THE 3rd ORGANIC CHEMISTRY FRONTIERS INTERNATIONAL SYMPOSIUM

01 March 2016, St. Hugh's College, Oxford

http://rsc.li/ocfis16

Dear Colleagues,

It is our great pleasure to welcome you to the 3rd Organic Chemistry Frontiers International Symposium, at St Hugh's College, Oxford. It is particularly appropriate that the meeting is held in the Dickson Poon University of Oxford China Centre Building at St Hugh's College, which signifies the links between China and the University of Oxford. *Organic Chemistry Frontiers* is a journal published collaboratively by the Chinese Chemistry Society, the Royal Society of Chemistry and the Shanghai Institute of Organic Chemistry, that publishes high quality research and seeks to promote interactions between China and international scientists.

Supported by the journal *Organic Chemistry Frontiers*, the symposium has been successfully held in Shanghai, China in 2014 and Hangzhou, China in 2015. Thanks to the contributions from many excellent scientists, these meetings have developed into a series of symposia on advancing research in organic chemistry. We hope that the scientific talks will stimulate the exchange of ideas and experiences between all participants, and that the symposium will foster new international collaborations.

Organic Chemistry Frontiers publishes the leading edge research from across the field and ensures that every submission to the journal receives high quality publication service, including rapid publication time, free charge of colour in the text, flexible length and a platform with exceptional high visibility for dissemination of your work. We do hope that we will have the opportunity to publish some of your work soon and if you would like to be a referee for the journal, please let us know. Further information about the journal can be found on the internet http://rsc.li/frontiers-organic.

Finally, we sincerely hope that all delegates will benefit from a successful conference. Thank you all for your contributions; please enjoy the meeting.

Sincerely yours,

Professor Stuart Conway

Chair, the 3rd Organic Chemistry Frontiers International Symposium
Professor, Department of Chemistry, University of Oxford

Dr. Daping Zhang

Executive Editor, Organic Chemistry Frontiers
Royal Society of Chemistry

PROGRAME

Lecture Theatre 1, Dickson Poon University of Oxford China Centre Building

09h00	**Registration**
10h00	**Opening Remarks**
	Session Chair: Cristina Nevado, University of Zurich
10h15	Shengming Ma, *Shanghai Institute of Organic Chemistry (SIOC), China* **Recent Advances on the Enantioselective Construction of Axially Chiral Allenes**
10h45	Edward Anderson, *University of Oxford, UK* **Rational Ligand Design in Asymmetric Transition Metal-catalyzed Cycloisomerization**
11h15	**Coffee & Break**
	Session Chair: Chulbom Lee, Seoul National University
11h45	Cristina Nevado, *University of Zurich, Switzerland* **Challenging Targets, Unique Binding Modes: Novel Strategies against Cancer**
12h15	Frank Würthner, *University of Würzburg, Germany* **Supramolecular Structures and Materials based on Dipolar Organic Semiconductors**
12h45	**Lunch**
	Session Chair: Edward Anderson, University of Oxford
13h45	Zhangjie Shi, *Peking University, China* **Direct Transformations of Aliphatic C-H Bonds: from Amides to Free Amines**
14h15	Chulbom Lee, *Seoul National University, South Korea* **Transition Metal Vinylidene Mediated Catalysis for Use in Organic Synthesis**
14h45	Louis Fensterbank, *UPMC, France* **Silicates as New Partners for Dual Redox/Nickel Catalysis**
15h15	Stuart Conway, *University of Oxford, UK* **Targeting Epigenetic Reader Domains with Medicinal Chemistry and Chemical Biology**
15h45	**Coffee & Break**
	Session Chair: Stuart Conway, University of Oxford
16h15	Veronique Gouverneur, *University of Oxford, UK* **Chemical, Radiochemical and Clinical Advances**
16h45	Guy Bertrand, *University of California, San Diego, USA* **Stable Carbenes: Powerful Tools in Organic and Organometallic Chemistry**
17h15	**Plenary Talk** Stephen G. Davies, *University of Oxford, UK* **Asymmetric Synthesis of Biologically Important Amines**
18h00	**Closing remarks**

