# EuCHeMS conference on Organic Free Radicals (ECOFR 2018)

## *17-20 June 2018 Marseille (France)*

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*SPONSORS:*

## Sunday, June 17, 2018

| TIME | EVENT |
|---|---|
| 16:00 - 19:00 | **REGISTRATION -** |
| 19:00 - 21:00 | **WELCOME MIXER -** |

## Monday, June 18, 2018

| TIME | EVENT |
|---|---|
| 09:00 - 09:15 | **INTRO&WELCOME- Didier GIGMES** |
| 09:15 - 10:00 | Plenary Lecture - Chair : Didier GIGMES |
| 09:15 - 10:00 | › Sulfur Free RAFT polymerisation and polymerisation of acrylamides in water - ***David HADDLETON***, *Department of Chemistry, University of Warwick - UK* |
| 10:00 - 10:15 | Coffee break |
| 10:15 - 10:45 | Invited Lecture - Chair : Didier GIGMES |
| 10:15 - 10:45 | › Aspects of Catalysis in Single Electron Steps - ***Andreas GANSAUER***, *Kekulé-Institut für Organische Chemie und Biochemie der Universität Bonn, Bonn - Germany* |
| 10:45 - 11:15 | Invited Lecture - Chair : Didier GIGMES |
| 10:45 - 11:15 | › Structural and Medium Effects on Hydrogen Atom Transfer Based Functionalization of Aliphatic C-H Bonds - ***Massimo BIETTI***, *Università di Roma "Tor Vergata", Roma - Italy* |
| 11:15 - 11:30 | Oral Communication - Chair : Didier GIGMES |
| 11:15 - 11:30 | › Mild and metal-free access to tetracyclic indoles and 7-azaindoles through Single Electron Transfer (SET) induced enolate arylation - ***Cherif ADOUAMA***, *Université Lyon 1, CNRS, INSA, CPE-Lyon, ICBMS, Lyon - France* |
| 11:30 - 12:00 | Invited Lecture - Chair : Didier GIGMES |
| 11:30 - 12:00 | › New Horizons for Nitroxide Mediated Polymerization - ***José ASUA***, *POLYMAT University of the Basque Country, Donostia/San Sebastián - Spain* |
| 12:00 - 12:15 | Oral Communication - Chair : Didier GIGMES |
| 12:00 - 12:15 | › Regenerable Preventive and Peroxyl Radical Trapping Ebselenamine Antoxidants - ***Vijay SINGH***, *Department of Chemistry & Centre for Advanced Studies in Chemistry, Chandigarh - India* |
| 12:15 - 14:00 | Lunch |
| 14:00 - 14:45 | Plenary Lecture - Chair : Maurice MEDEBIELLE |
| 14:00 - 14:45 | › Lipid Peroxidation, its Role in Cell Death and Slowing it with Small Molecules - ***Derek PRATT***, *Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa - Canada* |
| 14:45 - 15:15 | Invited Lecture - Chair : Maurice MEDEBIELLE |
| 14:45 - 15:15 | › Air-stable Neutral Radicals with Spin-delocalized Structure: Full-cell Battery Application - ***Yasushi MORITA***, *Aichi Institute of Technology, Toyota - Japan* |
| 15:15 - 15:45 | Invited Lecture - Chair : Maurice MEDEBIELLE |

| TIME | EVENT |
|---|---|
| 15:15 - 15:45 | › Do Radical Enzymes Control the Reactivity of Reactive Intermediates using the Quantum Coulombic Effect? - ***Gino DILABIO***, *Department of Chemistry and Faculty of Management, The University of British Columbia, Kelowna, British Columbia - Canada* |
| 15:45 - 16:00 | Coffee break |
| 16:00 - 16:30 | Invited Lecture - Chair : Emmanuel LACOTE |
| 16:00 - 16:30 | › Photocontrolled Cationic Polymerizations of Vinyl Ethers - ***Brett FORS***, *Cornell University, Department of Chemistry and Chemical Biology, Ithaca, NY* |
| 16:30 - 16:45 | Oral Communication - Chair : Emmanuel LACOTE |
| 16:30 - 16:45 | › Thiol Catalyzed Radical Deuteration with D2O: Mechanistic Insights - ***Valentin SOULARD***, *Universität Bern, Bern - Switzerland* |
| 16:45 - 17:15 | Invited Lecture - Chair : Emmanuel LACOTE |
| 16:45 - 17:15 | › Redox catalysis strategies for complex molecules - ***Corey STEPHENSON***, *Willard Henry Dow Laboratory, Department of Chemistry, University of Michigan, Ann Arbor - USA* |
| 17:15 - 17:30 | Oral Communication - Chair : Emmanuel LACOTE |
| 17:15 - 17:30 | › The Surprising Acidity of Radicals: Generality, Range and Applications - ***John WALTON***, *EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews - UK* |
| 17:30 - 18:00 | Invited Lecture - Chair : Emmanuel LACOTE |
| 17:30 - 18:00 | › Tailored microstructured hyperpolarizing matrices for optimal magnetic resonance imaging - ***Chloe THIEULEUX***, *Laboratory C2P2 UMR 5265-CNRS-CPE Lyon-Univ. Lyon 1, Villeurbanne - France* |
| 18:00 - 18:15 | Oral Communication - Chair : Emmanuel LACOTE |
| 18:00 - 18:15 | › The neglected reductive catalytic cycle of nitroxides with hydroperoxyl radicals - ***Luca VALGIMIGLI***, *University of Bologna, Bologna - Italy* |
| 18:15 - 19:30 | Break |
| 19:30 - 23:30 | BANQUET |

