NIR region covering from 300 to 800 nm (Figure 1). Finally, organic solar cells with these systems and PCBM as electron acceptor have been prepared.



1 R_1 = H, R_2 = Ph, R_3 = CN
2 R_1 = H, R_2 = Bu^t, R_3 = CN
3 R_1 = H, R_2 = Ph, R_3 = CO_2Me
4 R_1 = OC_6H_{13}, R_2 = Ph, R_3 = CN



5 R_1 = H, R_2 = Ph
6 R_1 = OC_6H_{13}, R_2 = Ph

Scheme 1

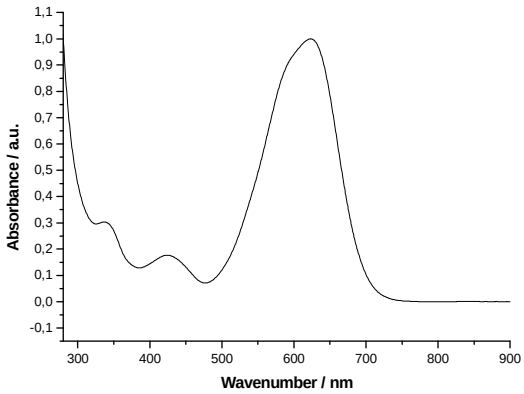


Figure 1

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Flash-109

Luminescent cyanostilbene bent- core molecules with liquid crystal properties

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Bent-core liquid crystals or banana shaped liquid crystals are a class of liquid crystals as a consequence of their peculiar arrangement. They have led to the discovery of novel polar mesophases, the novel induction of supramolecular chirality using achiral molecules and noticeable ferroelectric and antiferroelectric responses in the absence of molecular chirality. These properties have promoted the study of these compounds and their possible applications.

In this work, novel bent core liquid crystals with cyanostilbene units have been synthetized (fig. 1) to get functional materials with optical properties. Their synthesis has been achieved using multistep reactions such us etherifications, esterifications, Suzuki coupling, etc.

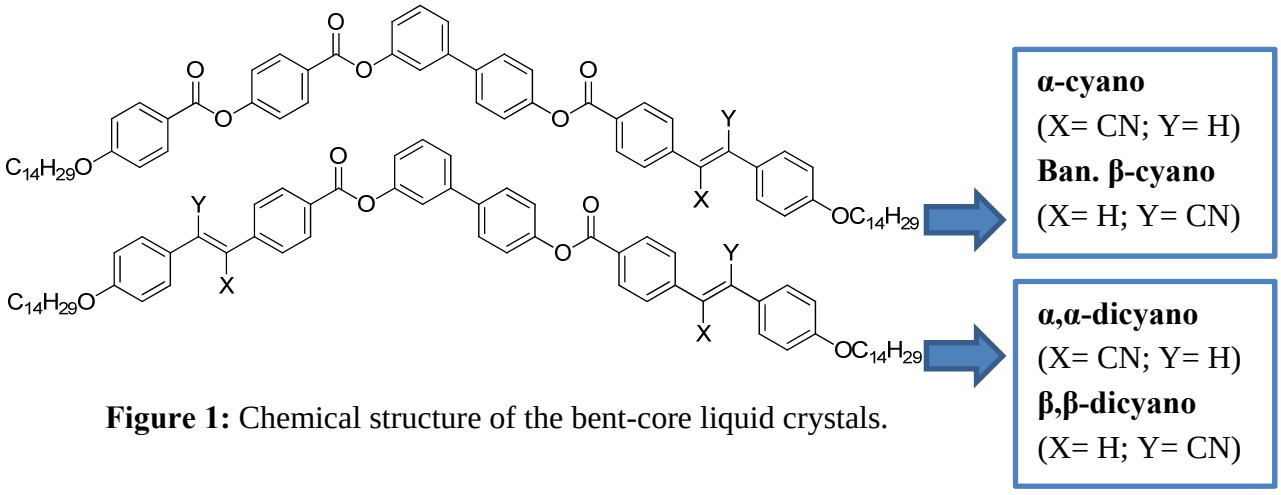

Figure 1: Chemical structure of the bent-core liquid crystals.

Chemical structures of the bent-shaped liquid crystals have been confirmed by IR spectroscopy, ^{1}H-RMN, ^{13}C-RMN and mass spectrometry. The thermal and liquid crystals properties of the compounds have been studied by polarized optical microscopy (MOP), differential scanning calorimetry (DSC) and X-ray diffraction. The optical properties have been measured by UV-vis spectroscopy, luminescence spectroscopy and by nonlinear optic and electro-optic studies.

Acknowledgments. Financial support from the Spanish Government (CICYT-FEDER MAT2009-14636-C03-01), Aragon Government (research group E04) and CSIC (JAE Predoc program) are gratefully acknowledged.

DNJ-[60]Fullerene and DNJ-βCD conjugates: Multivalent Effect on Glycosidase Inhibition

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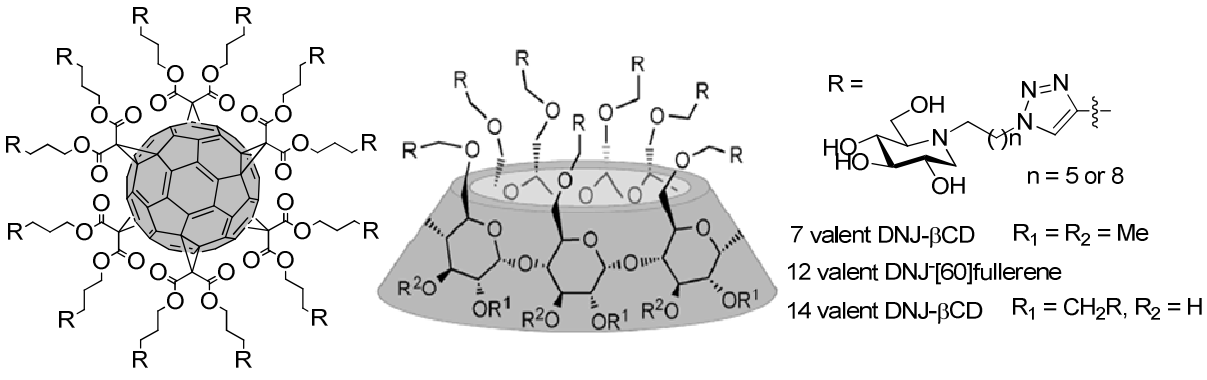
Iminosugars are important tools in glycobiology, aiding at both unraveling the mechanism of action of glycosidases and the development of new pharmaceuticals.[1] Howerer, most of them behave as broad range glycosidase inhibitors. Presentation of a ligand in multiple copies is very often found in nature as a way to increase affinity and modulate selectivity towards a given receptor, and is a concept profusely exploited in the field of glycobiology to generate useful glycoligands for therapeutically relevant lectins. In stark contrast, the possibility of implementing the multivalency concept to control the interaction between glycosyl hydrolases and complementary glycomimetics has been almost unexplored.

To explore the potential of multivalency on glycosidase inhibition, unprecedented fullerene[2] and cyclodextrin-based iminosugar conjugates[3] have been designed and prepared. After biological evaluation using a panel of glycosidases, the most impressive results were obtained for α-mannosidase of Jack Bean. Multivalent iminosugars were found to be excellent inhibitors of this enzyme whereas theirs monomeric analogues presented low activity. ITC experiments confirmed that binding between the enzyme and multivalent iminosugars is controlled by enthalpy. Comparative thermodynamic data will be presented.