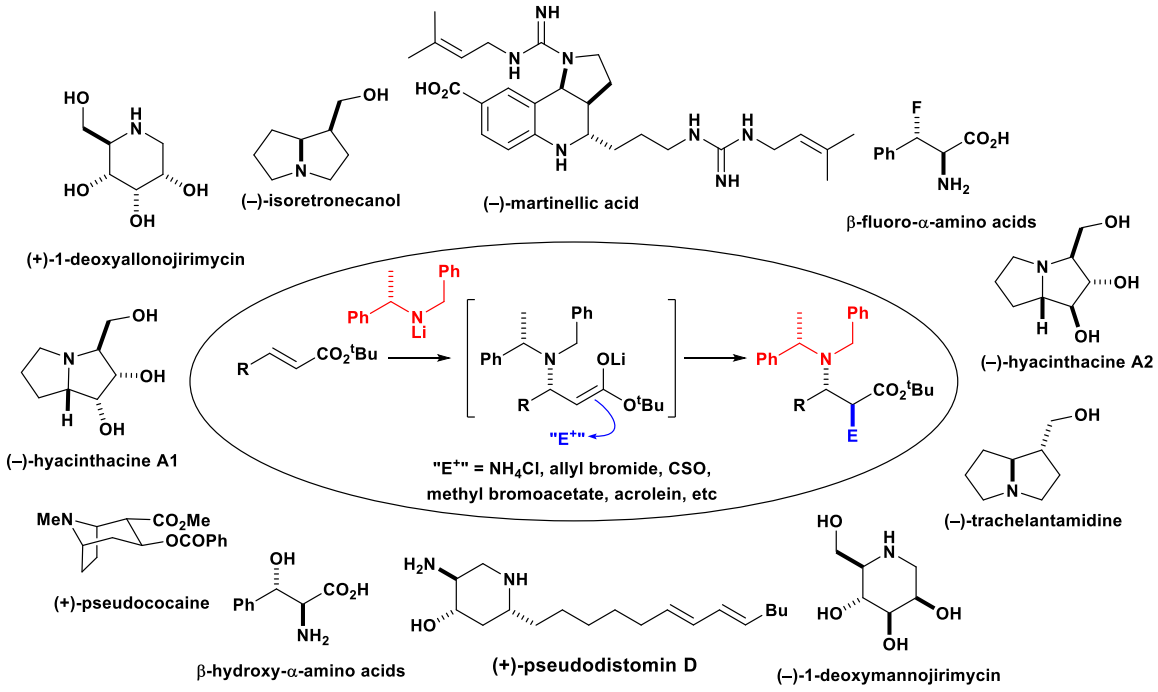
PLENARY TALK

Asymmetric Synthesis of Biologically Important Amines

Stephen G. Davies

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.
steve.davies@chem.ox.ac.uk

The conjugate addition of enantiopure lithium amides derived from α-methylbenzylamine proceeds with very high diastereoselectivity (usually >99:1 dr) to give the corresponding β-amino esters in good yield. α-Substituted β-amino esters can also be accessed directly upon either alkylation of the intermediate lithium (*Z*)-β-amino enolate derived from conjugate addition with various electrophiles (such as allyl bromide, methyl bromoacetate, acrolein, etc.), or via oxidation of the intermediate enolate with capmphor-sulfonyloxaziridine (CSO).[1] This methodology has been widely applied in target asymmetric syntheses of natural products and compounds of biological interest, and has recently been reviewed.[2,3]