## Tuesday, June 19, 2018

| TIME | EVENT |
|---|---|
| 08:30 - 09:15 | Plenary Lecture - Chair : Armido STUDER |
| 08:30 - 09:15 | › Harvesting Radicals to Functionalize π-Systems - ***Cristina NEVADO***, *University of Zurich, Department of Chemistry. Winterthurerstrasse 190, 8057 Zurich - Switzerland* |
| 09:15 - 09:45 | Invited Lecture - Chair : Armido STUDER |
| 09:15 - 09:45 | › Organocobalt(III) based on Co(acac)2 as a source of alkyl radicals under mild conditions: application to the precision synthesis of unprecedented copolymers - ***Christophe DETREMBLEUR***, *Center for Education and Research on Macromolecules, CESAM Research Unit, University of Liege, Liege - Belgium* |
| 09:45 - 10:00 | Oral Communication - Chair : Armido STUDER |

| TIME | EVENT |
|---|---|
| 09:45 - 10:00 | › A new water-compatible N-heterocyclic Carbenes-Borane: photopolymerization efficiency, relationship between structure and reactivity - ***Berengere AUBRY***, *Institut de Science des Matériaux de Mulhouse (IS2M) - UMR CNRS 7361 – UHA – Université de Strasbourg, Mulhouse - France* |
| 10:00 - 10:15 | Coffee break |
| 10:15 - 10:45 | Invited Lecture - Chair : Derek PRATT |
| 10:15 - 10:45 | › Chemistry in living cells: covalent chemical capture for the discovery of new therapeutic targets - ***Anna MAPP***, *Life Sciences Institute, University of Michigan, Ann Arbor - USA* |
| 10:45 - 11:15 | Invited Lecture - Chair : Derek PRATT |
| 10:45 - 11:15 | › KOtBu as Facilitator in Electron Transfer Reactions - ***John MURPHY***, *Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow - UK* |
| 11:15 - 11:30 | Oral Communication - Chair : Derek PRATT |
| 11:15 - 11:30 | › Antiferromagnetic Ordering Based on Dispersion Forces in Amphiphilic TEMPO Ammonium Salts - ***Jessica EXNER***, *Westfälische Wilhelms University Münster, Organic Chemistry Institute, Münster - Germany* |
| 11:30 - 12:00 | Invited Lecture - Chair : Derek PRATT |
| 11:30 - 12:00 | › Site and Stereoselective Aliphatic C-H Oxidation with Biologically Inspired Catalysts - ***Miquel COSTAS***, *Institut de Quimica Computacional I Catàlisi, Facultat de Ciències, Universitat de Girona, Girona - Spain* |
| 12:00 - 12:15 | Oral Communication - Chair : Derek PRATT |
| 12:00 - 12:15 | › Stereoselectivity of the radical cyclisation of alpha-bromaluminium acetals: New developments and Strategies to access pyrrolidines, pyrrolizidines and tetrahydrothiophene derivatives - ***Fabrice DENES***, *CEISAM, Université de Nantes, Nantes - France* |
| 12:15 - 14:00 | Lunch |
| 14:00 - 14:45 | Plenary Lecture - Chair : Denis CURRAN |
| 14:00 - 14:45 | › Electron Catalysis - ***Armido STUDER***, *Westfälische Wilhelms University Münster, Organic Chemistry Institute, Münster - Germany* |
| 14:45 - 15:15 | Invited Lecture - Chair : Denis CURRAN |
| 14:45 - 15:15 | › Metalloradical Catalysis for Stereoselective Radical Chemistry - ***Peter ZHANG***, *Department of Chemistry, Boston College, Chestnut Hill - USA* |
| 15:15 - 15:45 | Invited Lecture - Chair : Denis CURRAN |
| 15:15 - 15:45 | › Structural basis for semiquinone radical reactivity in bioenergetics enzymes: New insights from EPR spectroscopy, isotopic labeling and DFT calculations - ***Bruno GUIGLIARELLI***, *Bioénergétique et Ingénierie des Protéines, CNRS and Aix-Marseille University, Marseille* |
| 15:45 - 16:00 | Coffee break |
| 16:00 - 16:30 | Invited Lecture - Chair : Michelle COOTE |
| 16:00 - 16:30 | › Successful combination of RAFT and emulsion polymerization: from the formation of amphiphilic block copolymer particles to the synthesis of surfactant-free latexes - ***Muriel LANSALOT***, *Université Claude Bernard Lyon 1, CPE Lyon, UMR 5265, C2P2, Villeurbanne* |
| 16:30 - 16:45 | Oral Communication - Chair : Michelle COOTE |

