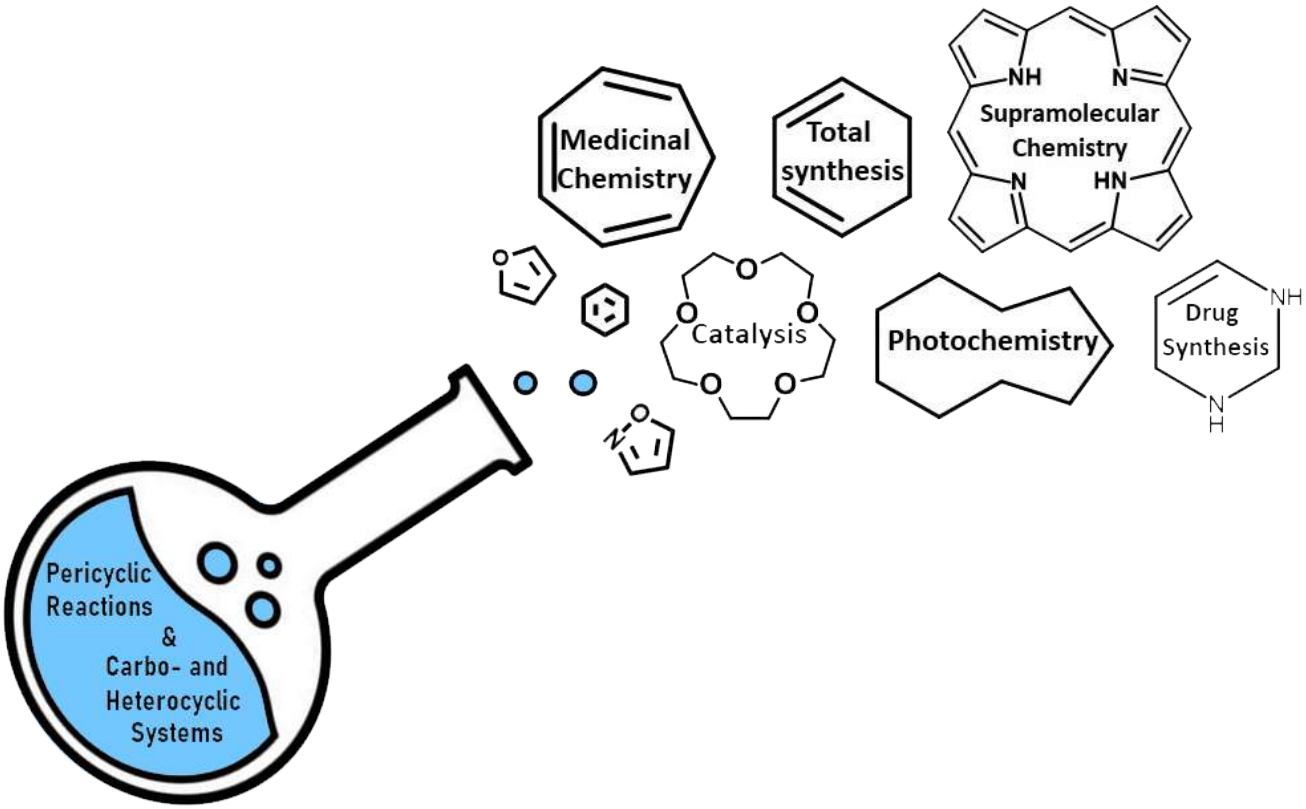
C.I.R.P

Centro interuniversitario di ricerca sulle reazioni pericicliche e sintesi di sistemi etero e carbociclici

November 24-25, 2020

1st Virtual Symposium on Pericyclic Reactions and Synthesis of Carbo- and Heterocyclic Systems

Book of Abstract



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Proceedings of the

1st Virtual Symposium on Pericyclic Reactions and Synthesis of Carbo- and Heterocyclic Systems

Edited by:

Francesca Foschi and Valentina Pirovano

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Welcome

The "*Interuniversity Centre on Pericyclic Reactions and Synthesis of Hetero- and carbocyclic Systems* (CIRP)" is a national group, supported by the Italian Chemical Society. For nearly 20 years, CIRP has connected over 10 Universities working in the area of pericyclic reactions. During the years, the focus of the group has been extended besides pericyclic reactions including nowadays various aspects of synthetic organic chemistry directed towards the synthesis of carbo and – especially - heterocyclic compounds.

On this basis, the "young section" of CIRP organised the "*1st Virtual Symposium on Pericyclic Reactions and Synthesis of Carbo- and Heterocyclic Systems*" to share research results of young researchers (Ph.D. students and PostDocs) working in different area of organic chemistry, ranging from catalysis, applied organic synthesis and supramolecular chemistry, and allowing them to gain insights to each other's research works. In this way, we aim to reinforce connections between young scientists favouring exchange of ideas, supporting national and international collaborations and connections.

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IS1 - Photoinduced Assembly of C–N and C–C Bonds

Daniele Leonori[a]

[a] *Department of Chemistry, University of Manchester, Manchester M13 9PL, UK*
daniele.leonori@manchester.ac.uk

Photoinduced Assembly of C–N Bonds. The first part of the presentation will illustrate the work my group has carried exploring the reactivity of nitrogen radicals for the assembly of C–N bonds. This includes C–H amination of aromatics,[1] olefin diamination[2] and dehydrogenative aniline synthesis.[3] This will include a discussion of the key mechanistic aspects related to the reactivity of nitrogen radicals as well as their synthetic implications.

Photoinduced Assembly of C–C Bonds. The second part of the talk will discuss the development of an alternative strategy for C-radical formation from alkyl and aryl halides.[4] This will illustrate the unique ability of α-aminoalkyl radicals to undergo halogen-transfer reactions and how this can be used in synthetic chemistry.

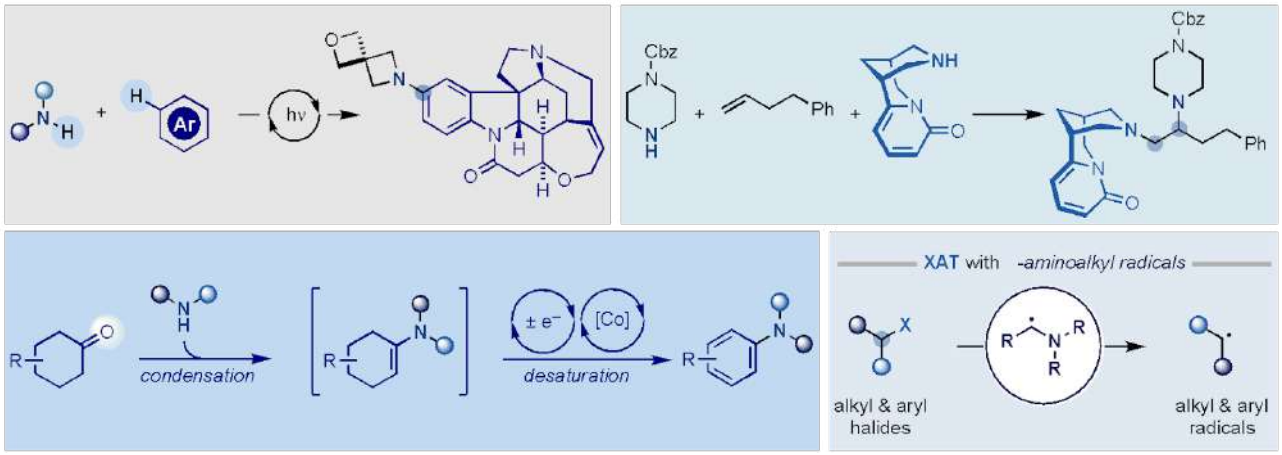

Figure 1.

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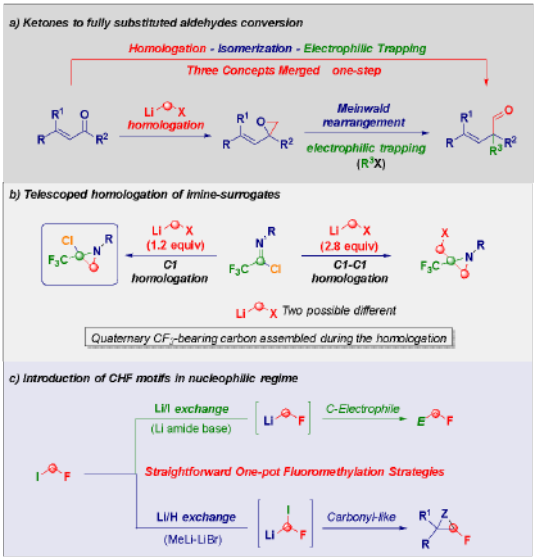
[4] D. Leonori *at al. Science*, **2020**, 367, 1021 – 1026.

IS2 - Designing New Synthetic Concepts for Imparting Molecular Complexity with C-1 Sources

Vittorio Pace[a, b]

[a] *University of Torino, Department of Chemistry, Via P. Giuria 7, 10125 Torino, Italy*
[b] *University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse 14, 1090 Vienna, Austria*
e-mail:vittorio.pace@unito.it ; web: https://drugsynthesis.univie.ac.at/, Twitter: @LabPace

The direct transfer of a reactive nucleophilic CH_2X unit into an existing linkage enables the formal introduction of the moiety with the precisely defined degree of functionalization.[1] Upon the fine tuning of the reaction conditions governing the transformation, the initial homologation event can serve as the manifold for triggering unusual rearrangement sequences leading to complex architectures through a unique synthetic operation. The direct – full chemoselective - conversion of a ketone into the homologated all-carbon quaternary aldehyde (*via* a)[2] and, the telescoped homologation of imine-surrogates to quaternary aziridines (*via* b)[3] will illustrate these unprecedented concepts. Additionally, the one-step mono-fluoromethylation of carbon electrophiles with extremely labile fluoromethyllithium reagents will provide a novel entry to valuable fluorinated building-blocks without the needing of using protecting elements for fluoro-containing carbanions (*via* c).[4] Moreover, novel strategies for introducing the difluoromethyl group through the proper activation of the commercially available $TMSCHF_2$ with an alkoxide will be discussed.[5]



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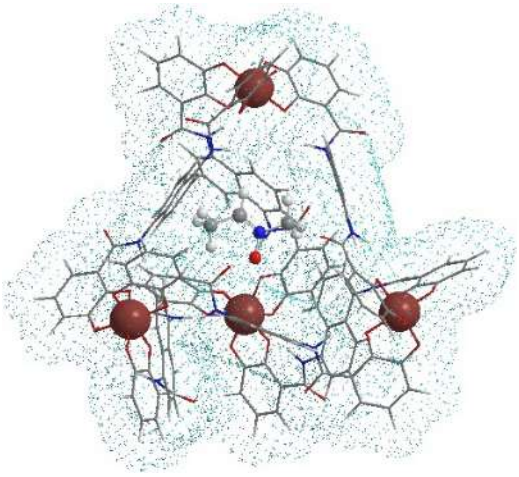
[4] a) G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace, R. Luisi, *J. Am. Chem. Soc.* **2017**, *139*, 13648-13651; b) S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi, V. Pace, *Org. Lett.* **2019**, *21*, 584-588.
[5] a) M. Miele, R. D'Orsi, V. Sridharan, W. Holzer, V. Pace, *Chem. Commun.* **2019**, *55*, 12960-12963; b) M. Miele, A. Citarella, N. Micale, W. Holzer, V. Pace, *Org. Lett.* **2019**, *21*, 8261-8265.