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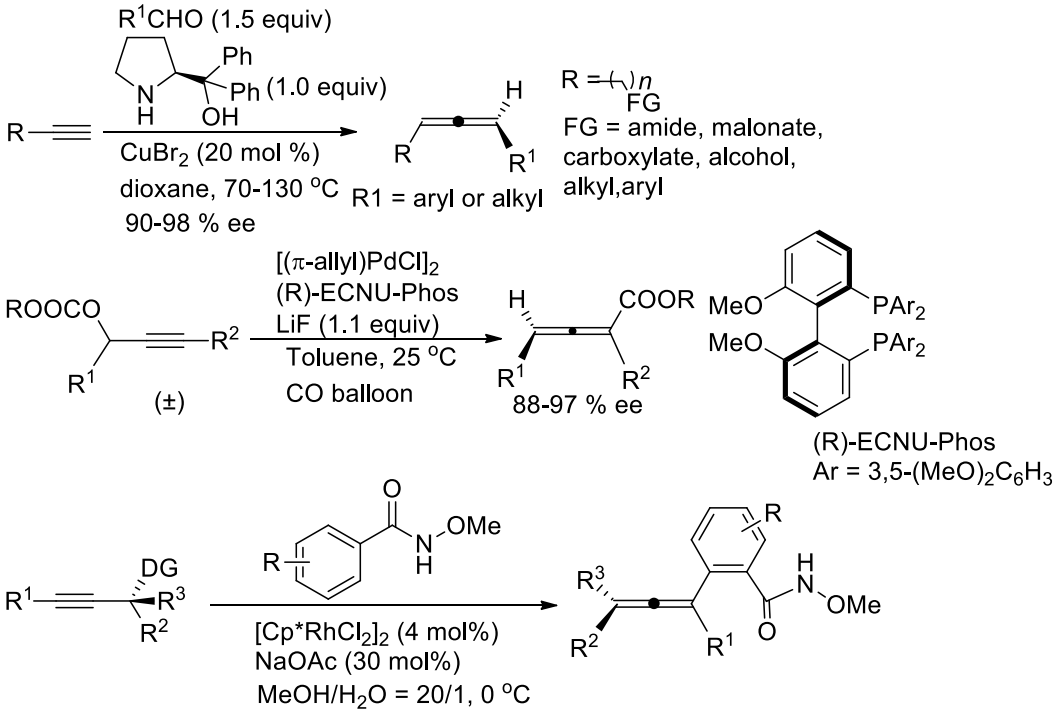
Recent Advances on the Enantioselective Construction of Axially Chiral Allenes

Shengming Ma

Research Center on Molecular Recognition and Synthesis, Department of Chemistry, Fudan University, 220 Handan Lu, Shanghai 200433 & State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, People's Republic of China

masm@sioc.ac.cn

In this lecture, the following approaches to optically active allenes with an axial chirality including EATA (enantioselective allenylation of terminal alkynes) [1-3], enantioselective carboxyklation of propargylic carbonates [4], and C-H activation-based SN_2'-type coupling[5] will be discussed.



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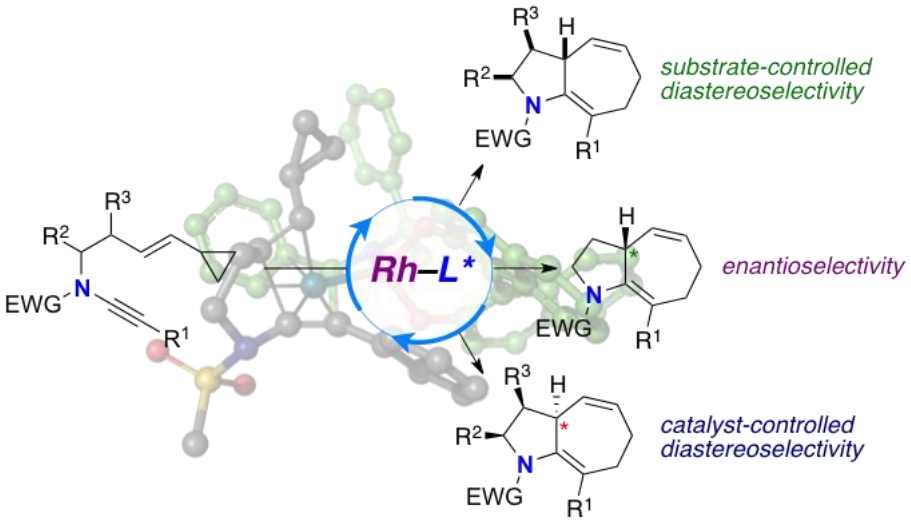
Rational Ligand Design in Asymmetric Transition Metal-catalyzed Cycloisomerization

Edward A. Anderson*, Robert N. Straker, Qian Peng and Robert S. Paton

Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, U.K.
edward.anderson@chem.ox.ac.uk

Asymmetric transition metal-catalyzed cycloisomerization represents a highly atom-efficient means for the stereoselective synthesis of functionalized organic ring systems.[1] The development of asymmetric cycloisomerization reactions of enynamides will be discussed, including diastereoselective and enantioselective transformations, and the first successful examples of catalyst-controlled double stereodifferentiating cycloisomerization, in which a chiral catalyst overturns the strong stereochemical preference of single enantiomer substrates.[2] The development of a highly reactive catalyst system relied on a synergistic experimental and theoretical ligand optimization process, which has provided new insight into the properties and influence of phosphoramidite ligands in asymmetric catalysis.