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Flash-111

Integrative Self-Sorting Synthesis of a $Fe_8Pt_6L_{24}$ Cubic Cage

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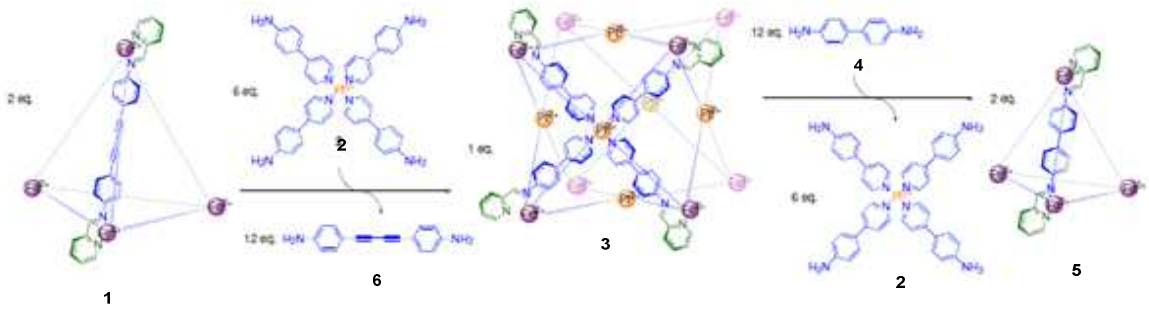
Self-assembled metal-organic capsules[1] have been shown to be useful for a variety of applications, including guest binding, separation, and other interesting ends. One strategy pursued by researchers to create progressively more complex metal-organic architectures has been the preparation of heteroleptic species.
The two-step synthesis of cube **3** starts from a tetrafunctional amine (*i.e.* compound **2**), which stands in contrast to the preparation of tetrahedral cages previously reported by our group[2] . Since in all these metal-organic capsules the dynamic Fe^{II}–tris(pyridylimine) moiety is present at the capsule's vertices, we set out to investigate whether a cage-to-cage conversion *via* amine-residue-exchange[3] was possible (Scheme 1).



To this end, tetrahedral cage **1** was prepared by reaction of the electron-poor diamine **6**, ($Fe(NTf_2)_2$ and 2-formylpyridine. Upon addition of tetra-amine **2** to **1**, the formation of cubic cage **3** and diamine **6** was observed. We infer that this cage-to-cage transformation is entropically favorable because for each tetra-amine **2** that is incorporated in cube **3**, two equivalents of diamine **6** are released. Subsequent addition of benzidine **4** to cubic cage **3** **r**esulted in the formation of **5** and concomitant release of ligand **2.** Although entropically disfavored, this transformation appears to be driven by the incorporation of diamine **4**, which is more electron-rich than to tetra-amine **2.**

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Flash-112

Preorganizing cyclodextrins for DNA complexation through selective chemical functionalization

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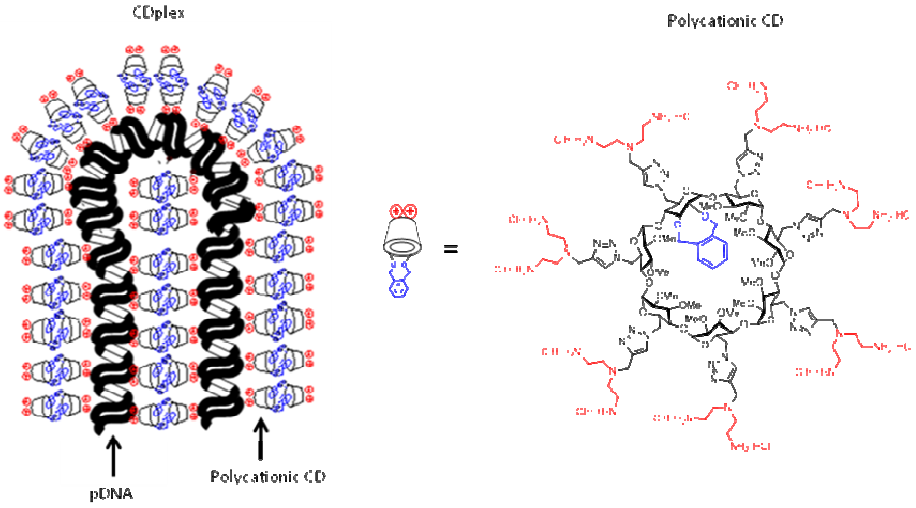
Monodisperse polycationic amphiphilic cyclodextrins (paCDs) have been shown to form complexes with DNA (CDplexes) that protect genetic material from degradation and promote cellular internalization.[1] The complexation process is driven by electrostatic interactions followed by self-assembling of the paCD units onto the DNA chain to form bilayers where the hydrophobic domains of the facial amphiphile architecture are faced. We conceived that preorganizing the polycationic CD platform by the incorporation of functional elements to favor face-to-face dimerization will improve the whole process leading to DNA compaction.

We have previously shown that the introduction of a xylylene moiety at the secondary face of *β*-cyclodextrin (*β*CD) is a way of promoting self-assembling phenomena through hydrophobic interactions.[2] Polycationic prototypes were obtained by regioselective xylylenation at the secondary face in the per-(C-6)-azido precursor and further characterized and tested as pDNA carriers. Gel electrophoresis experiments, dynamic light scattering and transmission electron microscopy revealed that these macromolecules bind and compact pDNA into spherical nanoparticles in the size range of 50-200 nm. Luciferase transfection experiments were carried out in COS-7 cells and showed that polycationic xylylene derivatives condense and transport pDNA to the cell transfection.



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Flash-113

INTRODUCING AXIAL CHIRALITY INTO MESOIONIC 4,4´-BIS(1,2,3-TRIAZOLE) DICARBENES[1]

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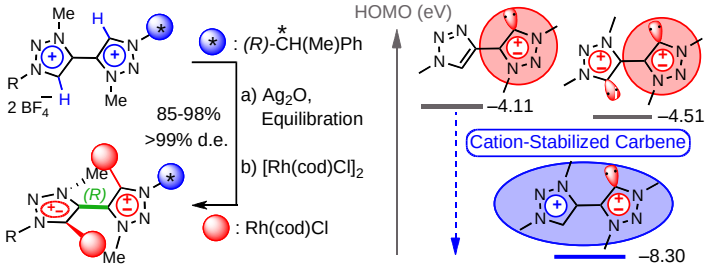
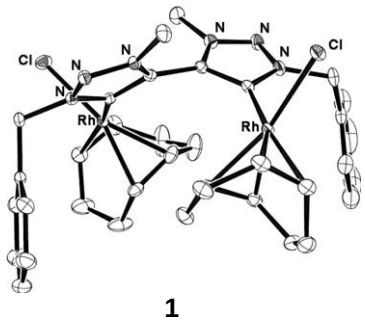
Nonsymmetrically substituted 4,4'-bis-(1,2,3-triazolium) salts were prepared in a totally site-controlled manner by Cu(I)-catalyzed "click" [2+3] cycloaddition of 3-alkyl-4-ethynyl-1,2,3-triazolium salts with alkyl or aryl azides[2,3]. These compounds were found to be excellent precursors of mesoionic carbenes (MIC)[4] upon reaction with Ag_2O reagent and further transmetallation with $[Rh(cod)Cl]_2$. The resulting atropoisomeric dirhodium complexes **1** having C2 chiral 4,4´-axis were obtained in virtually complete de. Their structure and configurational integrity were assessed by NMR spectroscopy, X-ray diffraction and chiral HPLC. In addition, computational analysis of the MICs involved in the reaction suggested the formation of a highly stable and unprecedented catio-carbene intermediate species, which could be evidenced experimentally by cyclic voltammetry (CV) analysis.