OC1 - One-Pot Nanoconfined Synthesis of Isoxazolidines in Water

Vincenzo Patamia,[a] Davide Gentile,[a] Giuseppe Floresta,[a] Antonio Rescifina[a]

[a]*Department of Drug Sciences, University of Catania, V.le A. Doria 6, 95125 Catania, Italy*
vincenzo.patamia@unict.it

Naturally occurring supramolecular systems can promote reactions with remarkable speed, substrate specificity, and product selectivity. A supramolecular chemist, inspired by nature, can develop supramolecular catalysts for increasingly complex organic transformations. This communication will report the application of an assembled supramolecular tetrahedral capsule (Figure), in the presence of gallium(III), starting from 2,3-dihydroxybenzoic acid,[1] as an effective catalyst in the synthesis of nitrones and isoxazolidines in water.[2] The inclusion of reagents and products in the supramolecular catalyst was investigated by NMR spectroscopy experiments and molecular modeling calculations.



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OC2 - New approaches for the cyclization of amino allenes

C. Loro,[a] R. Sala,[a] F. Foschi,[a] G. Broggini[a]

[a]*Dipartimento di Scienza e Alta Tecnologia, Università degli Studi dell'Insubria, 22100, Como, Italy*
cloro@uninsubria.it

Allenes are a class of substrate particularly attractive for different kind of process due to their high reactivity arising from the presence of two cumulated carbon-carbon bonds. Thus, this structural feature makes the allenes versatile precursors in the synthesis of highly substituted molecules.[1]

The multifaceted reactivity of allenes is observed in intra and intermolecular procedures with or without catalyst.[2] In the case of cyclization reactions, the presence of a transition metal catalyst or a hypervalent iodine reagent allows to obtain different complex structures; in particular, compounds which contain an amino group afford heterocyclic rings.[3] Since aminoiodination reactions are a successful synthetic way to obtain iodomethyl substituted heterocyclic rings, we investigated aminocyclization reactions of allenes with different type of iodine source. The change of solvent such as ethanol instead of acetonitrile gave also aminoalkoxylation products.

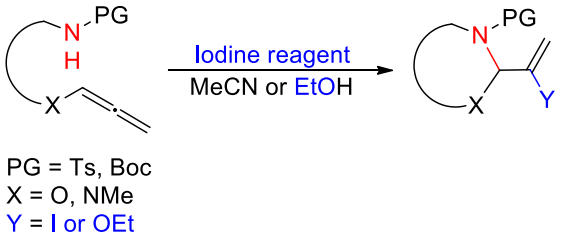

Figure 1: Aminoiodination and aminoalkoxylation reactions of allenes.

Following the interest of our research group toward transition metal-catalysed reactions,[4] we reported also a new AgOTf promoted procedure with *N*-Boc amino allenes as a fruitful way to access to heterocyclic rings bearing an acrolein moiety. A crucial role is given by the triflate as counterion, which determines the key intermediate of the reaction.

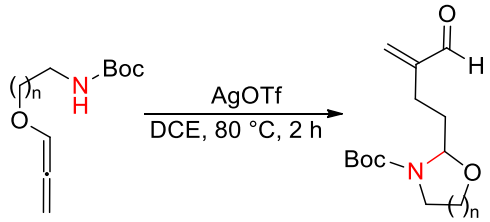

Figure 2: Silver-catalyzed cyclization.

References:

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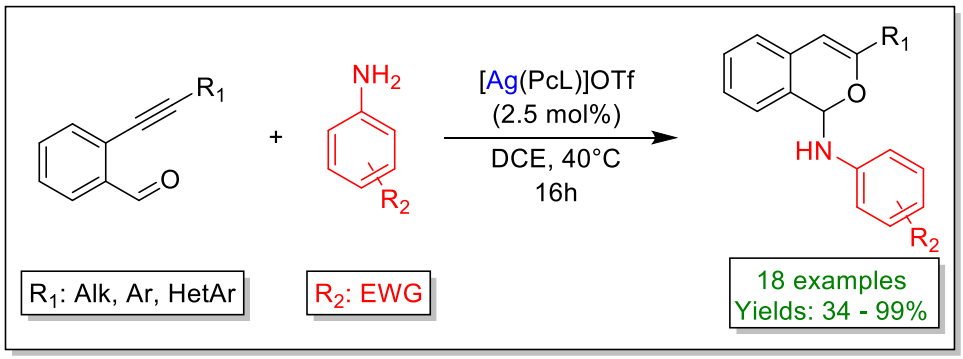
OC3 - Synthesis of 1-Aminoisochromenes trough reaction of 2-alkynylbenzaldehydes with electron-poor anilines promoted by [Ag(PcL)] catalyst

D. Garanzini,[a] E. Brambilla,[a] V. Pirovano,[a] E. Rossi,[a] G. Abbiati[a]

[a] *Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via Venezian, 21 – 20133 Milano – Italy*
davide.garanzini@unimi.it

Isochromene is an interesting oxygen-containing heterocycle characterizing different synthetic bioactive molecules[1] and natural products.[2] The isochromene core can be synthetized exploiting a regioselective *6-endo-dig* domino approach starting from 2-alkynylbenzaldehydes and suitable nucleophiles, under transition metal catalysis, able to activate the triple bond.[3] Most employed nucleophiles are oxygen- and carbon-based compounds, otherwise nitrogen-containing nucleophiles usually bring to the formation of isoquinoline derivatives, trough the formation of the corresponding imine intermediate. Herein we report the first synthesis of 1-amino substituted isochromene derivatives starting from different 2-alkynylbenzaldehydes exploiting the features of electron-poor anilines and PcL silver complex catalysis.[4]



Scheme 1: Synthesis of 1-aminoisochromenes

A series of 1-arylaminoisochromene was prepared, differently substituted in 3 position with alkyl, cycloalkyl, aryl or heteroaryl moiety (**Scheme 1**).

Reaction conditions, scope and limitation of the approach and a plausible mechanism of the reaction will be presented and discussed.

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[1] W. Wang, T. Li, R. Milbum, J. Yates, E. Hinnant, M. J. Luzzio, S. A. Noble, G. Attardo, *Bioorg. Med. Chem. Lett.* **1998**, 8, 1579–1584.
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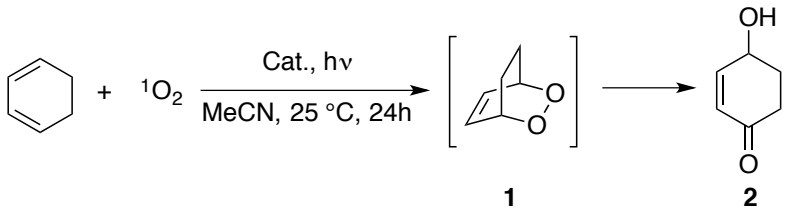
OC4 - g-C_3N_4/Perovskite Composites as Photocatalysts for Singlet Oxygen Generation

M. Corti,[a] R.Chiara,[a] L. Romani,[a] B. Mannucci,[a] L. Malavasi,[a] P. Quadrelli.[a]

[a] *Dipartimento di Chimica, Università degli Studi di Pavia, Viale Taramelli 12, 27100 − Pavia, Italy*
[b] *Centro Grandi Strumenti, Università degli Studi di Pavia, Via Bassi 21, 27100 − Pavia, Italy*
marco.corti03@universitadipavia.it

Singlet Oxygen ($^1O_2$) is a highly reactive and short-lived oxygen species and could sustain a variety of reactions such as the hetero Diels-Alder (HDA) [4+2] cycloadditions, the [2+2] cycloadditions, the ene reactions, and epoxidations. We recently approach this topic by proposing the catalytic use of oxidized graphitic carbon nitride (g-C3N4) for 1O2 generation under photochemical conditions.[1] In the present study, g-C3N4/Perovskite composites were prepared by following established methodologies[2] and used as photocatalysts for the in situ $^1O_2$ generation to perform HDA, ene and oxidation reactions with suitable dienes and alkenes. To optimize the reaction conditions, HDA cycloaddition reaction with 1,3-cyclohexadiene and cyclopentadiene were used as benchmark reactions.



Scheme 1: HDA cycloaddition reaction of 1,3-cyclohexadiene and $^1O_2$ used as benchmark reaction to test the efficiency of all the catalysts.

Moreover, the investigations were conducted on a variety of alkenes, acyclic and cyclic, ranging from the highly C=C double bond substituted to a monosubstituted. The studies were also performed on some aromatic alkenes. Some limitations were observed, especially in the case of the alkene oxidations, as well as poor chemoselectivity was somewhere observed in this work that is the first application of MHP-based composites for in situ $^1O_2$ generation. The experimental protocol can be used as a platform to further expand the knowledge and applicability of MHPs to organic reactions, since perovskites offer a rich variety of tuning strategies which may be explored to improve reaction yields and selectivities.

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[1] P.R. Ogilby, Chem. Soc. Rev. **2010**, *39*, 3181-3209.
[2] I. Camussi, B. Mannucci, A. Speltini, A. Profumo, C. Milanese, L. Malavasi, P. Quadrelli, *ACS Sustainable Chemistry & Engineering* **2019**, *7*, 8176-8182.
[3] L. Romani, A. Bala, V. Kumar, A. Speltini, A. Milella, F. Fracassi, A. Listorti, A. Profumo, L. Malavasi, *Journal of Materials Chemistry C* **2020**, 9189-9194.

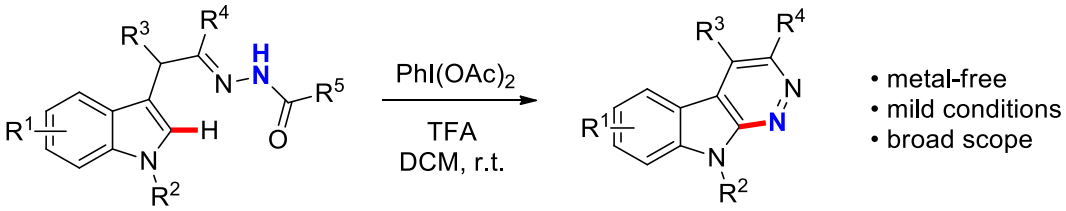
OC5 - Transition Metal-Free Synthesis of Indole-fused Pyridazines through PhI(OAc)$_2$-Mediated Oxidative C(sp^2)−N Bond Formation

M. Corrieri,[a] L. De Crescentini,[a] G. Favi,[a] F. Mantellini,[a] G. Mari, S. Santeusanio[a]

[a]*Department of Biomolecular Sciences, Section of Chemistry and Pharmaceutical Technologies, University of Urbino "Carlo Bo", Via I Maggetti 24, 61029 Urbino, Italy*
m.corrieri@campus.uniurb.it

Within the context of heterocyclic compounds synthesis, the development of methods aimed to form new carbon-heteroatom bonds is of fundamental interest. The transition metal (TM)-catalyzed coupling reactions involving heteroatoms,[1] especially nitrogen, are well established in organic chemistry. However, despite their numerous useful applications and interesting reactivities, TMs are associated with drawbacks such as toxicity, sensitivity to atmospheric oxygen and moisture, high costs and harsh reaction conditions. In recent years, the use of hypervalent iodine reagents (HIRs)[2] as alternative metal-free promoters for C(sp$_2$)−N oxidative coupling reactions have received much attention owing to their low toxicity, low prices and bench stability. Cognizant of these advantages and in conjunction with our recent research on the synthesis of N-fused heterocycles, we herein present an unprecedented synthesis of highly functionalized indole-fused pyridazines from easily prepared[3] α-indolylhydrazone derivatives. This method involves oxidative conditions using a combination of phenyliodine (III) diacetate (PIDA) and trifluoroacetic acid (TFA) (Scheme 1). The procedure allows for an intramolecular coupling between the unfunctionalized indole C$_2$-H and the N-H donor of the hydrazone moiety.