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Challenging Targets, Unique Binding Modes: Novel Strategies against Cancer

Cristina Nevado*, A. Caflisch, Andrea Unzúe

Department of Chemistry, Winterthurerstr. 190, CH 8057, Switzerland
cristina.nevado@chem.uzh.ch

Bromodomains are considered an emerging topic in the field of drug discovery due to their involvement in the regulation of many genes.[1] Bromodomains are protein interaction modules, part of large protein architectures, which function as epigenetic readers able to specifically recognize the ε-N-acetylated lysine residues (KAc group) present in proteins (especially in histones) altering the process of chromatin remodelling. [2] A computer based high-throughput screening study followed by a structure-based medicinal chemistry optimization campaign, has led to the discovery of small-molecule, nM potent bromodomain ligands. These compounds, highly selective towards specific bromodomain proteins, can be used as chemical probes to dissect both the specific function as well as the biological implications of these protein targets.[3,4]

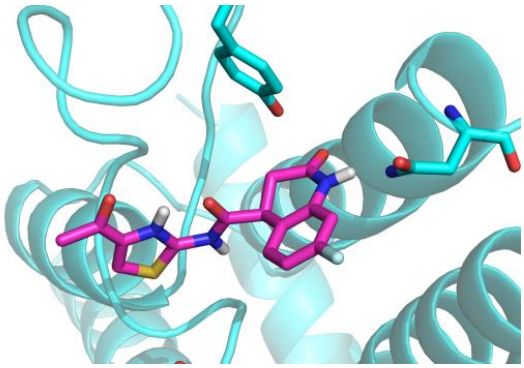

Figure **1**. Docked pose of a nanomolar, highly selective, bromodomain ligand.

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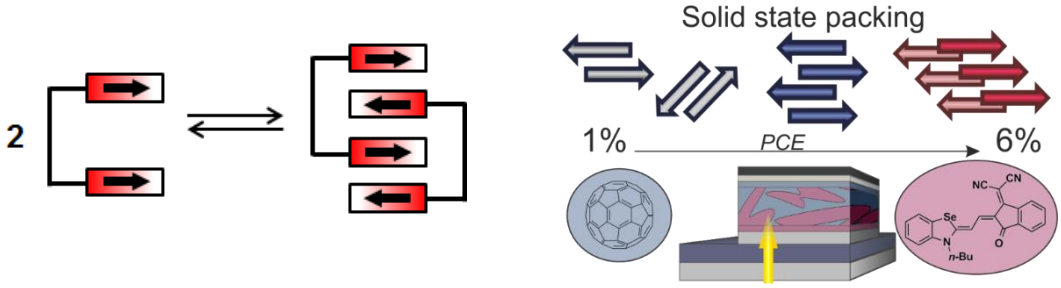
Supramolecular Structures and Materials based on Dipolar Organic Semiconductors

Frank Würthner*

Institut für Organische Chemie & Center for Nanosystems Chemistry, Universität Würzburg, 97074 Würzburg, Germany
Email: wuerthner@chemie.uni-wuerzburg.de

One of the pillars of the field of organic electronics is the dipolar disorder concept based on which amorphous photoconductors were developed from fundamental research up market products.[1] However, as shown by our work on the self-assembly of donor-acceptor substituted π-scaffolds (DA dyes, push-pull chromophores), dipole-dipole interactions between dipolar dyes direct these π-conjugated molecules into perfect antiparallel arrangements with vanishing overall dipole moments.[2] In this lecture I will show that dipole-dipole interactions can be utilized to build up highly defined π-stacks from dimers to tetramers up to octamers, as well as folding-driven polymers. In the second part of this lecture the applicability of dipolar dyes for organic transistors and bulk heterojunction solar cells will be elucidated and charge carrier mobilities > 1 cm^2/Vs and power conversion efficiencies > 6% will be demonstrated.[3-5]