| TIME | EVENT |
|---|---|
| 16:30 - 16:45 | › Homogeneous aerobic oxidation catalyzed by NHPI dervivatives: Co-solvent or not co-solvent, that is the question - ***Carlo PUNTA***, *Department of Chemistry, Materials, and Chemical Engineering "G. Natta", Politecnico di Milano, Milano* |
| 16:45 - 17:15 | Invited Lecture - Chair : Michelle COOTE |
| 16:45 - 17:15 | › Synthesis of Structurally Controlled Dendritic Hyperbranched Polymers by Radical Polymerization - ***Shigeru YAMAGO***, *Institute for Chemical Research, Kyoto University - Japan* |
| 17:15 - 17:30 | Oral Communication - Chair : Michelle COOTE |
| 17:15 - 17:30 | › Kinetic Studies on the Effect of Metal Ions on Hydrogen Atom Transfer from Alkanols and Alkanediols to the Cumyloxyl Radical - ***Teo MARTIN***, *Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma "Tor Vergata", Roma - Italy* |
| 17:30 - 18:00 | Invited Lecture - Chair : Michelle COOTE |
| 17:30 - 18:00 | › New Transformations in Synthesis Enabled by Organic Photoredox Catalysis - ***David NICEWICZ***, *Department of Chemistry University of North Carolina at Chapel Hill, Chapel Hill - USA* |
| 18:00 - 18:30 | Invited Lecture - Chair : Michelle COOTE |
| 18:00 - 18:30 | › Synthesis of Heterocycles through Electrochemical Dehydrogenative Cyclization and Annualtion Reactions - ***Hai-Chao XU***, *Xiamen University, Xiamen - China* |
| 18:30 - 19:45 | POSTER SESSION |

## Wednesday, June 20, 2018

| TIME | EVENT |
|---|---|
| 08:30 - 09:15 | Plenary Lecture - Chair : Jacques LALEVEE |
| 08:30 - 09:15 | › Photochemically Generated Radicals for Coupling, Functionalization and Polymerization Processes - ***Yusuf YAGCI***, *Istanbul Technical University, Department of Chemistry, Istanbul - Turkey* |
| 09:15 - 09:45 | Invited Lecture - Chair : Jacques LALEVEE |
| 09:15 - 09:45 | › New radical cyclizations mediated by SmI2 - ***David PROCTER***, *School of Chemistry, University of Manchester, Manchester - UK* |
| 09:45 - 10:00 | Oral Communication |
| 09:45 - 10:00 | › Charge-Transfer Complexes as a Linchpin for Transition Metal-Free Solar Light Assisted Synthesis - ***Alex SZPILMAN***, *Ariel University, Ariel - Israel* |
| 10:00 - 10:15 | Coffee break |
| 10:15 - 10:45 | Invited Lecture - Chair : Philippe RENAUD |
| 10:15 - 10:45 | › Recent Advances in Site-Selective C(sp3)-H Functionalization by Radicals - ***Ilhyong RYU***, *Department of Chemistry, Osaka Prefecture University, Osaka - Japan* |
| 10:45 - 11:15 | Invited Lecture - Chair : Philippe RENAUD |
| 10:45 - 11:15 | › Taming CO2 reduction to methane. Fe based molecular complexes as catalysts, radicals (ions) as intermediates - ***Marc ROBERT***, *Université Paris Diderot, Sorbonne Paris Cité, Paris - France* |