This presentation will cover the details of this procedure, the scope, the limitations and the mechanistic insights.



Scheme 1

References:

[1] Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301.

[2] T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656–3665.

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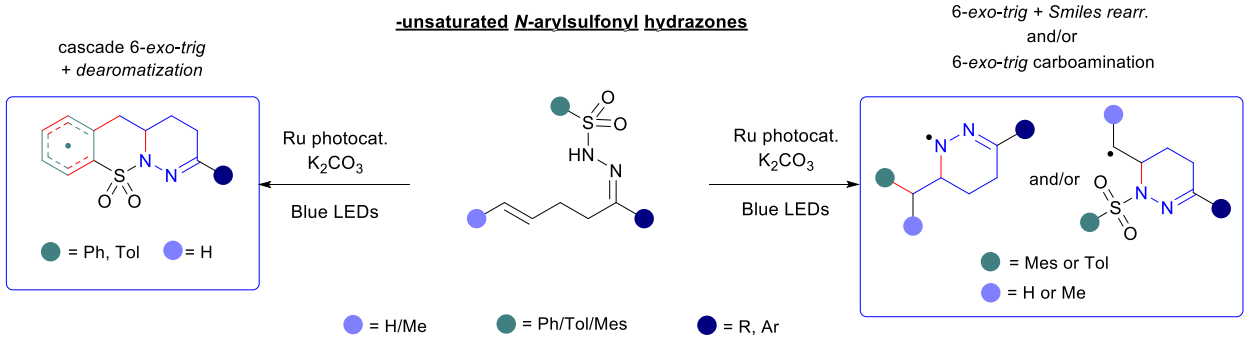
OC6 - Visible Light Mediated Photocatalytic N-radical cascade Reactivity of γ,δ-unsaturated N-Arylsulfonylhydrazones: A General Approach to Structurally Diverse Tetrahydropyridazines

E. Azzi[a], G. Ghigo[a], S. Parisotto[a], F. Pellegrino[a], E. Priola[a], P. Renzi[a] and A. Deagostino[a]

[a]*Department of Chemistry, Università di Torino, via P. Giuria 7, 10125 Turin, Italy*
emanuele.azzi@unito.it

Tetrahydropyridazines (hydrogenated derivatives of pyridazines) are considered as privileged structures in medicine[1]. Since Xiao[2] reported an efficient synthesis of dihydropyrazoles and tetrahydropyridazines under photocatalytic conditions from β,γ-unsaturated *N*-tosylhydrazones, the visible light induced approaches to these scaffolds have gained remarkable interest over thermal alternatives. In 2017[3] our group investigated the reactivity of α,β-unsaturated *N*-tosylhydrazones and observed the photoinduced generation of a vinyl radical intermediate affording biologically active allyl sulfones upon migration of the tosyl moiety. In order to join the interest of our group in the synthesis of potential drugs and in visible light promoted processes we further moved to the study of γ,δ-unsaturated *N*-arylsulfonylhydrazones reactivity. Indeed, we envisaged that the further shift of unsaturation to the γ,δ position might afford an alternative route to several functionalized tetrahydropyridazines.

Herein, we report a catalytic protocol to generate three main classes of different tetrahydropyridazines simply changing the structural features of the starting hydrazones (Scheme 1). These reactions occur at room temperature under blue light irradiation and are catalysed by the combination of a Ru(II) photocatalyst and potassium carbonate, giving rise to three reactive pathways from the same N-hydrazonyl radical. For instance, a photoinduced dearomatization process, in alternative to a radical Smiles rearrangement and a carboamination process are described.



Scheme 1: Photoinduced reactivity of unsaturated γ,δ-unsaturated *N*-arylsulfonylhydrazones.

References:

[1] C. G. Wermuth, *MedChemComm*, **2011**, 2, 935-941
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OC7 - Intramolecular coupling of two C(sp^3)–H bond for the synthesis of C(sp^3)–C(sp^3) bond using 1,4-Pd shift strategy

Ioannis Anastasiou[a], Ronan Rocaboy[b], Olivier Baudoin[b], Luigi Vaccaro [a]

[a]*Laboratory of Green Synthetic Organic Chemistry, Dipartimento di Chimica, Biologia e Biotecnologie, di Perugia, Via Elce di Sotto 8, 06123 Perugia, Italy*
[b]*University of Basel, Department of Chemistry St. Johanns-Ring 19, CH-4056 Basel (Switzerland).*
ioannis.anastasiou@studenti.unipg.it

The development of catalytic carbon-carbon or carbon-heteroatom bond formations at nonacidic C(sp^3)–H bonds is still a challenge in organic chemistry, due to the absence of π-electrons capable of providing a favourable reactant-catalyst interaction, present instead in the C(sp^2)–H activation processes.[1,2] By using the 1,4-Pd shift strategy we have successfully achieved the intramolecular coupling of two C(sp^3)–H bonds adjacent to an oxygen or nitrogen atom on one side and a benzylic or adjacent to a carbonyl group on the other side. A variety of fused heterocycles was obtained from easily accessible ortho-bromo phenol and aniline precursors.

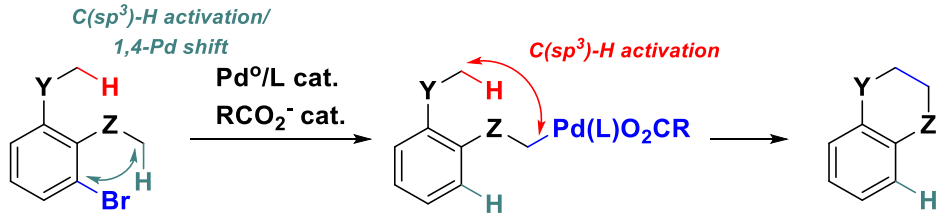


Figure 1: Reaction design.

References:

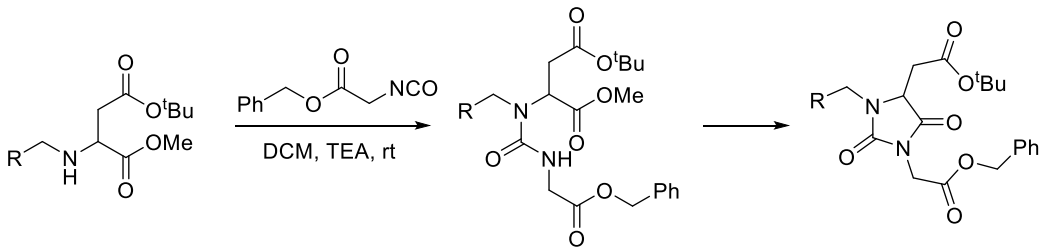
[1] S. A. Girard, T. Knauber, C.-J. Li. *Angew. Chem. Int. Ed*., **2014,** 53, 74.
[2] C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei. *Chem. Rev*., **2015**, 115, 12138.

OC8 - Synthesis and Biological Evaluation of Novel Hydantoin-based Peptidomimetics

A.M.Caramiello[a], Prof. Dr. A.Sacchetti[a], Prof. Dr. A.Volonterio[a]

[a]*Department of Chemistry, Materials and Chemical Engineering "G.Natta" – Politecnico di Milano, Via Mancinelli 7, 20131 Milano (MI)*
alessiomaria.caramiello@polimi.it

Peptidomimetic compounds have almost overcome peptide and peptide-derived drugs because they offer better transport properties, resistance to enzymatic cleavage/degradation and even to immune response. These molecules are very attractive in the realm of targeted therapy. One of the most attractive strategies consists in the modulation of the hot-spot (a contact region between two proteins) where key protein-protein interactions (PPIs) occur. Among many different molecules, we knew that we needed an easily accessible β-turn mimetic scaffold able to target PPIs in the hot-spot region and that this scaffold should offer virtually unlimited screening possibilities due to its ease of modification. We then demonstrated[1] that the chemical structure needed to achieve the previously mentioned benefits was a molecule containing an hydantoin core. This scaffold showed to be very important since it can be properly functionalized, allowing the molecule to adapt to a wide range of kinetically and thermodynamically accessible conformations, that can subsequently mimic selected secondary protein structures. The target of our study is Insulin Degrading Enzyme (IDE), involved in the degradation of insulin and other amyloidogenic substrates. By modulation of the action of this enzyme, it is possible to open new therapeutic strategies to treat many IDE-dependent pathologies (like diabetes and Alzheimer's disease)[2,3]. The synthetic sequence for our hydantoins implies the formation of an isocyanate that will react with an amine to form a urea. This urea is the key intermediate for the preparation of the hydantoin core, since it is involved in an intramolecular cyclization in basic conditions. The key step for its preparation is reported in Scheme 1. We synthesized different derivatives after having optimized this cyclization, and we are going to perform biological assays to study their activity. We plan to enrichen our research with studies on docking poses, XRPD experiments and NMR studies.



Scheme 1: Key step for the formation of the hydantoin core

References:
[1] M.C. Bellucci, *et. al.*, *Org. & Biomol. Chem.*, **2018**, 16 (4), 521-525.
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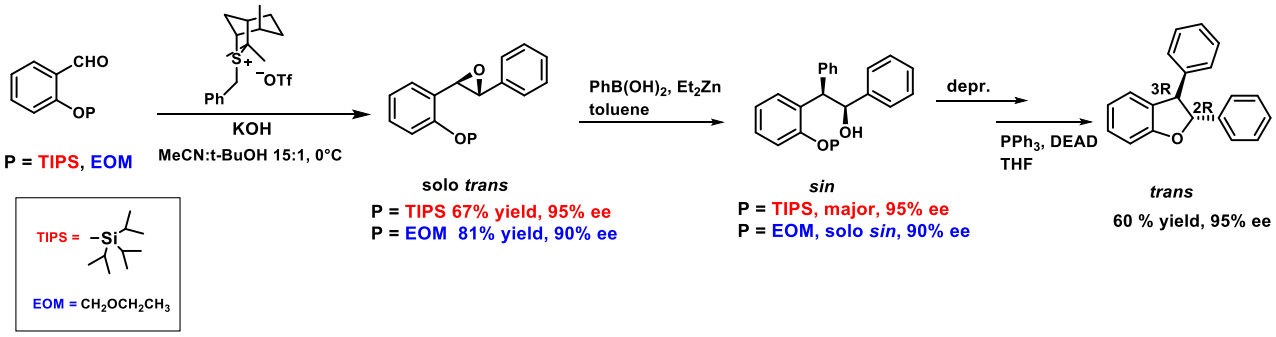
OC9 - From diaryloxiranes to dihydrobenzofurans: a story of ring opening and cyclization

T. Laurita,[a] R. D'Orsi,[a] M. Funicello,[a] L. Chiummiento,[a] P. Lupattelli,[a]

[a]*Department of Science, University of Basilicata, via dell'Ateneo Lucano 10, Potenza*
tlaurita@unisa.it

The 2,3-dihydrobenzofuran ring-system constitutes the core skeleton of numerous biologically active compounds, as resveratrol oligomers[1]. Ortho oxo-substituted trans 2,3-diaryloxiranes, prepared taking advantage of the Corey-Chaykovsky reaction between the suitable o-substituted benzaldehyde and benzylidene sulfur ylide[2], proved suitable starting materials for the first stereoselective access to trans 2,3-diphenyl-2,3-dihydrobenzofuran (**Scheme 1**). The epoxides were regio- and stereoselectively opened by phenyl zinc reagent, which was obtained in situ from phenylboronic acid via a facile B-Zn exchange. Deprotection reactions of orto-oxo substituted affording the corresponding hydroxyphenols and the last Mitsunobu type cyclization with Ph_3P/DEAD afforded in high yield trans 2,3-diphenyl-2,3-dihydrobenzofuran. The use of enantioenriched starting diaryloxiranes resulted in no loss of stereochemical integrity in the final trans 2,3-dihydrobenzofuran, which was characterized for the first time in enantioenriched form[3].