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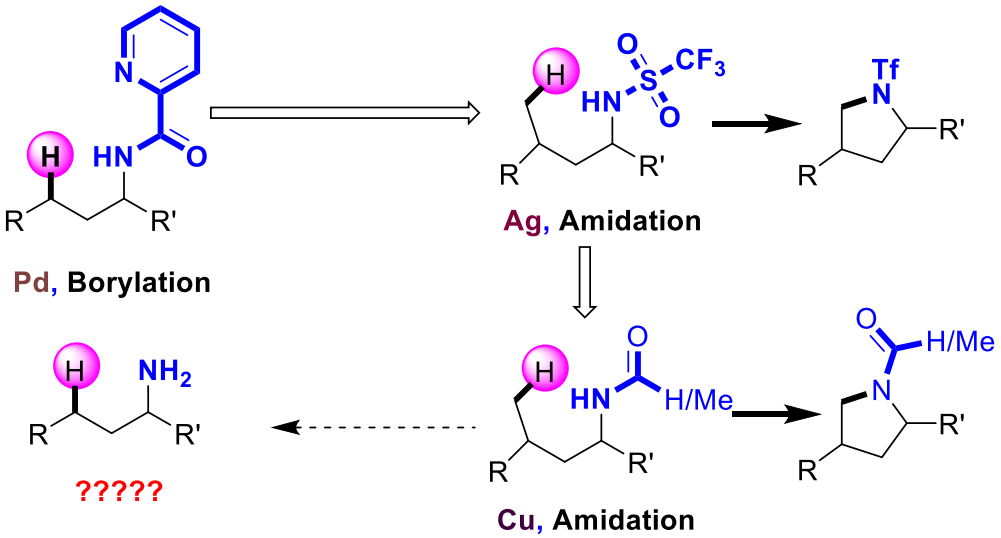
Direct Transformations of Aliphatic C-H Bonds: from Amides to Free Amines

Zhang-Jie Shi

College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China
zshi@pku.edu.cn

Bidentated directing groups showed their beauty in remote C-H functionalization of aliphatic amine derivatives.[1] With picolamide as directing group, we first developed the oxidative borylation of aliphatic C-H bonds *via* Pd catalysis.[2] To simplify the directing system, we further explored the Ag-/Cu-catalyzed amidation of triflic amides and carboxyl amides through remote C-H functionalizations.[3], [4] Both of these processes were considered through the radical pathway. Undoubtedly, direct transformation of remote C-H bonds of simple amines are of great importance to both fundamental researches and potential applications. We planned to carry out the primary free amino group directed inert aliphatic C—H functionalization in good chemo- and regio-selectivity.



Scheme 1. Direct Functionalization of Remote C-H Bonds Directed by Amino Derivatives.

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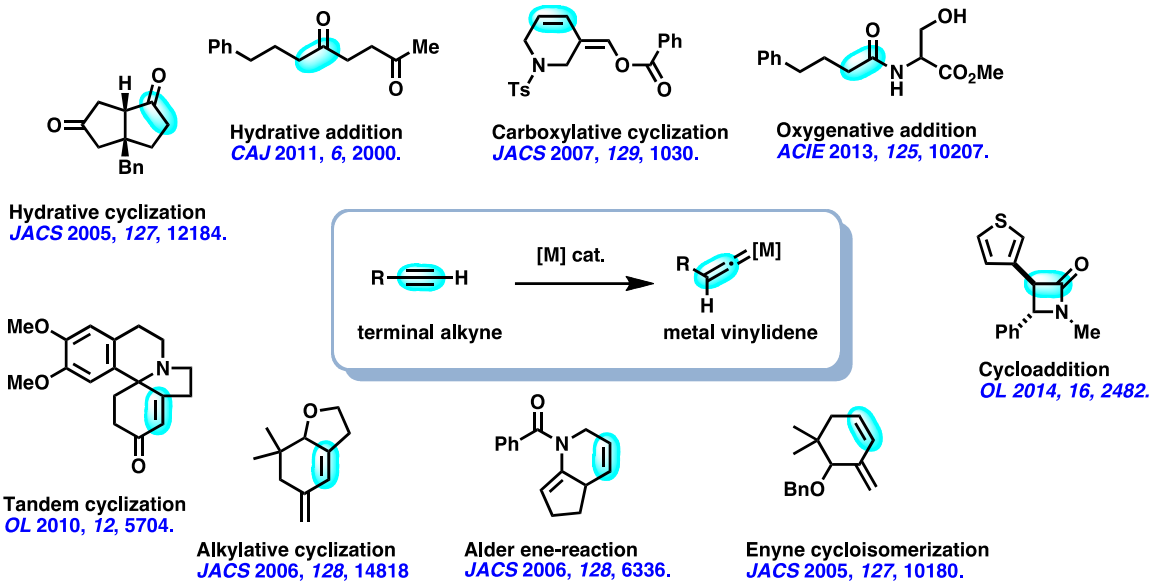
Transition Metal Vinylidene Mediated Catalysis for Use in Organic Synthesis