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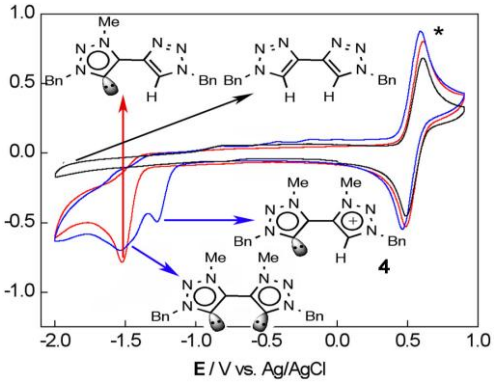

Acknowledgement: M. S.-A. thanks University of the Basque Country UPV/EHU (UFI QOSYC 11/22) for financial support

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Flash-114

Modular chemical synthesis of *N*-glycans

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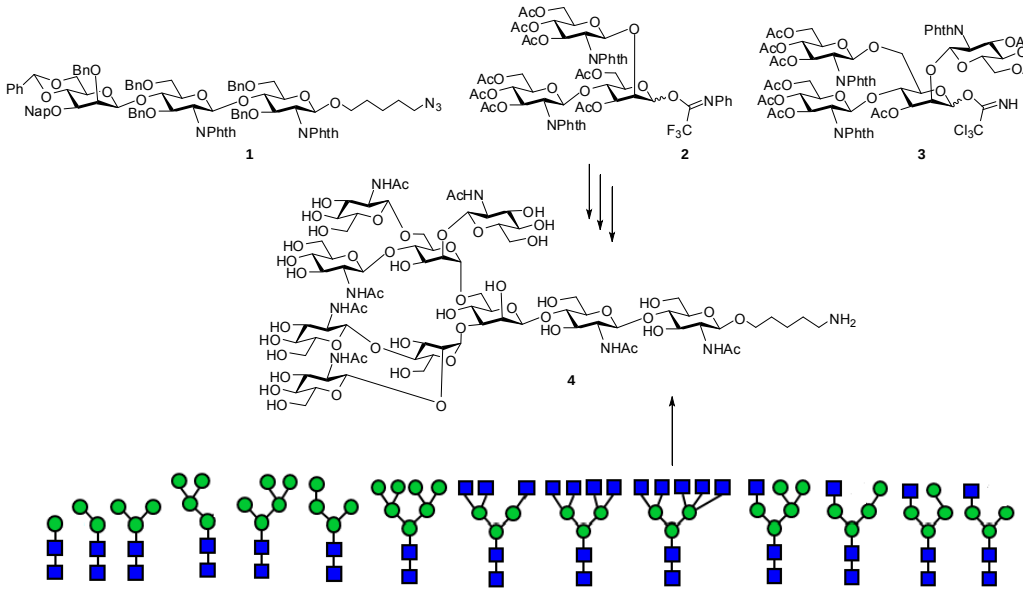
Glycan arrays are increasingly important tools in Functional Glycomics, the high-throughput search for functional receptors of the myriad of glycan structures covering the cellular membranes of all living beings. A bottleneck of glycan array preparation is the supply with well-defined and pure glycan ligands ideally functionalized with a linker for covalent attachment on the microarray. In this regard we have developed a strategy based on the modular synthesis of core structures and their subsequent enzymatic on-chip elongation the help of recombinant glycosyltransferases[1-4]. Employing this approach glycan microarrays *N*-glycan microarrays with unprecedented structural diversity can be prepared by a single lab with affordable synthetic effort.

As an example of this strategy we present the high-yielding convergent synthesis of the penta-antennary decasaccharide **4** functionalized with an anomeric linker from the building blocks **1, 2** and **3.** After an efficient 3-step deprotection sequence the decasaccharide was ready for printing.



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Flash-115

Tracking the controlled release of Doxorubicin from magnetic thermo-responsive polymer nanobeads in a microfluid channel on a chip

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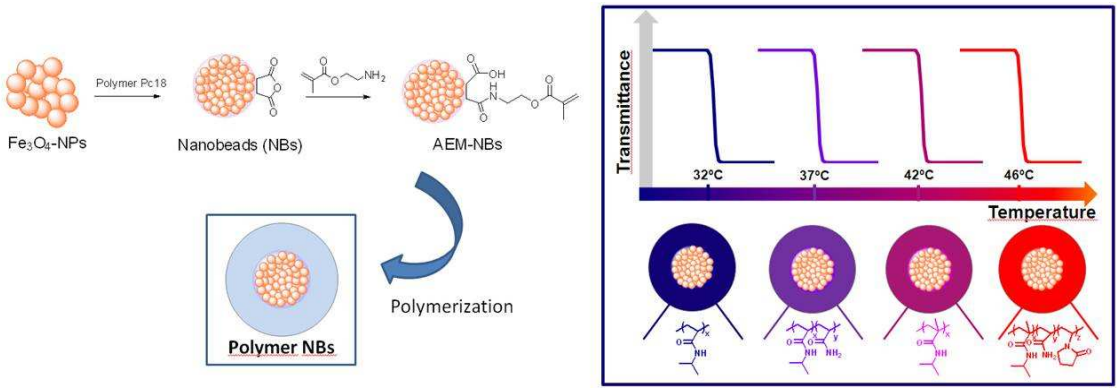
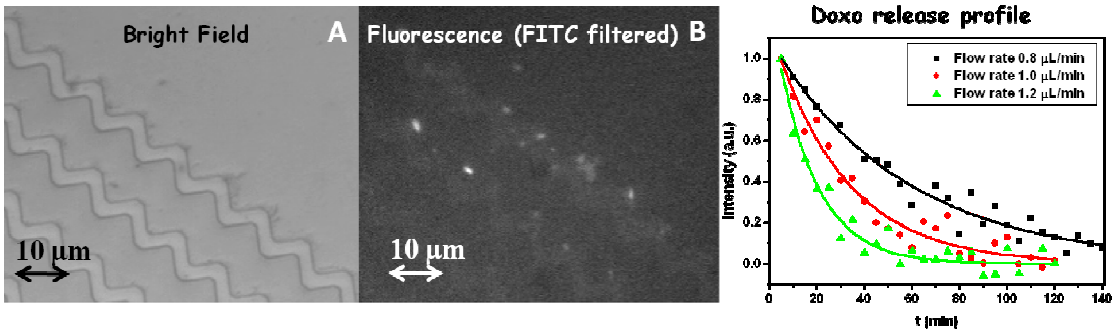
In the present study, we report a procedure to fabricate magnetic thermo-responsive nanocarriers based on multiple IONPs embedded in a double shell of polymer, which included an internal one made of poly (maleic anhydride-*alt*-1-ocatadecene) and an outer shell composed of thermo-responsive polymer. Depending on the co-monomers chosen and on their ratio tunable phase transition temperatures in the range between 26-46ºC could be achieved in physiological conditions.



Furthermore, we demonstrate the possibility to magnetically manipulate our magnetic thermo-responsive nanobeads in the microfluidic chip. Basically, we show the controlled entrapment and drug release of doxorubicin loaded nanobeads in specific points along the fluidic micro-channels based on a local temperature increase and application of a low magnetic field.[1,2].