Scheme 1: Synthesis of *trans*-(2*R*,3*R*)-2,3-diphenyl-2,3-dihydrobenzofuran

The reaction proved to be quite general using different aryl boronic acids as nucleophilic source and polysubstituted *trans* 2,3-diaryloxiranes as electrophilic acceptors. In particular, different *syn* aryl alcohols[4] were prepared in good yields. The preparation of functionalized *trans* 2-aryl-3-phenyl-2,3-dihydrobenzofurans and their activities as anti-inflammatories will be discussed.

References:

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[4] The notation *syn* refers to the relative stereochemistry of the incoming phenyl nucleophile and the OH group

OC10 - Synthesis of non-natural 3-Arylmorpholino-β-amino Acid as a PPII Helix Inducer

Francesco Vaghi,[a] Raffaella Bucci [a] and M. Luisa Gelmi [a]

[a]*DISFARM-Sez. Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, 20133 Milano, Italy*
francesco.vaghi@unimi.it

Amino acids (AAs) are the building blocks for peptides and proteins and although they are very simple molecules, they are able to build structures with high complexity and variability. Peptides ability to assume specific conformations and to organize in three-dimensional folded structures is indeed driven by the encoded amino acid sequences.

Small molecules or non-natural AAs are commonly useful as inducers of a particular secondary structure in peptidomimetics[1] characterized by similar features of the natural peptide but with increased proteolytic stability. For this reason, peptidomimetics are attractive tools for different applications, mostly for biology and nanomedicine.[2] Despite the large number of β–AAs able to induce α-helix and β-turn secondary structures, their use for generating PPII helices, to the best of our knowledge, is absent in the literature. Moreover, PPII helix is one of the secondary structures in proteins that play an important role in various biological processes.[3] Its importance in biological systems emerged in recent years: from the transcription to the cell motility and from the bacterial and viral pathogenesis to amyloidogenic proteins. Being PPII not stabilized by conventional intramolecular interactions, it is extremely challenging to enforce a peptide segment to adopt a PPII conformation.[4] Recently, our research group synthesized a new non-natural β-amino acid, named 3-Ar-β-Morph (via a regio- and diastereoselective Pd- catalyzed C(sp_3)H-arylation) able to stabilize a PPII-like helix when it is inserted in model peptide foldamer. As confirmed by IR/NMR and computational studies, 3-Ar-β-Morph can be used to stabilize PPII in peptides (Figure 1).[5]

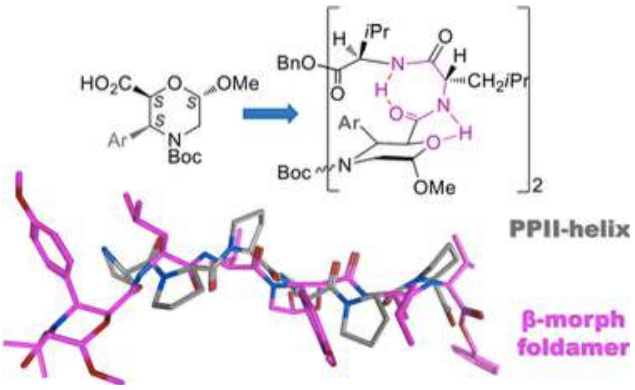

Figure 1: PPII-helix and β-morph foldamer overlapping

References:

[1] E. Lenci, et. al., *Chem. Soc. Rev* **2020**, *49*, 3262–3277.
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OC11 - Isoxazolidine/POSS based biocomposites for bone tissue engineering: synthesis, computational and biological studies

M. Fresta,[a] M. A. Chiacchio,[a] L. Legnani,[a] S. V. Giofré,[b] D. Iannazzo[c]

[a] *Dipartimento di Scienze del Farmaco, Università di Catania, Viale A. Doria 6, 95125, Catania, Italy.*
[b]*Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali, Università di Messina, Via S.S. Annunziata, 98168 Messina, Italy*
[c]*Dipartimento di Ingegneria, Università di Messina, Contrada Di Dio, 98166 Messina, Italy*
monica.fresta95@gmail.com

Biocomposites containing inorganic materials with inherent bioactive properties and cytocompatibility have attracted significant interest in tissue engineering, leading to the development of bone scaffolds to be used both as bone grafts and drug delivery systems.[1] Among the different investigated biopolymers, the natural polysaccharide, chitosan (CS), obtained from the deacetylation of chitin, due to its good biocompatibility, biodegradability, ease of chemical modifications and high affinity *in vivo* with macromolecules, represents an ideal organic material for the development of biopolymers based scaffold for organ and tissue regeneration.[2] POSS silica cages, due to their biocompatibility and physico-chemical properties, able to enhance the mechanical and rheological properties of biopolymers, have shown to be suitable for a wide range of composites for biomedical applications.[3] In order to improve the mechanical behavior and biological stability of chitosan based scaffolds, we exploited, in this study, the useful functionalization of cubic silsesquioxanes with $(RSiO_{3/2})_8$ formula in order to afford POSS substrates containing suitable functional groups able to form a covalent bond with the chitosan structure. The insertion of a reactive olefin moiety at the organic side chain (group R) of heptaisobutyl-POSS **2a** or **2b**, allowed the effective microwave assisted 1,3-dipolar cycloaddition reaction[4] with the *N*-methyl-*C*-alkoxycarbonyl nitrone **1**, affording the corresponding isoxazolidines **3a,b, 4a,b** and **5b**, containing an ethoxycarbonyl group at the C-3 position of heterocyclic nucleus (Figure 1).

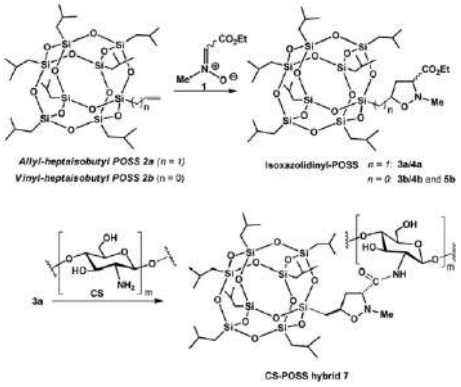

Figure 1. Functionalized isoxazolidine/POSS based biocomposites.

References:

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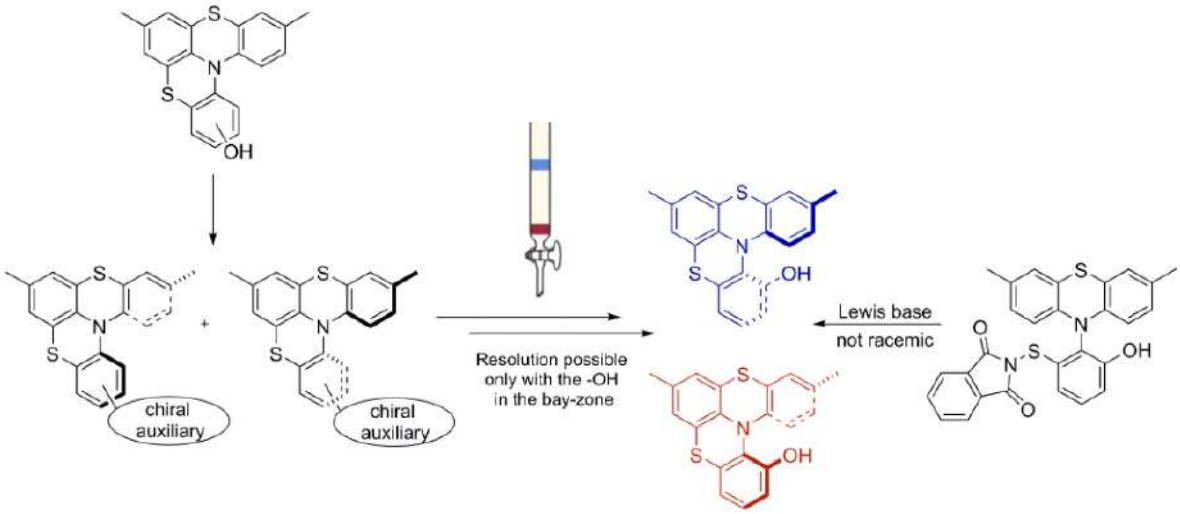
OC12 - Role of 'cape vs bay zone' introduction of chiral auxiliaries for the chemical resolution of thia bridged hetero[4]helicenes

M. Lupi,[a] S. Menichetti,[a] C. Viglianisi[a]

[a]*Department of Chemistry "Ugo Schiff", University of Florence, Via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy.*
michela.lupi@unifi.it

Thia-bridged triarylamine hetero[4]helicenes (TBTH-[4]H) are a peculiar class of red-ox active and geometrically stable [4]helicenes with high racemization barriers due to the long carbon-sulfur bonds, that cause a significant superimposition of the terminal aryl rings.[1-3] Indeed, racemization barriers are higher than those typically measured for carbo[5]helicenes allowing the resolution of these hetero[4]helicenes by HPLC using amylose-based chiral stationary phase columns.[1-3] In this communication we report how the optimization of the synthetic strategy[4] allowed the introduction of proper chiral auxiliaries in different positions of the helicene skeleton demonstrating the mandatory role of a bay-zone substitution since to achieve an efficient chemical resolution (Scheme 1). A preliminary approach to the enantioselective synthesis of TBTH-[4]H using enantiopure Lewis base catalysts as cyclization promoters will be presented as well.