Chulbom Lee

Department of Chemistry, Seoul National University, Seoul 08826, Republic of Korea
chulbom@snu.ac.kr

Transition metal vinylidene complexes are organometallic species derived from alkynes that are isomeric to pi- and sigma-alkyne complexes. Our laboratory has been engaged in the development of C–C bond-forming processes that make use of terminal alkynes via mechanisms involving a transition metal vinylidene as a catalytic intermediate. A range of new reactions have been developed such as cycloisomerization of enynes and *N*-propargylic enamines, which convert simple acyclic alkynynes to their cyclic isomers.[1] Also developed are tandem cyclizations such as hydrative, alkylative, and carboxylative cyclization reactions.[2-4] More recently, in a departure from these ring-forming processes, our explorations have been focused on the oxygen-transfer to the metal-bound carbene. This approach has led to the discovery of oxygenative coupling reactions that occur through the intermediacy of a metalloketene arising from oxidation of a metal vinylidene.[5] Presented in this talk are the design, implementation and mechanism of the oxygenative transition metal vinylidene-mediated catalytic reactions.



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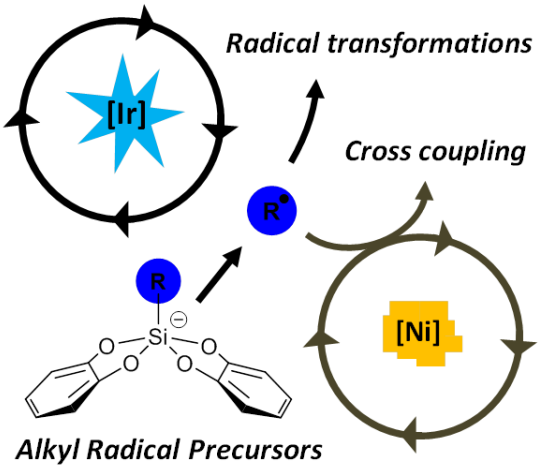
Silicates as New Partners for Dual Redox/Nickel Catalysis

Louis Fensterbank

Sorbonne Université, UPMC Univ Paris 06,
Institut Parisien de Chimie Moléculaire (UMR CNRS 8232),
4 place Jussieu, C. 229, 75005 Paris (France)
louis.fensterbank@upmc.fr

We have recently introduced hypervalent bis-catecholato silicon compounds as versatile sources of alkyl radicals upon visible light photocatalysis. Using Ir[(dF(CF_3)ppy)$_2$(dtbbpy)](PF_6) as catalytic photooxidant, a series of alkyl radicals, including highly reactive primary ones can be generated and engaged in various intermolecular homolytic reactions. Based on cyclic voltammetry, Stern-Volmer studies and supported by DFT calculations, a mechanism involving a single electron transfer from the silicate to the photoactivated iridium complex has been proposed. Finally, we have shown this oxidative photocatalyzed process can be efficiently merged with nickel-catalyzed C_{sp2}-C_{sp3} cross-coupling reactions.[1]



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Targeting epigenetic reader domains with medicinal chemistry and chemical biology

Stuart J. Conway

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX2 8JQ, UK.
stuart.conway@chem.ox.ac.uk

Epigenetics, defined as "a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence",[1] comprises regulatory mechanisms of chromatin state that control access to DNA, mediated by noncoding RNA, DNA methylation, nucleosome remodeling histone variants, and some histone post-translational modifications (PTMs).[2] Histone PTMs are dynamic, with cellular machinery identified that can add (write) these modifications and that can remove (erase) them.[3] A third class of proteins, termed "readers", has been identified, that binds to PTMs and thus stabilise large protein assemblies, which are often involved in transcriptional regulation. Bromodomains, protein modules that act as readers of lysine acetylation state, have emerged as important therapeutic targets for a number indication, especially in oncology.[4-6] We have developed small molecule inhibitors of the bromodomain and extra terminal domain (BET) family of bromodomain-containing proteins,[7,8] and the CREB-binding protein (CREBBP) bromodomain.[9,10] Recent developments in the optimisation of these probes will be discussed, with a view to the development of small molecule ligands for other non-BET bromodomains. The application of these probes to study the chemical biology of epigenetic reader proteins will be covered, including steps towards understanding the interplay between multiple epigenetic reader domains contained within the same protein.