| TIME | EVENT |
|---|---|
| 11:15 - 11:30 | Oral Communication - Chair : Philippe RENAUD |
| 11:15 - 11:30 | › Synthesis of alkylsulfonyl cyanides: Tin-free radical carbo- and sulfonyl-cyanation of olefins - ***Vincent PIRENNE***, *Institut des Sciences Moléculaires (ORGA) - Université de Bordeaux - France* |
| 11:30 - 12:00 | Invited Lecture - Chair : Philippe RENAUD |
| 11:30 - 12:00 | › Organic radicals in metallic complexes: cooperative catalysis with redox-active ligands - ***Marine DESAGE-EL MURR***, *OMECA team, Université de Strasbourg, Strasbourg - France* |
| 12:00 - 12:15 | Oral Communication - Chair : Philippe RENAUD |
| 12:00 - 12:15 | › Visible-Light-Mediated Photoredox-Catalyzed N-Arylation of NH-Sulfoximines with Electron-Rich Arenes - ***Alexander WIMMER***, *Departement of Chemistry and Pharmacy, Institute of Organic Chemistry, University of Regensburg, Regensburg - Germany* |
| 12:15 - 14:00 | Lunch |
| 14:00 - 14:30 | Invited Lecture - Chair : Cristina NEVADO |
| 14:00 - 14:30 | › New Macromolecular Designs for Nitroxide-Based MRI Contrast Agents: Enabling Metal-Free Tumor Imaging In Vivo - ***Jeremiah JOHNSON***, *MIT Department of Chemistry, Program in Polymers and Soft Matter, Koch Institute for Integrative Cancer Research, Cambridge - USA* |
| 14:30 - 15:00 | Invited Lecture - Chair : Cristina NEVADO |
| 14:30 - 15:00 | › Functionalization of Olefins with Organic Radicals - ***Shunsuke CHIBA***, *Division of Chemistry and Biological Chemistry, Nanyang Technological University - Singapore* |
| 15:00 - 15:30 | Invited Lecture - Chair : Cristina NEVADO |
| 15:00 - 15:30 | › Boosting NMR sensitivity: free radicals at work - ***Olivier OUARI***, *Institute of Free Radical Chemistry, Aix Marseille University / CNRS, Marseille - France* |
| 15:30 - 16:00 | Invited Lecture - Chair : Cristina NEVADO |
| 15:30 - 16:00 | › Oxidative NHC-organocatalysis: what are the radical intermediates? - ***David MARTIN***, *Département de Chimie Moléculaire de Grenoble, Université Grenoble Alpes, Grenoble - France* |
| 16:00 - 16:15 | Coffee break |
| 16:15 - 16:45 | Invited Lecture - Chair : Emmanuel LACOTE |
| 16:15 - 16:45 | › The redox activity of nitroxides and their derivatives - ***Steven BOTTLE***, *CPME, Science and Engineering Faculty, Queensland University of Technology, (QUT), Brisbane - Australia* |
| 16:45 - 17:30 | Plenary Lecture - Chair : Emmanuel LACOTE |
| 16:45 - 17:30 | › Electrostatic Catalysis of Radical Reactions - ***Michelle COOTE***, *ARC Centre of Excellence for Free-Radical Chemistry and Biotechnology, Research School of Chemistry, Australian National University, Canberra - Australia* |
| 17:30 - 17:45 | **CONCLUSION** |

## Monday, June 18, 2018 / Conference day 1

## MORNING SESSION

**Chair :**

**Didier GIGMES**
**CNRS, Univ. Aix-Marseille, France**

**Plenary lecture :**

**David M HADDLETON**
**University of Warwick, UK**

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# Sulfur Free RAFT Polymerisation and Polymerisation of Acrylamides in Water

David Haddleton *

*Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK*
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Polymer synthesis of vinyl monomers has changed tremendously over the last 30 years with developments in controlled and living radical polymerisation. This enables the use of monomers with many different functional groups without the requirement of protecting group chemistry. The use of protic solvents and even water containing salts and impurities and mixed alcohol/water solvents is now commonplace. This allows for block copolymers and terminally functional polymers with great diversity. We have used this chemistry for a family of bioconjugates for chemical modification of therapeutic proteins and peptides to increase efficacy, to give glycopolymers and sequence controlled polymers allowing for the glycocode to be used with synthetic polymers. The talk will describe how the chemistry has evolved and the applications we have investigated from stabilization of oxytocin to prevent death during childbirth to new viscosity modifiers for automotive and personal care applications.

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# Aspects of Catalysis in Single Electron Steps

A. Gansäuer

*Kekulé-Institut für Organische Chemie und Biochemie der Uniersität Bonn, Gerhard-Domagk-Str. 1*
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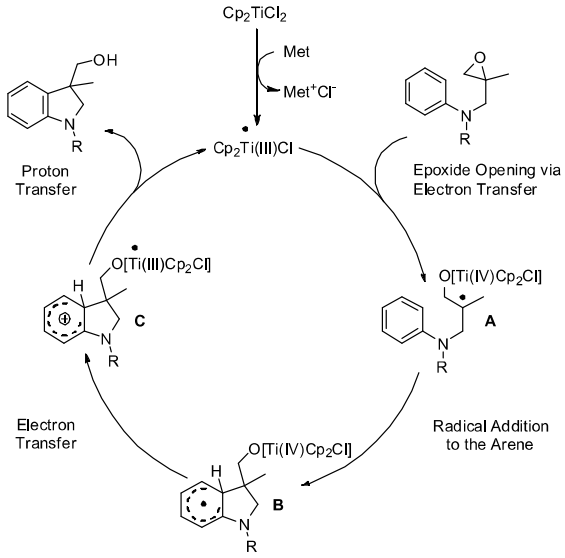
'Catalysis in single electron steps' or 'metalloradical catalysis' are concepts that allow the incorporation of radical transformations in metal catalyzed reactions. Key-aspects of this approach are oxidative additions and reductive eliminations in single electron steps that require an efficient shuttling of the catalyst between neighboring oxidation states. An efficient example of the realization of this concept is the atom-economic arylation of epoxide derived radicals (Scheme 1).




**Scheme 1:** Mechanism of the arylation of epoxide derived radicals.

In this talk, it will be discussed how the properties of the catalyst affect the outcome of the reactions, how the catalyst can be generated efficiently and which other oxidative additions and reductive eliminations can be employed for the design of catalytic reactions.