Scheme 1

References:

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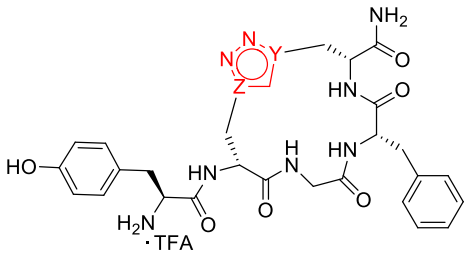
OC13 - On resin click chemistry mediated synthesis of novel enkephalin analogues with potent antinociceptive activity

M. P. Dimmito,[a] A. Stefanucci,[a] A. Della Valle,[a] A. Mollica[a]

[a]*University G. D'Annunzio, Via dei Vestini 31, Chieti*
marilisa.dimmito@unich.it

Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes (CuAAC) is a biorthogonal reaction, which leads to the formation of 1,4-disubstituted 1,2,3-triazoles;[1] this reaction has become popular in peptide chemistry, as 1,2,3-triazole has structural and electronic characteristics similar to those of the peptide bond.[2] The 1,2,3-triazole ring is stable to metabolic degradation and capable of hydrogen bonding with biomolecular targets.[3] DPDPE ((D-Pen^2, D-Pen^5)-Enkephalin) represents one of the most successful designed cyclic opioid peptides highly selective for δ-opioid receptor (DOP).[4] Even if DPDPE is widely used as radiolabelled standard for *in vitro* assays, it hasn't translated to therapeutic application due to a lack of activity when given peripherally, intrinsic metabolic instability and low blood brain barrier penetration.[5] In this work we reported the solid-phase peptide synthesis (SPPS) of two novel cyclic enkephalin analogues, namely NOVA1 and NOVA2 (Figure 1),[6] by on-resin CuAAC, with the aim to explore the biological profile of these two novel entities incorporating a triazole bridge. We found that NOVA2 showed good affinity and selectivity for the μ-opioid receptor, with Ki of 59.2 nM, EC_{50} of 12.9 nM and E_{Max} of 87.3% and a long lasting anti-nociceptive effect in mice in comparison to DPDPE. According with our findings, CuAAC is a promising approach for the development of novel therapeutics that could be used in the treatment of pain.



NOVA1: Y=N; Z=C
NOVA2: Y=C; Z=N

Figure 1: Structures of novel DPDPE analogues, NOVA1 and NOVA2.

References:

[1] Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007** 36, 1674–1689.
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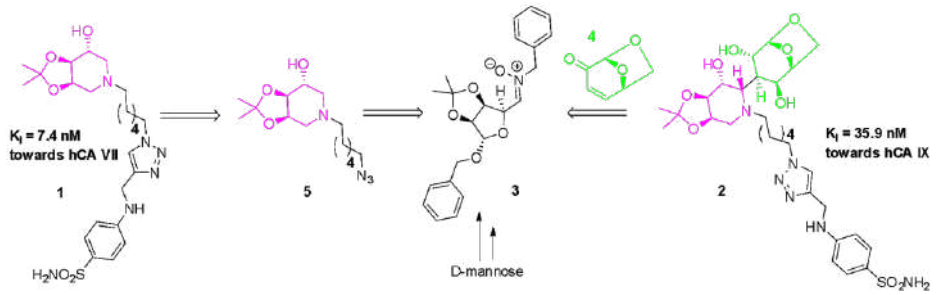
OC14 - Aza-glycomimetic based approach to selective carbonic anhydrase inhibitors

D. Pratesi,[a] C. Matassini,[a] A. Goti,[a] C. T. Supuran,[b] F. Cardona[a]

[a] *Dipartimento di Chimica 'Ugo Schiff', Università di Firenze, via della Lastruccia n. 3-13, Sesto Fiorentino (FI), Italy;*
[b] *Università degli Studi di Firenze, Dipartimento Neurofarba, Sezione di Scienze Farmaceutiche e Nutraceutiche, Via U. Schiff 6, 50019, Sesto Fiorentino, Florence, Italy.*
debora.pratesi@unifi.it

The human (h) expressed carbonic anhydrases (CAs, EC 4.2.1.1) play important roles both in physiological and pathological processes. Due to the large number of isoforms, the synthesis of selective inhibitors of human carbonic anhydrases (hCAs) is of paramount importance. One strategy to achieve this goal aimed to combine the sulfonamide group,[1] responsible for the interaction with the enzyme active site, with a sugar moiety (the so-called "sugar approach"[2]). Since glycomimetics are considered more selective than the parent sugars in inhibiting carbohydrate-processing enzymes, we explored the possibility of further tuning the selectivity of hCAs inhibitors by combining the sulfonamide moiety with a nitrogenated sugar analogue residue. We report the synthesis of two novel hCAs inhibitors **1** and **2** which feature the presence of a piperidine azasugar, originated by reductive amination of the carbohydrate-derived nitrone **3**. Compound **2** is connected to an additional carbohydrate moiety derived from levoglucosenone (**4**)[3]. Biological assays revealed that azasugar **1** is a very strong and selective inhibitor of the central nervous system abundantly expressed hCA VII (K_I = 7.4 nM) and showed a remarkable selectivity profile towards this isoform. Interestingly, the presence of levoglucosenone in glycomimetic **2** imparted an inhibitory activity towards the tumor associated hCA IX (K_I = 35.9 nM).



Scheme 1-Azasugar (purple) and levoglucosenone (green) fragments in hCAs novel inhibitors.

Exploiting this strategy, other potential CAs inhibitors have been synthesized by conjugating the piperidine scaffold **5** with the sulfonamide functionality through different functionalized linkers such as thioureido, ureido, amide and amino groups in order to evaluate their effect on the enzymatic inhibitory activity.

References:

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OC15 - Polarclean/water as a safe and recoverable medium for the selective C2-arylation of indoles catalyzed by Pd/C

Filippo Campana,[a] Beatrice Maria Massaccesi,[a] Stefano Santoro,[a] Oriana Piermatti,[a]* and Luigi Vaccaro[a]*

[a]*Laboratory of Green S.O.C. – Dipartimento di Chimica, biologia e Biotecnologie, Università degli Studi di Perugia, Via Elce di Sotto 8, 06123 – Perugia – I;*
filippo.campana91@gmail.com

The direct C−H bond functionalization is nowadays an attractive synthetic strategy both for academia and for industrial scale processes, allowing the obtainment of eco-friendly and economically attractive organic syntheses.[1] Notably, the C−2 selective arylation of indoles has gained special attention giving access to a large class of functionalized heterocycles particularly relevant to medicinal chemistry.[2] During the past years, the most explored synthetic routes to afford C−2 aryl decorated indoles implied the use of homogeneous catalysts and toxic organic solvents, dangerous both for the environment and for human health.[3]

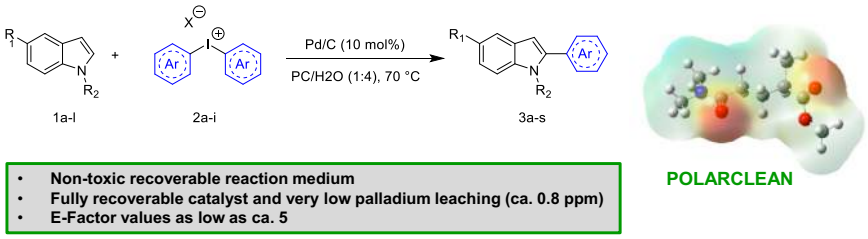

Figure 1: Selective Pd/C catalyzed C-2 arylation of indoles using Polarclean/water as medium

In this contribution we report our investigation on the use of Polarclean, an alternative biodegradable, safer and “industrial waste”-derived solvent as reaction medium for the selective synthesis of C2-arylated indoles using diaryliodonium salts as arylating agent and the cheap Pd/C as catalyst, showing that this approach combined with a purification procedure by recrystallization permits a significant minimization of the waste production.

Aknowledgment

The research leading to these results has received funding from the NMBP-01-2016 Programme of the European Union's Horizon 2020 Framework Programme H2020/2014-2020/ under grant agreement nº [720996]. The Università degli Studi di Perugia and MIUR are acknowledged for financial support to the project AMIS, through the program “Dipartimenti di Eccellenza - 2018-2022”. Regione Umbria is acknowledged for funding through "Umbria bo.R.do“, P.O.R. Programma Operativo Regionale F.S.E. (Fondo Sociale Europeo) Umbria 2014-2020 Asse III “Istruzione e formazione”. Sterling SpA is also thanked for useful suggestions and support

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OC16 - Chemodivergent synthesis of 2*H*-chromenes and dihydrobenzofurans from sulfoxonium ylides and salicylaldehydes: discovery, development, and mechanistic insights

G. D. Bisag,[a] S. Ruggieri,[a] M. Fochi, [a] L. Bernardi[a]

[a] *Department of Industrial Chemistry "Toso Montanari" Alma Mater Studiorum – University of Bologna. Viale del Risorgimento 4, 40136 Bologna, Italy.*
denisa.bisag@unibo.it

Sulfur ylides are formal internal salts characterised by a carbanion flanked by a positively charged sulfur atom. These ylides are able to react via typical (2 + 1) pathways (Corey-Chaykovsky epoxidation and related reactions) or can display less conventional reactivity such as insertion reactions[1] into X-H, C-H, C-X and X-Y bonds, generally characteristic of the arguably problematic diazo compounds.

This communication presents a tandem chemodivergent cyclization reaction between sulfoxonium ylides and salicylaldehydes. The literature reports the reaction of unstabilized sulfoxonium ylide with these aldehydes, giving benzofurans as products.[2] In our case,[3] reacting stabilized sulfoxonium ylides with salicylaldehydes, two different compounds are obtained, 2*H*-cromene and dihydrobenzofuran scaffolds, depending on the substituents around the aromatic ring and the presence of the catalyst (Figure 1). In particular, using electron poor salicylaldehydes, in the absence of catalyst, three different dihydrobenzofuran derivatives were achieved in excellent yields, while, using electron neutral or electron rich salicylaldehydes in the presence of 5 mol% of diphenyl phosphate, 16 examples of differently substituted 2*H*-cromenes were obtained in good yields. Mechanistic insight and comparison with the reactivity of sulfonium ylides are also given.

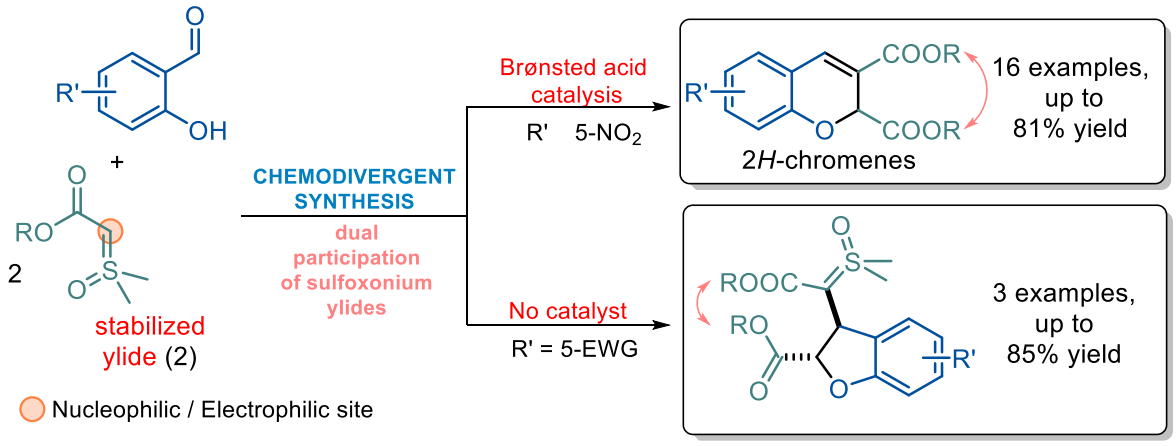

Figure 1: Tandem chemodivergent cyclization between sulfoxonium ylides and salicylaldehydes.