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Fluorine: Chemical, Radiochemical and Clinical Advances

Véronique Gouverneur

University of Oxford, Chemistry Research Laboratory,
12 Mansfield, Oxford, UK

The impact of fluorine chemistry in the life sciences is enormous. As many as 30−40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine. ^{19}F- and ^{18}F-labelled compounds are also finding increasing applications in imaging such as Magnetic Resonance Imaging [MRI] or Positron Emission Tomography [PET]. As a result, there is an increasing demand for facile methods allowing for the fluorination using ^{19}F and the radioisotope ^{18}F of a large variety of structurally complex and functionalised targets. This lecture will discuss our recent contributions to late stage fluorination and ^{18}F-radiochemistry and explain how we bridge the gap between fundamental research and direct clinical applications.

Stable Carbenes: Powerful Tools in Organic and Organometallic Chemistry

Guy Bertrand

UCSD-CNRS Joint Research Chemistry Laboratory (UMI 3555), Department of Chemistry and Biochemistry,
University of California San Diego,
La Jolla, CA 92093-0343 (USA)
guybertrand@ucsd.edu

Over the years, the success of homogeneous catalysis can be attributed largely to the development of a diverse range of ligand frameworks that have been used to tune the behavior of the various systems. Spectacular results in this area have been achieved using cyclic diaminocarbenes, the so-called N-heterocyclic carbenes (NHCs), mainly because of their strong σ-donor properties. Although it is possible to cursorily tune the structure of NHCs, any diversity is still far from matching their phosphorus-based counterparts, which is one of the great strengths of the latter. Beginning with our discovery in 1988 of a bottle-able (phosphino)(silyl)carbene, a variety of stable acyclic carbenes are known, but they give rise to fragile metal complexes. During the recent years, we have discovered new types of stable cyclic carbenes, as well as related carbon-based and boron-based ligands, which feature even stronger □-donor properties than NHCs. The synthesis, electronic properties, and catalytic activity of complexes bearing our ligands will be presented, and comparisons with their NHC cousins will be discussed. We will show that singlet carbenes with enhanced electrophilic properties, such as cyclic (alkyl)(amino)carbenes (CAACs),[1] allow for the metal-free activation of small molecules, and for the stabilization of organic radicals and metals in a formal zero oxidation state.[2]

We also found that CAACs allow for the isolation of catalytically active complexes, which were supposed to be only transient intermediates. Among them, bis(copper) complexes involved in the very popular CuAAC reaction (Click Chemistry) will be discussed.[3] We will show that this discovery allows us to develop novel catalytic transformations.

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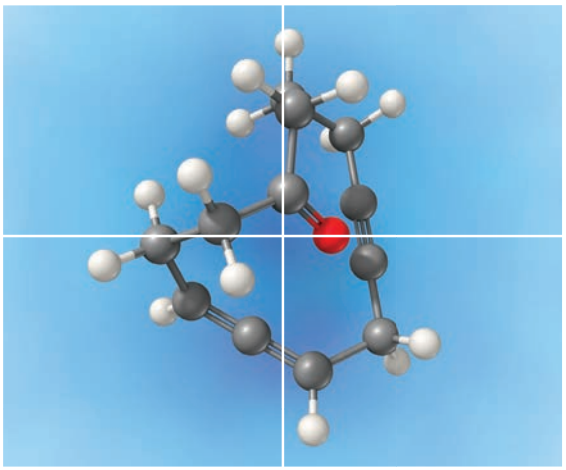

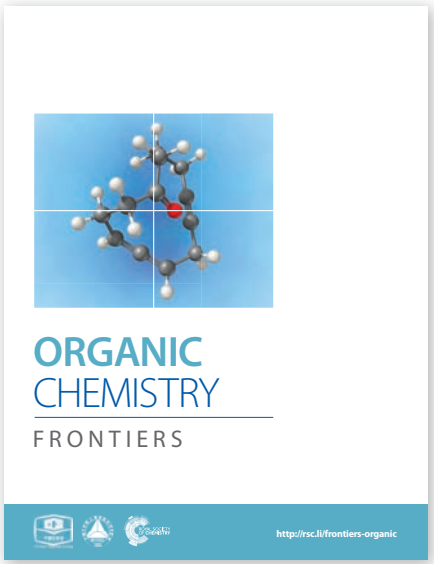

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Sheng-Ming Ma, Shanghai Institute of Organic Chemistry, China

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