**References** [1] Gansäuer, A. Hildebrandt, S.; Vogelsang, E; Flowers, R. A. II *Dalton Trans.* **2016**, *45*, 448-452. [2] Gansäuer, A.; Hildebrandt, S.; Michelmann, A.; Dahmen, T.; von Laufenberg, D.; Kube, C.; Fianu, G. D.; Flowers, R. A. II *Angew. Chem. Int. Ed.* **2015**, *54*, 7003-7006. [3] Richrath, R. B.; Olyschläger, T.; Hildebrandt, S.; Enny, D. G.; Fianu, G. D.; Flowers, R. A. II; Gansäuer, A. *Chem. Eur. J.* **2018**, *24*, in press. DOI: 10.1002/chem.201705707 [4] Liedtke, T.; Spannring, P.; Riccardi, L.; Gansäuer, A. *Angew. Chem. Int. Ed.* **2018**, *57*, **DOI:** 10.1002/anie.201800731. [5] Schwarz G. Henriques, D.; Zimmer, K.; Klare, S.; Meyer, A.; Rojo-Wiechel, E.; Bauer, M.; Sure, R.; Grimme, S.; Schiemann, O.; Flowers, R. A. II; Gansäuer, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 7671-7675.

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# Structural and Medium Effects on Hydrogen Atom Transfer Based Functionalization of Aliphatic C–H Bonds

M. Salamone and M. Bietti*

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*Via della Ricerca Scientifica, 1 00133 Rome, Italy*

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Site-selective aliphatic C–H bond functionalization represents an important goal of modern synthetic organic chemistry. By avoiding the prefunctionalization of substrates associated to traditional functional group manipulations and interconversions, the direct functionalization of these bonds represents a transformation of high synthetic potential that can offer advantages both in terms of decreased waste generation and reaction step economy.
Among the methodologies that have been developed for this purpose, those based on hydrogen atom transfer (HAT) from aliphatic C–H bonds to radical and radical-like species play a prominent role and accordingly, the factors that govern reactivity and site-selectivity have been discussed in detail. These include bond strengths, electronic, steric and stereoelectronic effects, conjugation and hyperconjugation, and, with cyclohexane derivatives, torsional effects.[1-3] Medium effects have also emerged as a powerful tool that has been successfully employed to dramatically alter both reactivity and site-selectivity in HAT based C–H functionalization procedures.[4]
Within this framework, we have been interested in the study of HAT reactions from aliphatic C–H bonds, with the main objective of obtaining quantitative kinetic information on the role of structural and medium effects on the reactivity and selectivity patterns. This goal has been mostly achieved through time-resolved kinetic studies on the reactions of the cumyloxyl radical ($PhC(CH_3)_2O$, $CumO^{\bullet}$) with a wide variety of substrates. These studies have provided a consistent set of second order rate constant for HAT ($k_H$), through which useful guidelines for the description of the factors that govern these reactions have been defined. The results of these studies will be discussed, accompanied by recent examples on the application of these concepts to synthetically useful C–H functionalization procedures.

[1] T. Newhouse and P. S. Baran, Angew. Chem. Int. Ed., 50, (2011), 3362-3374.
[2] M. C. White, Science, 335, [2012], 807-809.
[3] M. Salamone and M. Bietti, Acc. Chem. Res., 48, (2015), 2895-2903.
[4] See for example: (a) V. Dantignana, M. Milan, O. Cussó, A. Company, M. Bietti and M. Costas, ACS Cent. Sci. 3, (2017), 1350-1358. (b) D. M. Schultz, F. Lévesque, D. A. DiRocco, M. Reibarkh, Y. Ji, L. A. Joyce, J. F. Dropinski, H. Sheng, B. D. Sherry and I. W. Davies, Angew. Chem. Int. Ed. 56, (2017), 15274-15278. (c) J. B. C. Mack, J. D. Gipson, J. Du Bois and M. S. Sigman, J. Am. Chem. Soc. 139, (2017), 9503-9506. (d) M. Lee and M. S. Sanford, Org. Lett. 19, (2017), 572-575. (e) J. M. Howell, K. B. Feng, J. R. Clark, L. J. Trzepkowski and M. C. White, J. Am. Chem. Soc. 137, (2015), 14590-14593.

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# Mild and metal-free access to tetracyclic indoles and 7-azaindoles through Single Electron Transfer (SET) induced enolate arylation.

Chérif Adouama;[a] Walter D. Guerra[b] Marcelo Puiatti[b] M. Eugenia Buden[b] Silvia Barolo[b] Roberto A. Rossi[b] and Maurice Médebielle[a,*]

[a] *Univ Lyon, Université Lyon 1, CNRS, INSA, CPE-Lyon, ICBMS, UMR 5246, France.)*
[b] *Instituto de Investigaciones en Físico Quimica de Cordoba (INFIQC), Departamento de Química Orgánica, Facultad de Ciencias Quimicas, Universidad Nacional de Córdoba, Argentina*
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Indoles (and 7-azaindoles) are important heterocycles found in many natural products and clinical drug candidates [1]. Tetracyclic indole (carbo- or heterocycles joined at the indole 1,2 or 2,3 or 3,4-positions) represent a common structural motif found in a variety of alkaloids with known biological activities [2]. A widely used strategy to prepare these tetracyclic structures is based on palladium catalyzed cross coupling reactions [3].
In this work, we proposed an electron-transfer mild strategy to access to these tetracyclic skeletons that does not require any metal catalysts and operating under mild conditions (Figure). An unexpected fast, sustainable and efficient methodology had been discovered.