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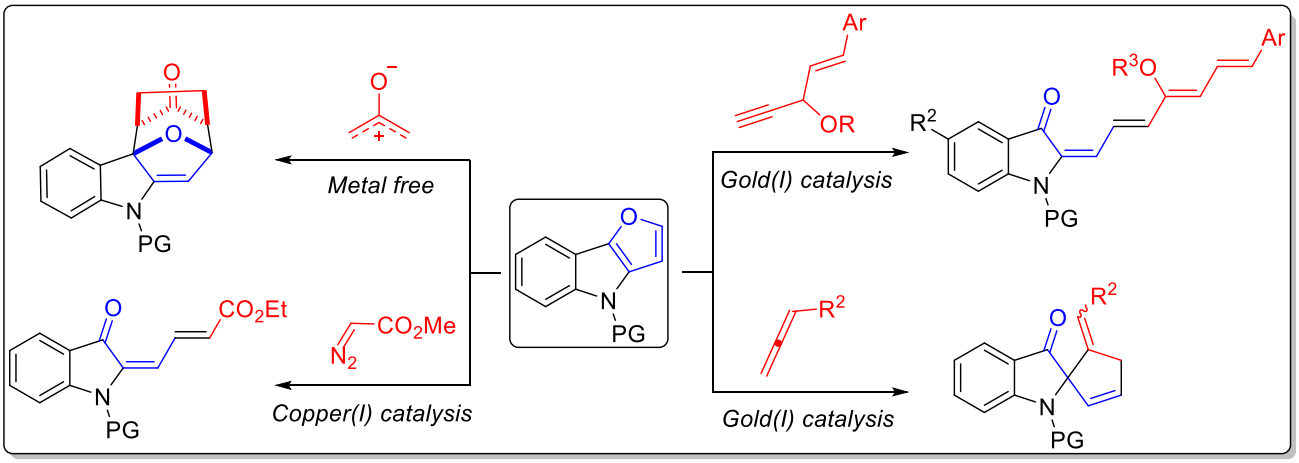
OC17 - 4*H*-furo[3,2-*b*]indoles in the synthesis of complex indole derivatives

E. Brambilla,[a] V. Pirovano,[a] E. Rossi,[a]
[a]Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", 21, Via Venezian, 20133 Milano, Italy
elisa.brambilla@unimi.it

4*H*-furo[3,2-*b*]indoles has been seldom reported in the literature for their promising anti-inflammatory/analgesic properties.[1] However, the investigation on the reactivity of 4*H*-furo[3,2-*b*]indoles concerned only simple N- or C2 functionalization reactions. The peculiarity of 4*H*-furo[3,2-b]indole is its skeleton containing a 4π-system embedded in the rigid framework of a furan ring. Thus, theoretically, 4*H*-furo[3,2-*b*]indoles could participate in cycloaddition reactions as dienes or dienophiles or react with electrophiles as electron-rich heterocycles.[2]

Herein we present the reactivity of 4*H*-furo[3,2-*b*]indoles with four electrophilic partners, in order to synthetize different functionalized indole derivatives.



Scheme 1: Reactivity of 4*H*-furo[3,2-*b*]indoles

In particular, we employed electrophiles generated under gold(I) catalysis from propargyl esters and allenes.[2] Moreover, copper(I)-carbene from diazo compounds were tested in presence of 4*H*-furo[3,2-*b*]indoles.[3] Finally, metal free generation of oxyallyl cations from α-haloketones were investigated for the synthesis of polycyclic indole derivatives[4].

References:

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OC18 - Recoverable POLITAG palladium catalyst for the regioselective C–H alkenylation of quinoline N–Oxide

D. Sciosci,[a] F. Valentini,[a] F. Ferlin,[a] S. Chen,[b] Y. Gu,[b] O. Piermatti,[a] L. Vaccaro[a]

[a]*Laboratory of Green S.O.C. – Dipartimento di Chimica, biologia e Biotecnologie, Università degli Studi di Perugia, Via Elce di Sotto 8, 06123 – Perugia, Italy*
[b]*Hubei Key Laboratory of Material Chemistry and Service Failure, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, China*
daniele.sciosci@studenti.unipg.it

Direct transformation of the C–H bonds is in constant development, proving to be a handy tool in material science and, therefore, the synthesis of natural products and pharmaceuticals.[1] Many C–H functionalization protocols are realized by exploiting functional groups' potentiality to form weak interactions with C–H bonds positioned in their vicinity.[2] In this context, N–Oxide functionality is intriguing because of its ability to control regioselectivity,[3] and, therefore, the possibility of using this functionality to stir C–H activation and work as an internal oxidant. Despite recent progress realized with heterogeneous or heterogenized catalytic systems, the palladium-catalyzed C-2 selective C–H functionalization of quinoline N–oxide moiety has been solely restricted to the employment of homogeneous catalysts. Within our research program, focused on the design and definition of recoverable catalytic systems for C–H functionalization reactions,[4] we developed the first recoverable heterogeneous catalyst for the C-2 selective alkenylation of quinoline N–oxide.

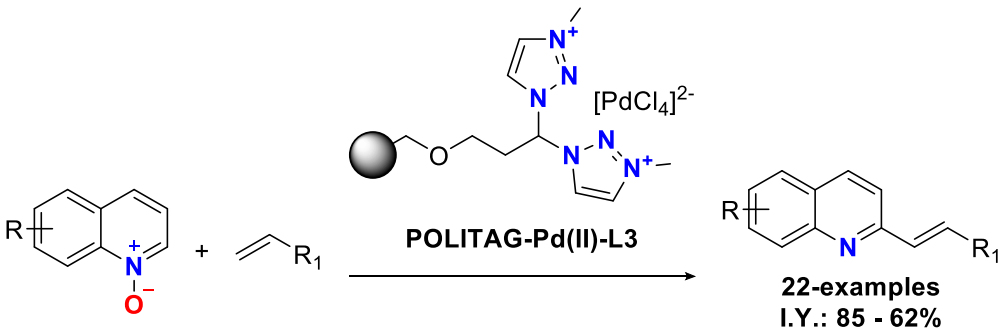

Figure 1: Reaction Scheme

Acknowledgments

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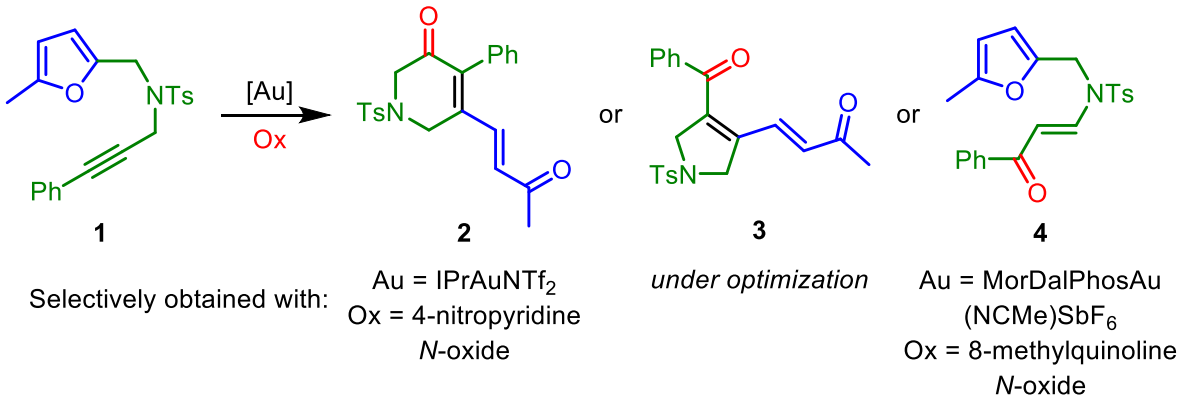
OC19 - Gold(I)-catalysed divergent reactivity of furans with *N*-oxides: synthesis of substituted dihydropyridones

S. Nejrotti,[a] F. Marra,[a] E. Priola,[a] C. Prandi[a]

[a]*Università degli Studi di Torino, Dipartimento di Chimica, via Pietro Giuria 7, 10125 Torino, Italy*
stefano.nejrotti@unito.it

The reactivity of furans under conditions of gold catalysis often opens the way to peculiar and unique reaction pathways. A classical example is Hashmi's synthesis of phenols from alkyne-tethered furans ("furan-ynes") through ring opening of the heterocyclic moiety.[1] More recently, Echavarren and Shi reported on the reactions of furans with gold carbenes, generated from propargyl acetates, 1,6-enynes or *retro*-Buchner reaction.[2] On this basis, we wanted to investigate the gold-catalysed reactivity of furan-ynes **1** in the presence of *N-O* oxidants, such as pyridine or quinoline *N*-oxides, which are known to convert the triple bond into reactive α-oxo gold carbene species.[3] Our results disclosed a divergent mechanistic picture, in which three products are possible: dihydropyridone **2**, dihydropyrrole **3** and furan **4** (Scheme 1). More importantly, the selectivity of the reaction can be tuned by the choice of the right gold catalyst and oxidant, allowing for the successful synthesis of a series of dihydropyridones **2**.



Scheme 1: Reactivity of furan-yne with *N*-oxide under gold catalysis.

References:

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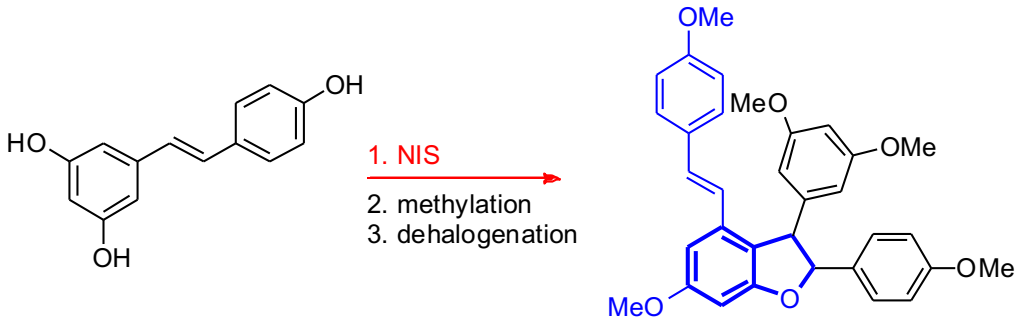
OC20 - Radical resveratrol dimerization to dihydrobenzofuran system by NIS

R. D'Orsi,[a] T. Laurita,[a] M. Funicello,[a] P. Lupattelli,[a] L. Chiummiento[a]

[a]*Department of Science, University of Basilicata, via dell'Ateneo Lucano 10, Potenza*
rosarita.dorsi@gmail.com

Interest of organic chemistry in biomimetic synthesis is constantly increasing in order to obtain bioactive natural products in steps and atoms economy. In the light of these, during iodination of resveratrol as starting material to obtain natural compounds, unexpectedly, an interesting by-product was obtained. In fact, in addition to iodinated resveratrol NMR signals showed the presence of a compound with a 2,3-dihydrobenzofuran motif. The only explanation for this event is the radical generation on resveratrol by NIS[1], used as iodinating agent[2]. Oxidation of the phenol moiety can generate a hypothetical phenoxyl radical, that leads to dimerization, affording to a 2,3-dihydrobenzofuran moiety[3]. Therefore, formation of radical and subsequently dimerization, as naturally occurs, makes this strategy as a new biomimetic synthesis of resveratrol dimer. Herein, we present our study performed to optimize the 2,3-dihydrobenzofuran formation conditions and to identify the structure of the obtained compound.