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Flash-116

ProLeuGly-containing CEST contrast agents for tissue-selective MRI imaging

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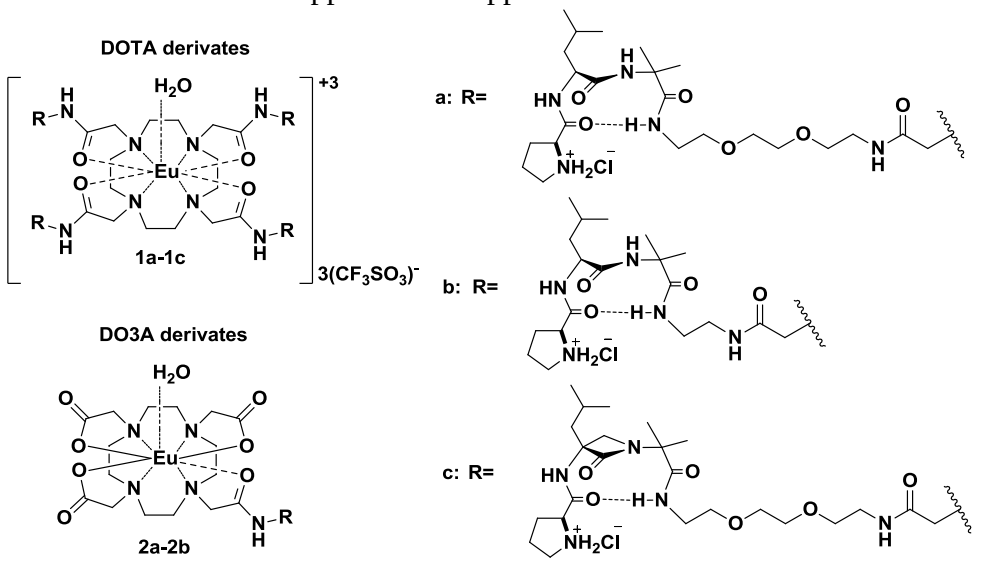
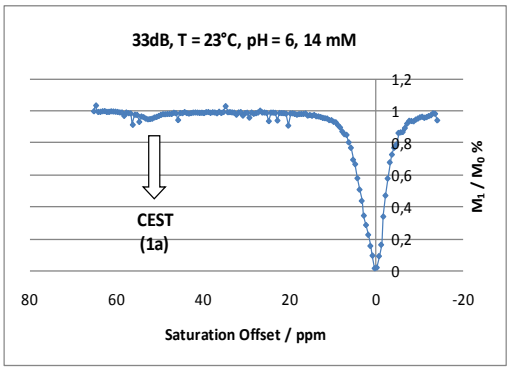
Chemical Exchange dependent Saturation Transfer (CEST), a new class of MRI contrast agents, is characterized by water or proton exchange sites that differ from bulk water in their chemical shifts and exchange rate with bulk water molecules or protons. Selective radiofrequency (RF) irradiation of those unique water or proton sites can result in a reduction in total water magnetization, thereby providing a unique mechanism to introduce MR contrast into an image by RF frequency selection. [1,2]Lanthanide complexes derived respectively from tetraamides DOTA **1** and DO3A monoamides **2** containing terminal Pro-Leu-Gly (PLG) tripeptide surrogates have been successfully synthesized and some of them showed efficient CEST effect in water with resonances of the Eu^{3+} -bound water at ~ 50 ppm and ~70 ppm.





Acknowledgement: E. A. thanks University of the Basque Country UPV/EHU (UFI QOSYC 11/22) for financial support

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Flash-117

Factors Influencing the Inhibition Potency of an Essential Enzyme in Bacteria: Synthesis, Biological Evaluation and Molecular Dynamics Simulations Studies

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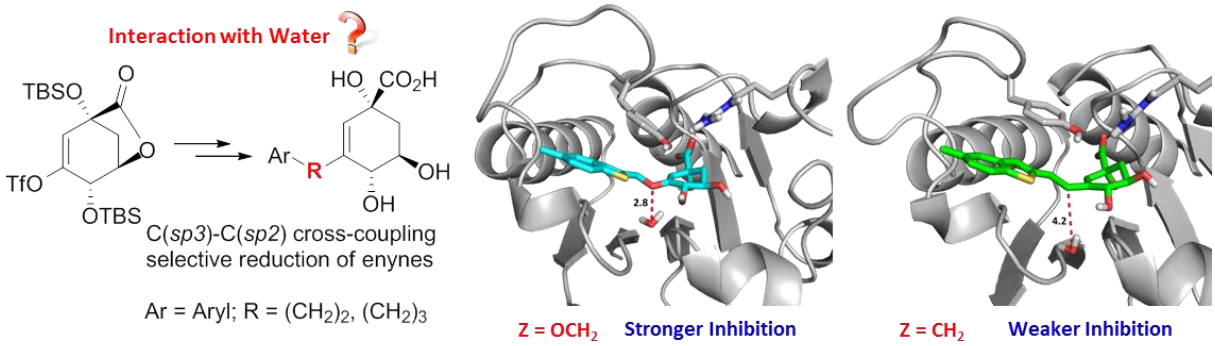
In recent years, we have been working on the development of new antibiotics for the treatment of bacterial infections, by inhibition of type II dehydroquinase enzyme (DHQ2) that catalyzes the reversible dehydration of 3-dehydroquinic acid to form 3-dehydroshikimic acid. The reaction proceeds through an enol intermediate **3**, which is stabilized by a conserved water molecule. In particular, we have focused on the inhibition of two pathogenic bacteria, *Mycobacterium tuberculosis*, the causative agent of tuberculosis and *Helicobacter pylori*, the causative agent of gastric and duodenal ulcers, which has also been classified as a type I carcinogen.

Recently, we have solved the crystal structures of DHQ2 from *H. pylori* and *M. tuberculosis* in complex with several enol mimics that show that inhibitors cause an important change in the conformation and flexibility of the loop that closes over the substrate binding site and highlight an important interaction with the conserved water molecule involved in the catalysis.[1] In order to investigate the effect in the inhibition potency of the later interaction, several 3-alkylaryl mimics of the enol intermediate were synthesized and tested with these enzymes. The results of inhibition studies of these compounds against DHQ2-Mt and DHQ2-Hp, docking studies using GOLD 5.0 and molecular dynamics simulations studies will be presented.[2,3]



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3. Financial support from the Xunta de Galicia (10PXIB2200122PR and GRC2010/12) and the Spanish Ministry of Science and Innovation (SAF2010–15076) is acknowledged.

Gold nanoparticles in assembled gene delivery carrier

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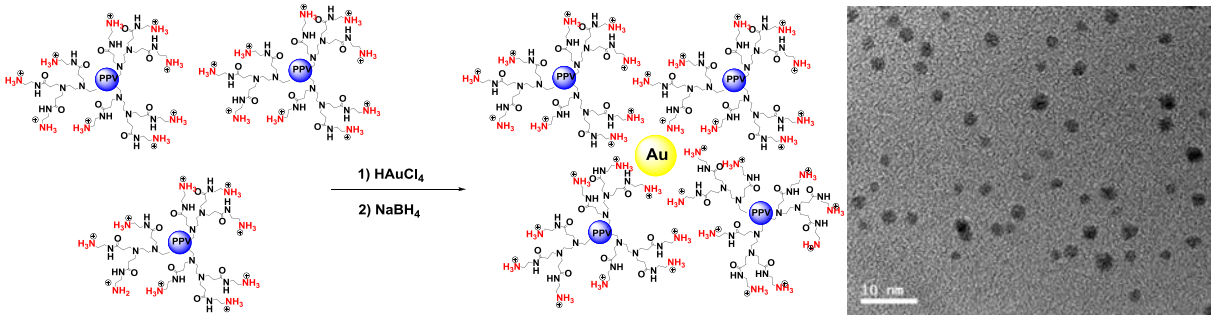
Dendrimers have emerged as a novel class of nanoparticle platform in nanobiotechnology because of their well-defined architecture and unique characteristics.[1] The void area within a dendrimer, the extent of its branching, its ease of modification and preparation, and size control offers great potential within the focus of nanomedicine among other interdisciplinary fields.[2] Recently, we reported the synthesis and characterization of a new polyphenylenevinylene-polyamidoamine (PPV-PAMAM) hybrid dendrimer (TGD) that was able to bind and release small interfering ribonucleic acid (siRNA) and lacks any toxicity on neurons at the concentrations used to deliver siRNA. We also demonstrated that dendriplexes formed by TGD and RNAs (siRNAs) could be incorporated into more than 90% of the neurons indicating that TGD might be a promising non-viral gene delivery carrier.[3]
In this sense, self-assembly interactions between molecules are interesting in order to understand the supramolecular organization of the TGD as well as their interactions with other molecules.
Here, we present the aggregation and self-assembly studies of first generation dendrimer TGD, as well as, second and third dendrimer. Taking advantages of the supramolecular organization very small gold nanoparticle can be stabilized by these dendrimers. This assembly allows us to combine the previously cited biological properties with the unique properties of gold nanoparticles that make them useful as biomarkers in living whole cells.