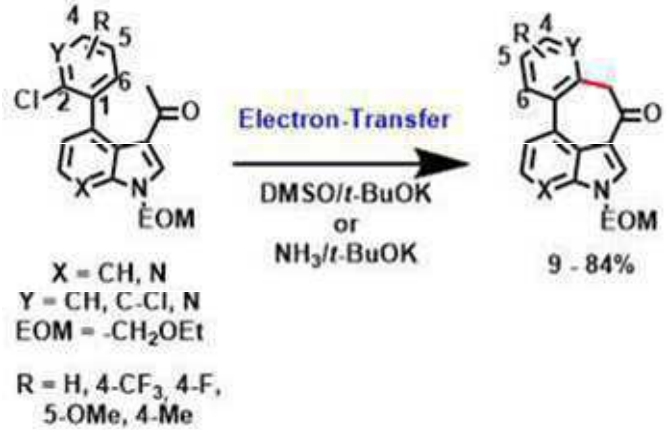


Figure. Single electron transfer approach towards tetracyclic indoles and 7-aza indoles

During this presentation we will present our latest results culminating in the preparation of a series of these tetracyclic skeletons as well as further insights into the mechanism of this reaction through experimental and density functional theory (DFT) studies.

**References.** [1] a) T.P. Singh et O.M. Singh, Mini-Rev. Med. Chem., 18 (2018) 9-25. b) A.A. Farahat, M.A. Ismail, A. Kumar, T. Wenzler, R. Brun, A. Paul, W. D. Wilson and D.W. Boykin, Eur. J. Med. Chem., 143 (2018) 1590-1596. [2] a) M. Ding, F. He, M.A. Poss, K.L. Rigat, Y. Wang, S.B. Roberts, D. Qiu, R.A. Fridell, M. Gao and R.G. Gentles, Org. Biomol. Chem., 9 (2011) 6654-6662. b) R.J. Capon, F. Rooney, L.M. Murray, E. Collins, A.T.R. Sim, J.A.P. Rostas, M.S. Butler and A.R. Carroll, J. Nat. Prod., 61 (1998) 660-662. [3] a) J.A. Mackay, R.L. Bishop and V. H. Rawal, Org. Lett., 7 (2005) 3421-3424. b) G. D. Cuny, M. Hellal and S. Singh, J. Org. Chem., 77 (2012) 4123-4130. c) L. Joucla, A. Putey and B. Joseph, Tetrahedron Lett., 46 (2005) 8177-8179.

# New Horizons for Nitroxide Mediated Polymerization

Nicholas. Ballard,[a] Alexadre Simula,[a] Miren Aguirre,[a] Jose R. Leiza,[a] Steven van Es[a,b] and José M. Asua[a]*

[a]POLYMAT University of the Basque Country UPV/EHU, 20018, Donostia/San Sebastián, Spain.

[b]Dispoltec BV, PO Box 331, 6160 AH Geleen, The Netherlands.

Recently considered as the top achievement of the polymer science over the last 50 years[1], reversible-deactivation radical polymerization (RDRP) has opened the possibility of synthesizing in a controlled way a wide range of polymer architectures from a broad set of monomers. However, the current RDRP technologies (NMP, RAFT, ATRP) have suffered from a series of drawbacks (inability to control methacrylates (NMP), undesired coloring (ATRP) and odor (RAFT) and high cost of all control agents) that are precluding its commercial implementation[2]. Cost is critical when aiming at low molecular weight polymers because each polymer chain contains a molecule of control agent.

On the other hand, control of temperature and therefore the safety of large scale synthesis requires the use of semibatch reactors working under starved conditions. However, this presents a major problem in RDRP because the low monomer concentration leads to a higher ratio termination over propagation than a similar reaction conducted in batch, namely to a poorer control.

This work reports on a new family of alkoxyamines that expands the limits of the NMP because they are produced by means of an inexpensive and easily scalable process and are capable of controlling the polymerization of methacrylates[3] at moderate temperatures, because disproportionation reactions are minimized. The alkoxyamines are also able to control the polymerization of styrene[4] and up to a certain conversion that of butyl acrylate.