Methylation and dehalogenation reactions confirmed the formation of the permethylated (±)-ε-viniferin[4].



Resveratrol — Permethylated (±)-ε-viniferin

Figure 1: Dimerization of resveratrol by NIS

References:

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OC21 - Organo-gold catalysis with bifunctional phosphine ligands for carbo- and heterocyclization reactions of alkynes

A. Franchino,[a] À. Martí,[a] S. Nejrotti,[a] A. M. Echavarren[a]

[a]*Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona (Spain)*
afranchino@iciq.es

Gold(I) complexes incorporating pendant H-bond donor groups on phosphine ligands have been prepared and tested in carbo- and heterocyclization reactions of alkyne substrates. Thanks to their H-bonding ability, these complexes contribute to the solution of two long-standing issues in the field of Au(I) catalysis:[1]

1 - The realization of challenging Au(I)-catalyzed enantioselective transformations of alkynes by placing the chiral information not on the ligand backbone, but on the counterion.[2] The successful implementation of this strategy has been demonstrated in the formal [4+2] cycloaddition of 1,6-enynes, enabled by a conceptually new H-bonded[3] chiral anion[4] approach (Figure 1, left).

2 - The necessity of a silver co-catalyst, which has the drawback of mandating the use of an additional precious metal, while often negatively impacting selectivity.[5] The novel phosphinosquaramide and phosphinourea Au(I) chloride complexes display high activity at room temperature in the model silver-free cyclization of N-propargyl benzamides (Figure 1, right).

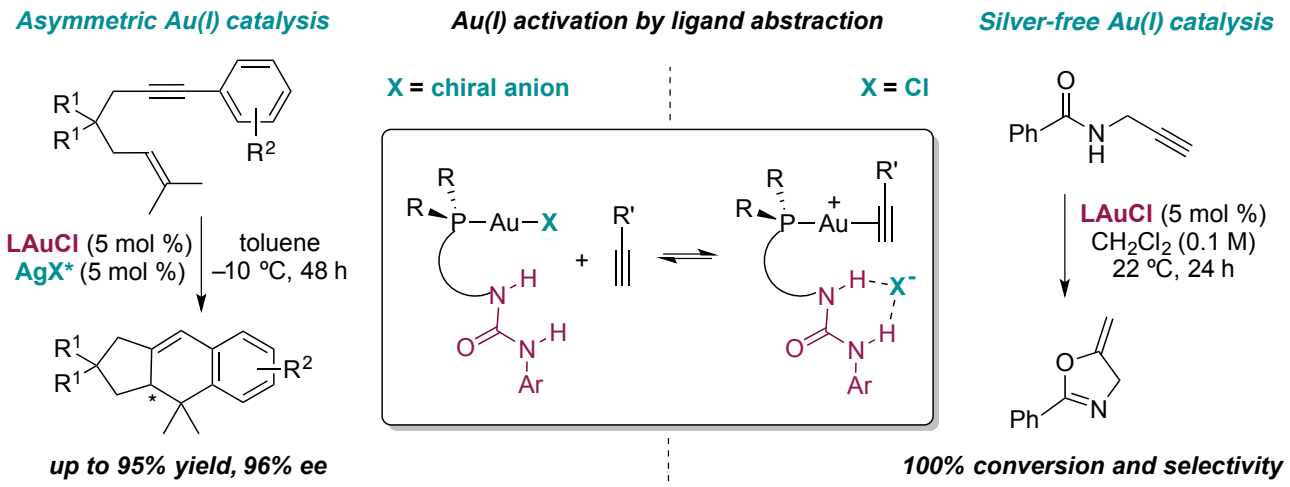

Figure 1: Bifunctional phosphine Au(I) chloride complexes for enantioselective (*left*) or silver-free (*right*) carbo- and heterocyclizations of alkynes.

References:

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OC22 - Carbenoids-Mediated Homologation Tactics: Expected and Unexpected Sequences for Imparting Molecular Complexity

Laura Ielo,[a] Vittorio Pace,[a,b]

[a]*University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse 14 – 1090 Vienna (Austria).*
[b]*University of Turin, Department of Chemistry, Via P. Giuria 7 – 10125 Turin (Italy)*
laura.ielo@univie.ac.at

Carbenoids are organometallic compounds employed in organic synthesis in order to realize a homologation event by inserting a reactive fragment featuring a precise substitution pattern.[1] Homologation reaction refers to a synthetic operations enabling the formation of a new carbon-carbon or carbon-heteroatom bond through the addition of methylene unit (*e.g.* $–CH_2X$, X = Halogen, CN, OR).[2] Functionalized methylenic units (*e.g.* MCH_2X, M = metal, X = halogen) act as nucleophilic synthons enabling the transfer of the CH_2X unit into a proper electrophilic partner. Depending on the inclusion (or not) of the halogen(s) inserted with the carbenoid in the final compound, we could individuate three different outcomes for the processes: 1) the *interrupted* homologation in which the halogen(s) remains in the resulting structures thus, being available for later functionalization; 2) the *ring-closure* through simple internal nucleophilic displacement (*e.g.* Corey-Chaykovski mode) and, 3) the *pure* homologation in which the halogen is conveniently displaced during the molecular rearrangement of the so-formed carbon skeleton, often exploited in ring-enlargement operations.[3] Evidently, the pathway is governed by both the nature of the substrate and the carbenoid. More reactive electrophiles (ketones, aldehydes and, in general, carbonyl-like substrates) are more prone to undergo ring-closure phenomena compared to less reactive ones (Weinreb amides, esters, etc) for which the interrupted homologation is preferentially observed.[4] We devoted several studies to design and develop synthetic methodologies paved on the initial C-C bond forged with nucleophilic halomethyl- lithiums that we want to present.[5]

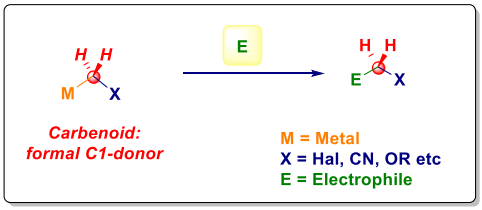

Figure 1: Homologation event *via* carbenoids reagents.

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OC23 - Eco-friendly Methodologies for the Synthesis of Heterocyclic Systems

Luciana Cicco,[a] Paola Vitale,[a] Antonio Salomone,[b] Filippo Maria Perna,[a] and Vito Capriati[a]

[a]*Dipartimento di Farmacia-Scienze del Farmaco, Università degli Studi di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S, Via E. Orabona 4, 70125 Bari, Italy*
[b]*Dipartimento di Chimica, Università degli Studi di Bari, Via E. Orabona 4, 70125 Bari, Italy*
luciana.cicco@uniba.it

The increasing awareness towards environmental pollution and climate changes has impelled research in organic synthesis to search for more environmentally responsible and less impactful solvents in place of toxic and often hazardous Volatile Organic Compounds (VOCs).[1] Over the last few years, our research group focused on the sustainable synthesis of heterocyclic compounds such as tetrahydrofuran,[2] thiophene,[3] and triazole derivatives[4] using biodegradable, nature-inspired designer solvents like the so-called *Deep Eutectic Solvents* (*DESs*)[5] and even water.[6] *N*-containing heterocyclic compounds such as 2,5-diarylpyrazines,[7] 2-aroylimidazoles and 2,4-diaroyl-6-arylpyrimidines[8] are important scaffolds in many biologically active and pharmaceutically relevant molecules. In this communication, the regiodivergent, sustainable synthesis of the aforementioned heterocycles from phenacyl azides is discussed using *DESs* as environmentally responsible media, acting both as solvents and catalysts, under very mild reaction conditions.

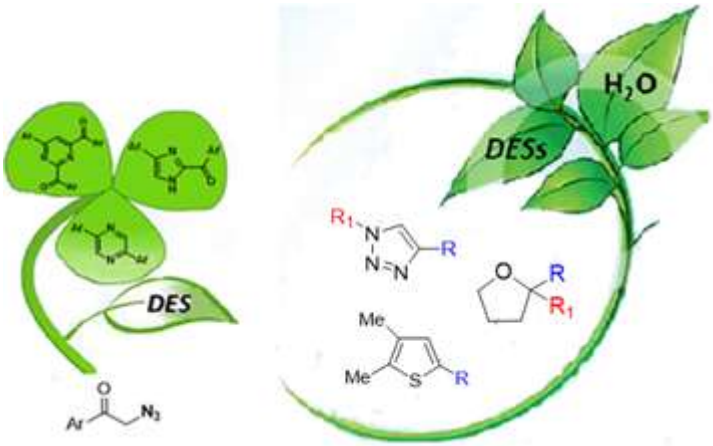

Figure 1: Synthesis of pyrimidines, imidazoles, pyrazines, tetrahydrofuns, triazoles and thiophenes in *DESs* and water.

References:

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OC24 - Click Chemistry Approach for the Synthesis of Triazole-based aminoglycerol Derivatives as novel lead compounds useful in antiviral drug discovery

S. Mazzotta,[a,b] F. Aiello,[c] J.M. Vega-Pérez,[b] F. Iglesias-Guerra,[b] J. Sánchez-Céspedes,[d] M. Vega-Holm,[b]

[a]*Department of Pharmaceutical Sciences, University of Milan, Via Luigi Mangiagalli 25, 20133 Milano,*
[b]*Department of Organic and Medicinal Chemistry, Faculty of Pharmacy, University of Seville, Profesor García González 2, 41071 Seville*
[c]*Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Edificio Polifunzionale, 87036 Rende (CS)*
[d]*Institute of Biomedicine of Seville (IBiS), University Hospital Virgen del Roció, E41013 Seville*
sarah.mazzotta@unimi.it

Over the years, the click chemistry has been recognised as an important synthetic tool useful in the area of the drug discovery, due to it allows to easily generate biologically active molecules, mainly heterocyclic ones.[1] Among them, triazole could be considered a privileged structure, widely present in different compounds characterized by several biological activities: antiviral, antibacterial, anticancer, among others.

In this work, a new small set of 1,2,3-triazole derivatives from 3-amino-1,2-propanediol were designed and synthesized in order to obtain new potential antiviral compounds against Adenovirus, a pathogen associated to severe infections with significant mortality in immunosuppressed patients as well as healthy individuals.[2]

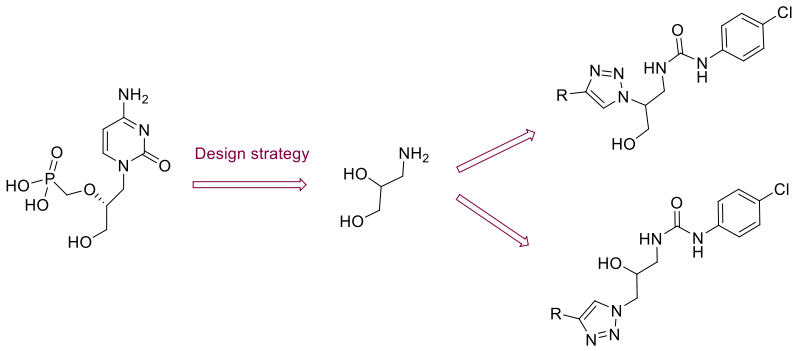

Figure 1: Design strategy for the synthesis of new compounds starting from antiviral drug cidofovir.