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Flash-119

SWCNTs/Glycolipids: New Biologically-active Supramolecular Assemblies

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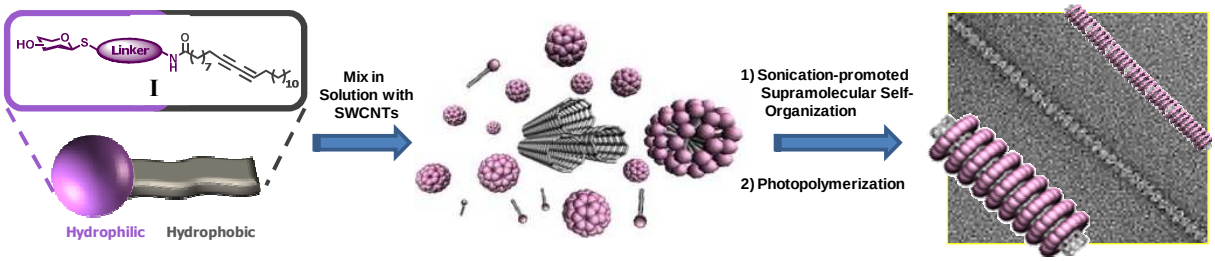
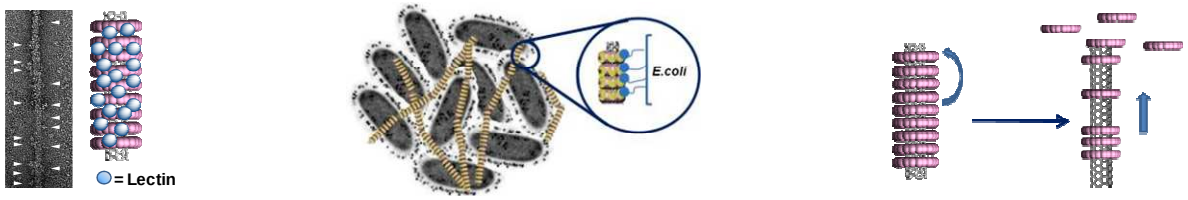
Single walled carbon nanotubes (SWCNTs)[1] have received an unrivalled interest as consequence of their unique structural, mechanical, electrical, and optical properties that make them promising candidates for biomedical applications.[2] Nevertheless, advances in these directions have been hampered by the insolubility of CNTs in most solvents, and most importantly in water, where they exist as ropes and large bundles. To overcome these problems we have recently development various approximations for the water-solubilization of SWCNTs with neoglycolipids,[3] such as **I**[3b] which shows the formation of glyconanobacuses with a biomimetic presentation of carbohydrates on their surface.[3d]



In the present communication, we are aimed at discussing: *i*) the synthesis and characterization of glyconanorings-coated SWNTs, *ii*) their selective binding to specific lectins and *iii*) to aggregate specifically the *Escherichia coli* bacteria, as well as *iv*) our effort for sliding the glyconanorings out of the carbon nanotubes, and the study of these resulting glyconanosomes to encapsulate a variety of guest lipophilic molecules.



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Flash-120

Synthesis of new pyrano[3,4-*c*]isoquinoline derivatives as analogues of natural products with interesting biological activities.

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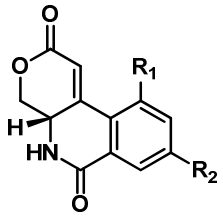
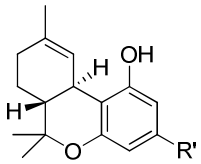
The synthesis of new pyrano[3,4-*c*]isoquinoline derivatives is described. These new structures are similar to natural products that display interesting biological activities, such as the phenanthridone alkaloids extracted from plants of the Amaryllidacea family[1] or some cannabinoids generated by *Cannabis sativa L.*[2]



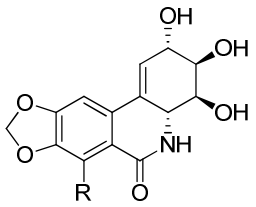
R_1= H, OMe
R_2= H, Alkyl, OR´

pyrano[3,4-c]isoquinoline derivatives



R'= Pentyl; Δ^9-THC
R'= Propyl; Δ^9-THCV

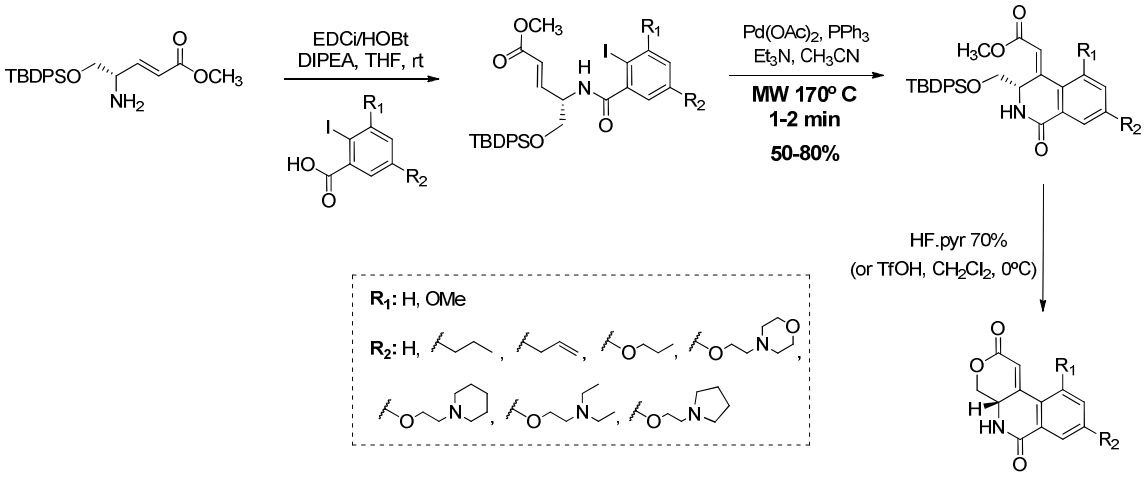
Cannabinoids



R = H; (+)-Lycoricidine
R = OH; Narciclasine

Amaryllidaceae alkaloids

These derivatives were synthesized according to a convergent strategy starting from an amino acid derivative and an aromatic fragment. The most relevant step of the synthesis is an intramolecular Mirozoki-Heck coupling reaction. This reaction takes place in a very effective manner by using the optimal experimental conditions developed in our research group providing a good isolated yield and a complete stereoselectivity. Finally, the tricyclic system is obtained by deprotection and cyclization of the bicyclic compound, in a one-pot synthetic procedure.