It is also shown that these alkoxyamines can control the challenging semibatch processes achieving at the same time high conversions, good MWD control and good retention of the chain ends, that even under these difficult conditions, allows the synthesis of poly(MMA) based block copolymers with a second block of either benzyl methacrylate, butyl acrylate or styrene[5]. In addition, it is shown that these alkoxyamines can be used in both miniemulsion and suspension polymerization[6]. In miniemulsion high conversions, high solids contents (up to 50 wt%), molecular weights up to 60,000 g/mol and the formation of block copolymers was achieved. In addition, the dispersions presented very good colloidal stability, which is remarkable because poor colloidal stability has been a major challenge in the development of all types of controlled radical polymerizations in dispersed media. In suspension high conversions, high solids contents (up to 40 wt%), molecular weights up to 100,000 g/mol and the formation of block copolymers can be achieved. In addition, unlike conventional free radical polymerization, the presence of nitroxide in the aqueous phase prevents the formation of polymer particles by emulsion polymerization which causes problems in the recovery of the suspension polymer and the recycling of the aqueous phase. Here, it is demonstrated that the absence of emulsion particles allows recycling of the aqueous phase for subsequent reactions, further enhancing the potential for the use of NMP on a large scale in aqueous media. It is hoped that this work may facilitate the industrialization of RDRP.

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**EuCHeMS conference on Organic Free Radicals (ECOFR 2018)**
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# Regenerable Preventive and Peroxyl Radical Trapping Ebselenamine Antoxidants

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Vitamin E, the most important lipid-soluble antioxidant in humans, offers protection against lipid peroxidation.[1] As α-tocopherol is regenerable and highly reactive it has been used as benchmark for novel synthetic radical-trapping antioxidants. Newly, developed syntetic compounds with introduction of selenium and tellurium atoms ortho to the phenolic[2] and aromatic amine[3] compounds can outperform α-tocopherol when it comes to its reactivity. In an effort to improve the radical trapping antioxidant activity of vitamin E as well as preventive activity of glutathione peroxidase (GPx),[4] novel ebselenamines have been prepared. Their radical-trapping antioxidative properties have been evaluated in a water/chlorobenzene two-phase lipid membrane-like model system. These novel compounds not only quench the harmful peroxyl radicals more efficiently than α-tocopherol but also turned out to be readily regenerable by aqueous reducing agent. These antioxidants also catalysed the reduction of hydrogen peroxide that mimicking the activity of the GPx enzymes. The best antioxidant quenched lipidperoxyl radicals much more efficiently and the inhibition time was six-fold higher than α-tocopherol by the aqueous phase L-ascorbic acid (AscOH). These antioxidants catalysed the reduction of hydrogen peroxide more than twice than Ebselen used a benchmark in this study. An unconventional mechanism has been proposed for the ebselenamine (**1**) involving O-atom transfer from peroxyl radical (ROO˙) to the Se atom (Figure), followed by H-atom transfer. The reduction of selenoxide A to selenide B will take place at the interface aqueous AscOH by dihydroascorbate (DHA) formation. The regeneration of antioxidant **1** brought about by the presence of AscOH to allow for a catalytic mode of action. We think that it would, therefore, seems worth-while to use such antioxidants in future treatment of several diseases where the natural antioxidant defenses are decreased (cancer, cardiovascular diseases, neurodegenerative diseases, Alzhiemer's and Parkinson's diseases etc).

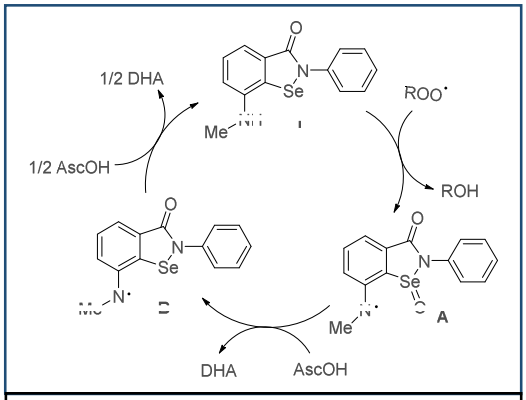


*Figure. Proposed mechanism for the radical-trapping antioxidant capacity of **1***

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## Monday, June 18, 2018 / Conference day 1

## AFTERNOON SESSION

**Chairs :**

**Maurice MEDEBIELLE**
**CNRS, Université de Lyon, France**
**Emmanuel LACOTE**
**CNRS, Université de Lyon, France**

**Plenary lecture :**

**Derek PRATT**
**University of Ottawa, Canada**

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# Lipid Peroxidation, its Role in Cell Death and Slowing it with Small Molecules