The introduction of 1,2,3-triazole nucleus (1,4-adduct) were performed employing the copper(I)-catalysed alkyne-azide 1,3-dipolar cycloaddition (CuAAC) reaction, the most used “click” reaction to obtain 1,2,3-triazoles, due to its reliability and regiospecificity.[3] A preliminary *in vitro* assay was performed to evaluate the antiviral properties of new synthesized compounds. Some of them showed a moderate inhibitory activity becoming suitable lead compounds for further modifications on triazole moiety and the development of new potential antiadenovirus agents.

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OC25 - New Fluorescent β-Turn Mimics

Marco Leusciatti,[a] Barbara Mannucci,[b] Teresa Recca,[b] Paolo Quadrelli[a]

[a] *Department of Chemistry University of Pavia, Viale Taramelli 12, 27100-Pavia*
[b] *Centro Grandi Strumenti (CGS) University of Pavia, Via Bassi 21, 27100-Pavia*
marco.leusciatti01@universitadipavia.it

Cyclopenta[d]isoxazoline aminols were used for the synthesis of the b-turn mimics.[2,4] The peptide chains choice ascertained the influence of their features of on the applicability/reliability/robustness of these scaffolds as b-turn inducers and their limitations.[1,3] The correct aminoacid selection can favor or disfavor the structure folding and the correct design of the peptide chains deeply influence the potential use of these nitrosocarbonyl-based compounds as turn-inducers.

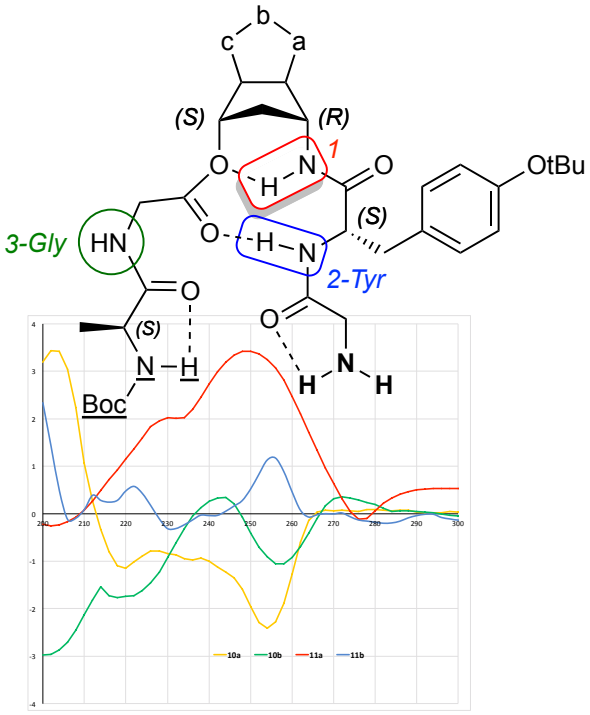

Figure 1: Role of the peptide chains linked to cyclopenta[*d*]isoxazoline aminol structures in the formation of the β-turn arrangement

References:

[1] A. M. C. Marcelino, L. M. Gierasch, *Biopolym.*, **2008**, 889, 380-391.
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OC26 - Unexpected oxidative rearrangement of a dopamine-resorcinol conjugate leading to a matlaline-like fluorophore

M.L. Alfieri,[a] M. Iacomino,[a] O. Crescenzi,[a] M. d'Ischia,[a] A. Napolitano[a]

[a]*Department of Chemical Sciences, University of Naples Federico II, Via Cintia 4, 80126, Naples, Italy*
marialaura.alfieri@unina.it

Because of their peculiar redox reactivity, which allows for efficient crosslinking reactions, oxidative polymerization, strong metal chelating properties and the ability to interact with a variety of functional groups and surfaces, catechol systems have been the focus of intensive research. Recently considerable attention has been directed to implement synthetic mimics of natural catecholic compounds for a broad range of biomedical and technological applications. In the 1990s, it was found that resorcins, such as the parent compound and phloroglucinol, react efficiently with catecholamine quinones to form covalent highly fluorescent adducts characterized by a methanobenzofuroazocine skeleton[1,2] that is akin to that of monardine in matlaline, the fluorescent product produced in *lignum nephriticum*.

Herein, we report an unexpected oxidative rearrangement of a methylene-bridged dopamine-resorcinol conjugate, 4-(2-((2,4-dihydroxybenzyl)amino)ethyl)benzene-1,2-diol (**1**) leading to the strongly fluorescent methanobenzofuroazocinone-containing adduct identical to that obtained from oxidative coupling of dopamine with resorcinol (Figure 1).[3]

Figure 1: Synthesis of the dopamine-resorcinol conjugate.

Chemical experiments and computational studies suggested a remarkable sequence of reactions involving autoxidation of **1** to the quinone followed by intramolecular cyclization and a complex rearrangement driven by irreversible loss of a carbon-containing group. The potential of **1** as an oxygen/superoxide scavenger as well as an oxygen or amine sensor with fluorescence read-out (*e.g.* for smart packaging applications) is also illustrated.[3] Compared to the parent bimolecular dopamine-resorcinol system, the unimolecular variant disclosed here expands the current tool-box of catechol-based functional systems and appears to be highly advantageous in terms of sensitivity, risk of interference by intermolecular processes in complex media and, especially, antioxidant activity.

References:

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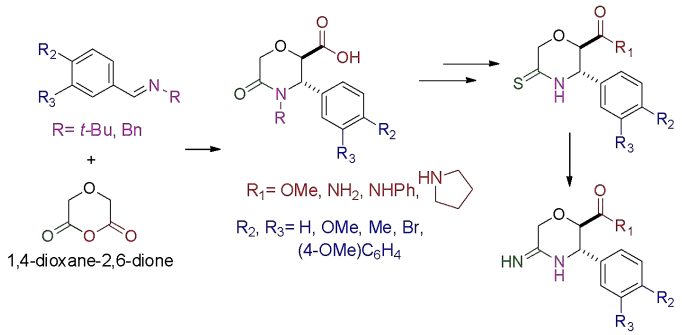
OC27 - Synthesis of BACE1 inhibitors using the Castagnoli-Cushman reaction

L. Calugi,[a,b] E. Lenci[a] R. Innocenti[a], A. Trabocchi[a]

[a]*Department of Chemistry "Ugo Schiff", Via della Lastruccia 13, 50019, Sesto Fiorentino (FI)*
[b]*NEUROFARBA Department, Via G. Pieraccini, 6, 50139, Florence*
lorenzo.calugi@unifi.it

Alzheimer's disease (AD) is the most common neurodegenerative syndrome affecting about 47 million people worldwide. One of the main causes is a progressive deposition of insoluble phosphorylated β-amyloid peptide and Tau protein on nerve cells causing difficulties in axonal transport. The pathogenic peptide β-amyloid is generated when the Amyloid Precursor Protein (APP) is degraded by β-secretase (BACE1) instead of α-secretase. In vivo studies demonstrated that in BACE1 knockout mice the presence of amyloid plaques was suppressed, so this enzyme has been one of the most studied targets for the pharmaceutical treatment of AD since its identification in 2000. There are several promising inhibitor candidates in clinical trials, although none of them could pass final steps.[1-2] Nevertheless, BACE1 is still considered a key therapeutic target for AD.



Scheme 1: Synthesis of morpholinone derivatives from Castagnoli-Cushman reaction and amide elaboration.

A novel approach in the synthesis of BACE1 inhibitors with C-2 aryl substituted morpholinone core was developed. Following the Castagnoli-Cushman reaction four thioamide and four amidine derivatives were obtained in five steps. The thioamide and the amidine derivatives were screened for the biological inhibition against BACE1, showing an unexpected activity for thioamide derivatives. The binding mode was also studied with docking simulation, finding a different interaction with respect to the one described for canonical BACE1 amidine inhibitiors.[3]

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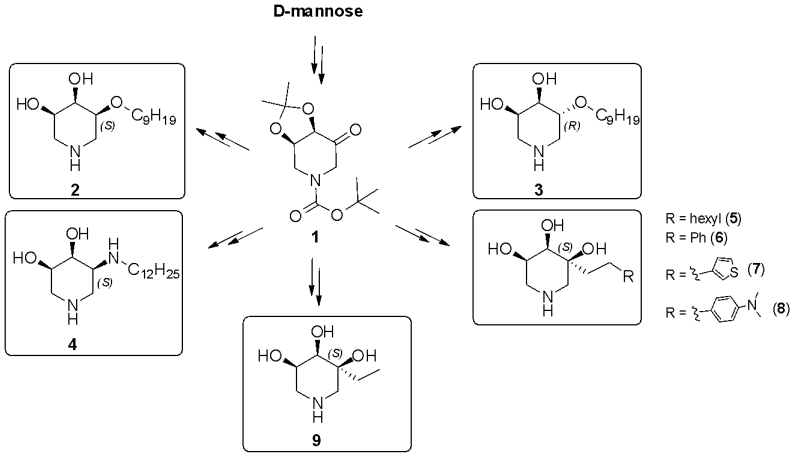
OC28 - Synthesis of "*all-cis*" trihydroxypiperidines from a D-mannose derived ketone as new GCase inhibitors

M.G. Davighi,[a] F. Clemente,[a] C. Matassini,[a] A. Goti,[a] F. Cardona[a]

[a]*Dipartimento di Chimica "Ugo Schiff", Università di Firenze, via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy*
mariagiulia.davighi@unifi.it

Gaucher Disease (GD), the most common lysosomal storage disease (LSD), is due to deficiencies in the activity of β-glucocerebrosidase (GCase), which hydrolyzes glucosylceramide to ceramide and glucose. The consequence is the accumulation of glucosylceramide in the lysosomes, leading ultimately to organ dysfunctions.[1] Pharmacological Chaperones (PCs) are small molecules able to rescue the enzymatic activity when they are used at sub-inhibitory concentration.[2] Glycomimetics, such as aza- and iminosugars, are the most promising PCs for LSDs.[2] With the aim of accessing new PCs for GD, this research is focused on the synthesis and biological evaluation of trihydroxypiperidines and congeners[3] obtained from the common ketone intermediate **1** derived from inexpensive D-mannose.[4] The Williamson reaction performed on the two diastereomeric alcohols (obtained en route to **1** and by diastereoselective reduction of ketone **1**, respectively), followed by deprotection of Boc and acetonide groups, provided the two epimers **2** and **3**.[3] The azasugar **4** was achieved through a reductive amination of **1** with dodecylamine.[3] The reaction of **1** with several lithium acetylides, followed by reduction of the triple bond and deprotection, allowed the stereoselective synthesis of the new azasugars **5-8** in high yields.[3] On the contrary, alkyl Grignard additions to **1** proved difficult and sluggish while the reaction between **1** and the sp_2 vinyl magnesium bromide furnished a single diastereoisomeric adduct, which was converted to **9** by reduction of double bond and deprotection.[3]



Scheme 1: Three different strategies to afford "*all cis*" trihydroxypiperidines substituted at C-3.

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