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Flash-121

Synthesis and anti-influenza A activity of novel polycyclic amines

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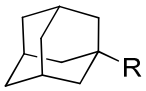
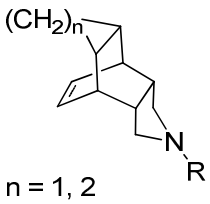
Human influenza A virus is a major health issue and there is an urgent need for new drugs that can target the different life-threatening mutants that have recently arisen.[1] The influenza virus possesses a proton channel called the M2 protein which is involved in the release of the viral genetic material to the cytoplasm.[2] Two polycyclic amines, amantadine and rimantadine, are known to bind to the internal hydrophobic cavity of the M2 protein, thus preventing its proton trafficking activity. Both amines have proven their efficacy against the influenza A virus and have been in clinical use for many decades.[3] However, with the recent emergence and spread of some amantadine- and rimantadine-resistant strains, carrying a mutant M2 protein, WHO has recently discouraged the use of these drugs.

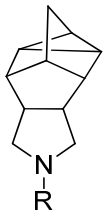
Two of the more common M2 protein mutants are the S31N mutant, with a smaller hydrophobic cavity, and the V27A mutant featuring a larger hydrophobic cavity. Our group has focused its research in the rational design of new polycyclic amines with the aim of developing new structures able to block the mutant M2 channels.[4] Herein we describe the synthesis and biological evaluation of a new family of polycyclic amines that displayed potent inhibition of the wild-type M2 channel although they were inactive against the mutant M2 channels.



$R = NH_2$ **AMANTADINE**
$R = CH(CH_3)NH_2$ **RIMANTADINE**



n = 1, 2
R = alkyl, aryl, $CH(NH)NH_2$



R = H , $CH(NH)NH_2$

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Flash-122

Nuevos derivados de 1,1'-binaftaleno en el campo del reconocimiento quiral: enantiodiferenciación y síntesis enantioselectiva

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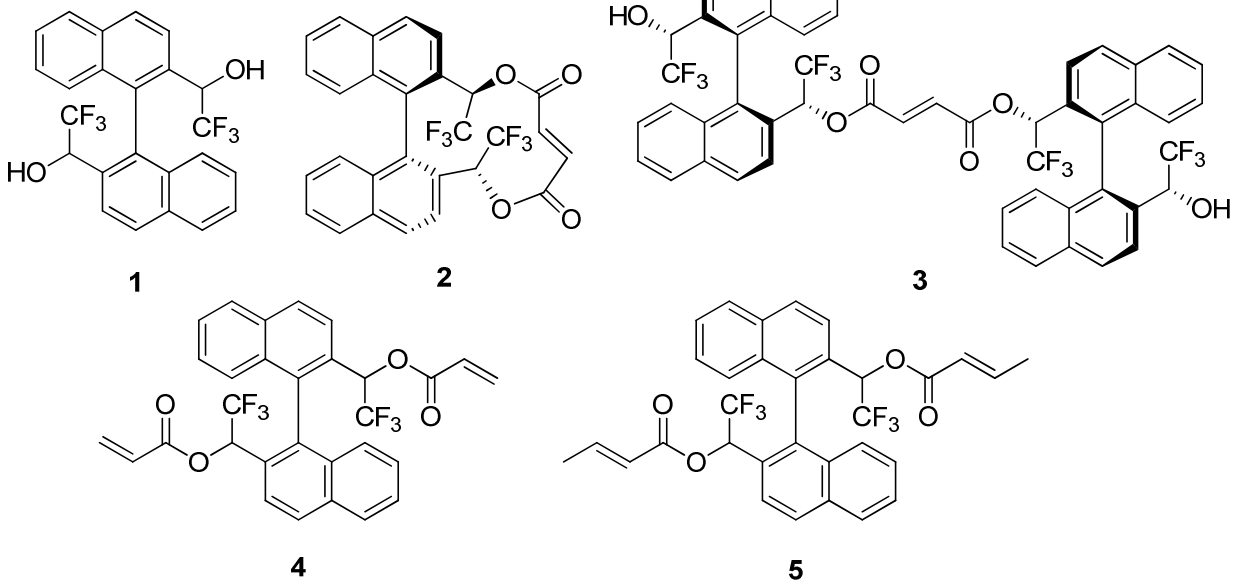
La línea principal de investigación de nuestro grupo se basa en la síntesis y el estudio de nuevos compuestos enantiopuros con una posible aplicación como agentes de solvatación quiral (CSA) y como auxiliares quirales.[1]

Actualmente, en nuestro grupo se está trabajando en la síntesis de compuestos derivados del binaftaleno sustituidos en las posiciones 2 y 2'. Esta estructura presenta, además de los centros quirales en las cadenas laterales, la característica de poseer un eje estereogénico.

De esta manera, se han sintetizado cinco estereoisómeros de 1,1'-(1,1'-binaftaleno-2,2'-diil)bis(2,2,2-trifluoroetanol), **1**, y se ha determinado la configuración absoluta de todos ellos mediante difracción de rayos X y CHPLC.

Se está estudiando el uso de estos nuevos auxiliares quirales en reacciones de Diels-Alder, reacción ya utilizada en nuestro grupo,[2] habiendo preparado como dienófilos los nuevos compuestos **2** y **3**. Además, se pretende estudiar las reacciones de fotocicloadición [2+2] intramoleculares usando los correspondientes acrilatos, **4**, y crotonatos, **5**, derivados de los dioles **1**.



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Flash-123

Design and Synthesis of a New Platform for Molecular Recognition of Organic Ammonium Ions

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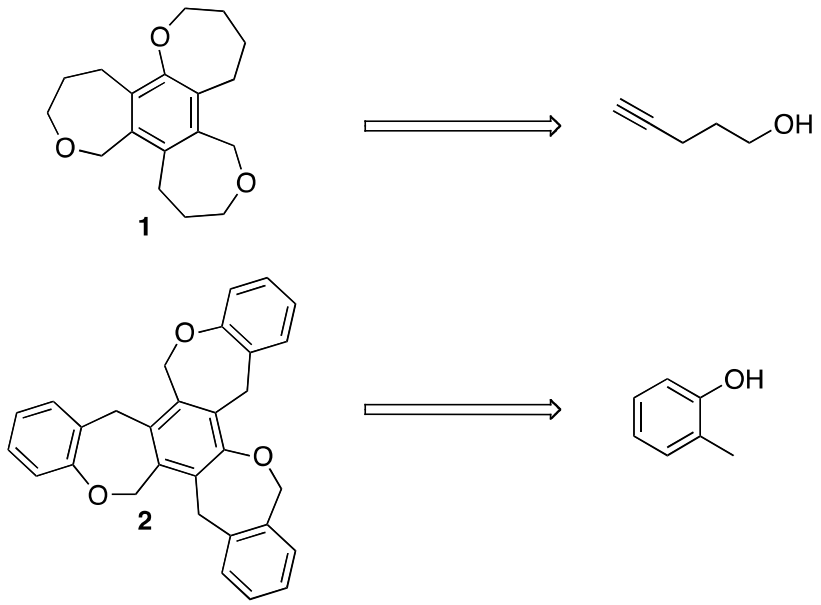
Many biological processes involve interactions between ammonium ions and protein receptors. Understanding the key elements in this process have inspired several groups to design artificial receptors to study and quantify the non-covalent forces present in this event. Important motifs for the recognition of ammonium ions are hydrogen bonds and cation–π interactions, and for this reason π-electron-rich cavities represent very suitable hosts. [1]

In the present work we designed and synthesized a new platform containing an aromatic ring fused to 3 oxepane rings (**1**). Based on this molecule we could synthesize, using similar synthetic strategy, a receptor having 4 aromatic rings and 3 oxepane rings (**2**) able to adopt a convenient geometry (bowl-shape) for the recognition of organic ammonium ions.

The preliminaries results in gas phase (MS-ESI) suggest that depending on the ammonium ion, a host-guest interaction is present at different stoichiometry (1:1 and/or 2:1, host-guest relation). Apart from the novelty of these structures, the synthetic route is a key feature in this work, which will allow us to generate new and more complex receptors in the future.



Acknowledgment: MICINN-FEDER (CTQ2011-22653) financially supported this research. FPC thank to CSIC for a JAE-Doc contract.

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Flash-124

Hydroazulenones by Tandem Enyneacetal-Nazarov Brönsted-Acid Promoted Carbocyclizations

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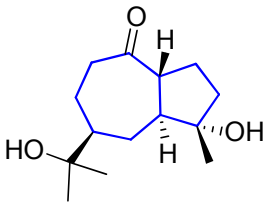
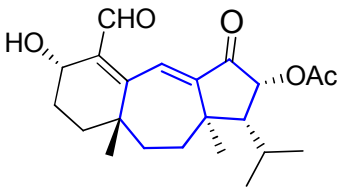
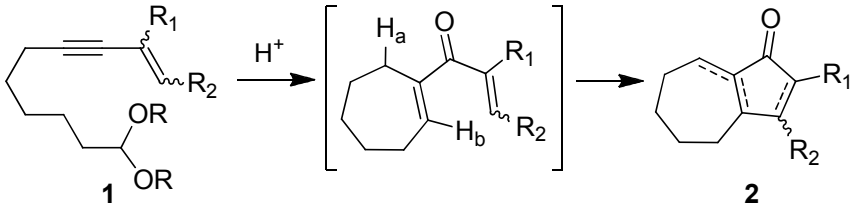
The presence of hydroazulen(on)e skeletons in many bioactive natural products, such as guanacastepene[1] or pleocarpenone,[2] has resulted in sustained interest in their syntheses. A wide variety of approaches have been described.[3] We now report the synthesis of hydroazulenones by tandem enyneacetal-Nazarov Brönsted-acid-promoted carbocyclizations.[4,5] This metal-free tandem reaction departs from simple enyneacetals **1** which are converted into bicyclo [5.3.0] decanes **2** (hydroazulenones) with good to excellent yields.



Pleocarpenone



Guanacastepene



55-90 %

Acknowledgements: we thank the MICINN (CTQ2011-28258), Consolider Ingenio 2010 (CSD2007-00006), Xunta de Galicia and FEDER (CN2011/054) for financial support. L.E. thanks XUGA for a predoctoral grant. C.G.R thanks MICINN for a Juan de la Cierva research contract.

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Flash-125

Highly Stereoselective Cyclocondensation Reactions. Enantioselective Synthesis of Substituted *cis*-Decahydroquinolines

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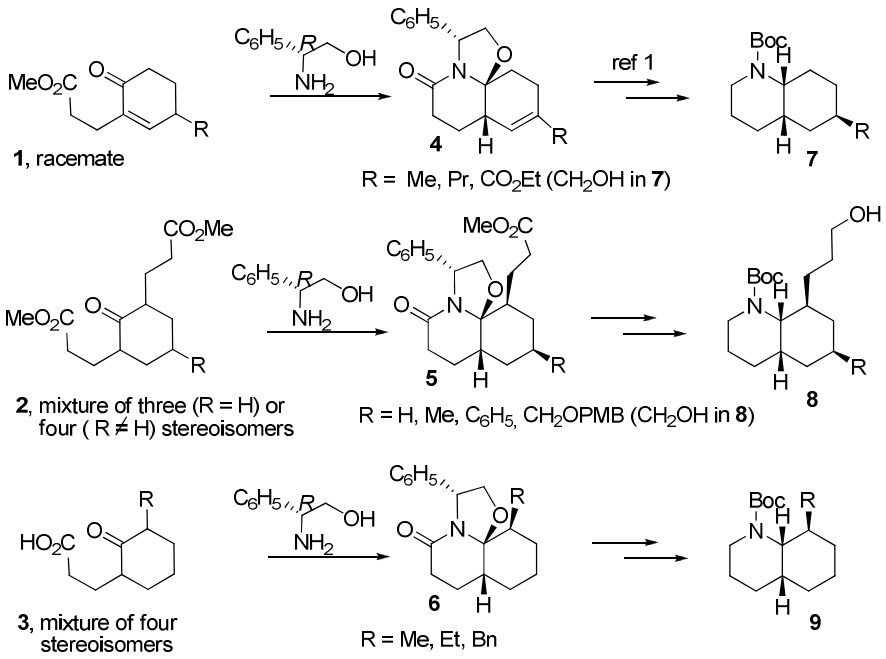
Cyclocondensation reactions of (*R*)-phenylglycinol with 2-oxocyclohexanepropionate derivatives **1**-**3** (racemates or mixtures of steroisomers) stereoselectively lead to enantiopure tricyclic lactams **4**-**6** in a process that involves the generation of up to four stereocenters in a single synthetic step via desymmetrization with differentiation of enantiotopic chains (from **2**) and/or dynamic kinetic resolution processes (from **2** and **3**). A rationale for the stereochemical outcome of these highly stereoselective transformations will be presented.



Lactams **4**-**6** have proven to be useful precursors of a variety of diversely substituted enantiopure *cis*-decahydroquinolines **7**-**9**.

Acknowledgements: Financial support from the MICINN, Spain (project CTQ2009-07021/BQU), and the DURSI, Generalitat de Catalunya (grant 2009-SGR-1111).

[1]Preliminary communication: Amat, M; Navío, L.; Llor, N.; Molins, E.; Bosch, J. *Org. Lett.* **2012**, *14*, 210−213.

Flash-126

Reacción de Mannich *anti*-selectiva de aldehídos con iminas desactivadas vía enamina. Aproximación a popargilaminas funcionalizadas.

Enrique Gómez-Bengoa, Jacqueline Jiménez, Irati Lapuerta, Miguel Maestro, Antonia Mielgo, Mikel Oiarbide, Itziar Otazo, Irene Velilla, Silvia Vera y Claudio Palomo
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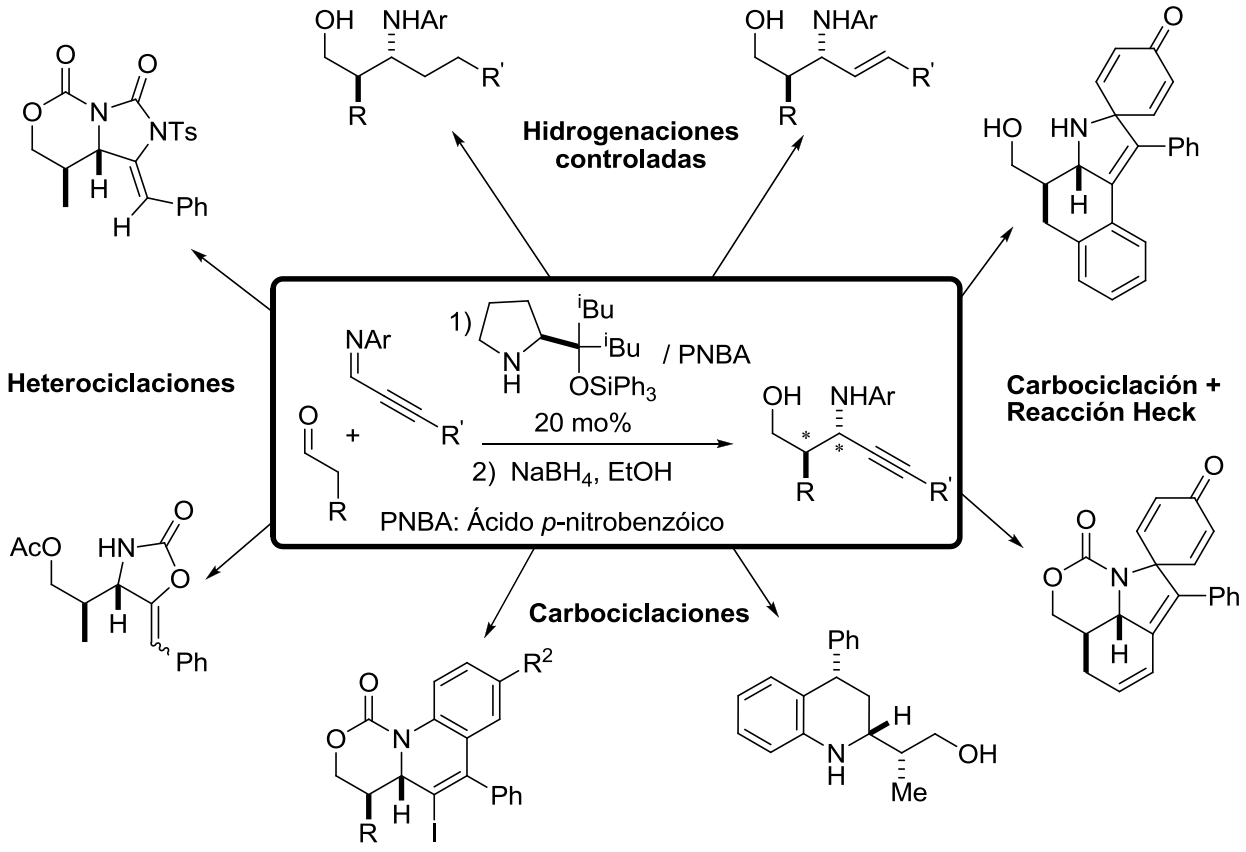
En este trabajo se presenta una nueva metodología para la obtención de propargilaminas mediante una reacción de Mannich *anti*-selectiva, catalizada por éteres de dialquilprolinol en combinación con un ácido de Brønsted externo. El proceso permite sintetizar aductos con dos centros estereogénicos contiguos y una alta funcionalidad con rendimientos en torno al 70-75%, relaciones *anti:sin* > 90:10 y enantioselectividades superiores al 95 %. También se describen distintas aplicaciones de los aductos resultantes en la obtención de compuestos nitrogenados más complejos tales como (poli)heterociclos, imidazolidinonas, oxazolidinonas, dihidro- y tetrahidro-quinolinas, y compuestos espiro tetracíclicos.



Flash-127

A PRACTICAL CONVERGENT SYNTHESIS OF 1α,25-DIHYDROXY-20-EPI-VITAMIN D_3

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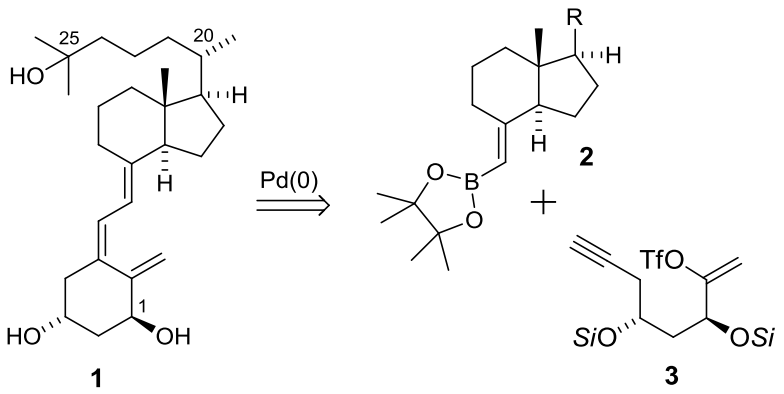
During the past few years, a new class of analogues of the hormone 1,25-dihydroxyvitamin D_3 characterized by a C20-epi-methyl group in the side chain has been identified as potent inhibitors of cell proliferation and inducers of cell differentiation. Among these analogues 1α,25-dihydroxy-20-epi-vitamin D_3 (**1**), also known as MC1288, is several orders of magnitude more potent than the natural hormone in inhibiting cell growth and inducing cell differentiation.

We describe here an efficient convergent of **1** synthesis using as the key step the Pd(0)-catalyzed coupling between the boronate ester **2** (CD-rings, side chain) and the enol triflate **3** (precursor of the A-ring). *Si* = Protecting group.



ACKNOWLEDGEMENTS: Financial support from the Spanish MEI (SAF2010-15291). B.L. thanks the Spanish MEI for a FPU fellowship.

Flash-128

Desarrollo de una Biblioteca de Productos Procedentes de la Síntesis Orgánica en la Búsqueda de Nuevos Fármacos

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En un proyecto de investigación encaminado a la búsqueda de nuevas moléculas bioactivas, se hace necesaria la evaluación de la actividad biológica de cada nuevo compuesto "en tiempo real". De este modo, este dato permite un desarrollo rápido y directo de nuevos análogos para posteriores estudios de Relación Estructura-Actividad (SAR). Cuando los productos analizados proceden de la síntesis orgánica se hace completamente necesario la clasificación y sistematización en una base de datos de tal manera que puedan obtenerse conclusiones rápidas acerca de las aproximaciones seguidas.

En nuestro grupo hemos procedido a la elaboración de una base de datos de los compuestos generados en diferentes proyectos de investigación asociados a la actividad biológica en diferentes frentes. Para la elaboración de dicha QUIMIOTECA se recopilan muestras de los compuestos en unas cantidades mínimas y, una vez verificada su pureza, se conservan en condiciones adecuadas de almacenaje. Al mismo tiempo, se incluyen datos tales como estructura, peso molecular, fórmula molecular, nombre sistemático, cantidad de muestra, datos espectroscópicos y procedimiento de síntesis organizándose mediante el uso del programa informático ChemFinder.

Actualmente, más de 300 moléculas han entrado a formar parte de nuestra Quimioteca, conformada tanto por derivados activos con estructuras simplificadas (síntesis orientada a un objetivo), como por cabezas de serie biológicos de baja masa molecular (síntesis orientada a la diversidad), productos naturales sintetizados y productos de partida no comerciales e intermedios avanzados de síntesis. En torno a 170 miembros de la Quimioteca han sido elegidos para ser evaluados biológicamente por el grupo BioLab. También se han establecido colaboraciones con otros grupos de investigación y compañías farmacéuticas con objeto de ampliar el número de datos biológicos disponibles.

Como beneficio añadido, la Quimioteca permite disponer de aquellas muestras de las que se tiene mayor cantidad para que sean empleadas como sustratos para los procesos de síntesis o para ensayos de reactividad, ahorrando con ello la necesidad de fabricarlos. Además, ofrece un escaparate del tipo de moléculas que se sintetizan en nuestro laboratorio, lo que abre la oportunidad de realizar síntesis bajo demanda.

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