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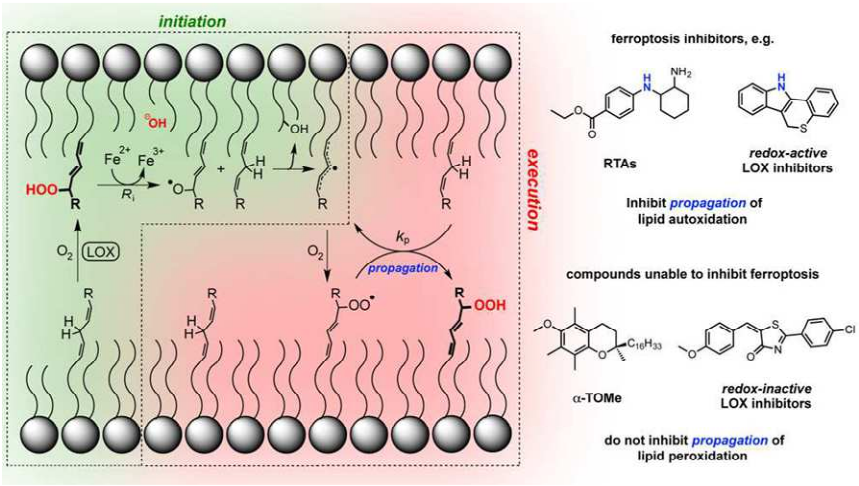
Lipid peroxidation, the free radical mediated autoxidation of lipids, has long been implicated in a wide variety of degenerative diseases, but only recently has it been unambiguously associated with a specific mechanism of cell death: ferroptosis.[1] Ferroptotic cell death can be cleanly initiated by pharmacological inhibition or genetic deletion of glutathione peroxidase 4, the enzyme responsible for the detoxification of (phospho)lipid hydroperoxides. Various types of compounds have been demonstrated to rescue cells from ferroptosis, including ferrostatins and liproxstatins, lipoxygenase inhibitors, mitochondria-targeted nitroxides and deuterated polyunsaturated fatty acids. The cytoprotective properties of these compounds have prompted various confounding hypotheses regarding the mechanism of ferroptosis.[2]

Enabled by our understanding of the mechanisms and kinetics of radical reactions relating to hydrocarbon autoxidation and its inhibition, and methods that we have developed to study them, we have worked to clarify the steps involved in the initiation and execution of ferroptosis. In doing so, we have elucidated the mechanism of cytoprotection of ferrostatins/liproxstatins,[3,4] resolved the debate surrounding the role of lipoxygenases in cell death,[5] advanced a reasonable mechanism for nitroxide-based cytoprotectants,[6] and attempted to clarify the role of mitochondria in ferroptosis. The radical chemistry that underlies these developments will be discussed.

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# Air-stable Neutral Radicals with Spin-delocalized Structure: Full-cell Battery Application

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Trioxotriangulene (**TOT**) is designed on the basis of phenalenyl radical and is an air-stable neutral radical possessing a 25π electronic system and a delocalizing electronic-spin on the whole molecular framework (chemical structure, see: Figure) [1]. These π-electronic extension and delocalizing electronic-spin nature of **TOT** cause strong intermolecular π-π and SOMO-SOMO interactions and thus formation of a one-dimensional columnar structure named "π-stacked radical polymer" [2]. These electronic and 1D structural features of neutral radical crystal realized *n*-type FET, near-infrared photo-absorption [3], and a high electrical conductivity (~$10^{-3}$ S $cm^{-1}$ at room temperature) as single component purely organic materials. Furthermore, the 1D columnar structure of **TOT** tolerates an excess electron and thus mixed valence salts formally comprising of neutral radical and its corresponding anion species are generally synthesized and isolated. Encouraged by these electronic features as well as calculated narrow SOMO–LUMO gap (~0.8 eV) with degenerated LUMOs, we developed high performance Li-ion secondary battery based on **TOT** neutral radicals as electrode-active materials utilized by their four-stage one-electron redox ability [1,4]. In the presentation, we disclose recent studies on full-cell battery application (Figure) realizing ultra-high speed of charge-discharge, conductive-additive-free thin-film, and all-solid-state with bipolar/tandem structures.

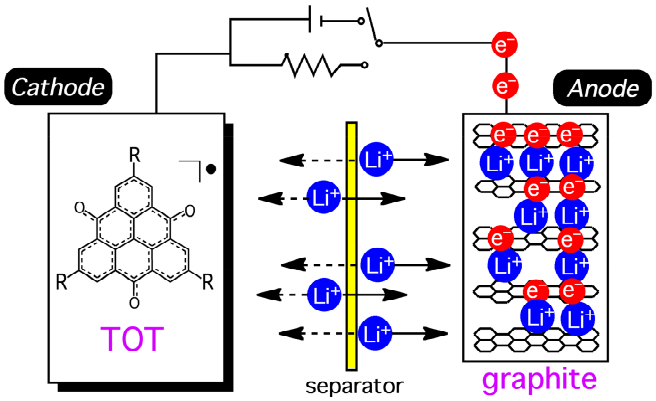


Figure Schematic representation of full-cell battery based on **TOT**.

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# Do Radical Enzymes Control the Reactivity of Reactive Intermediates using the Quantum Coulombic Effect?

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The ability of radical enzymes to exhibit extraordinary control over the radicals generated in their active sites remains a mystery. In this presentation I will discuss a potential strategy adopted by B12-dependent enzymes to manipulate the reactivity of their radical intermediate (5'-adenosyl radical) contained in their active site. Quantum mechanical calculations suggest that these enzymes utilize the quantum Coulombic effect (QCE), which causes the radical to acquire an electronic structure that contradicts the Aufbau Principle. This effect causes singly-occupied molecular orbital (SOMO) of the radical to be well below the highest-occupied molecular orbital (HOMO), which renders the radical less reactive toward off-target substrates. The dynamic nature of the enzyme and its structure is expected to be such that the reactivity of the radical is not restored until it is moved into close proximity of the target substrate. This effect may be a general phenomenon employed by all radical enzymes.

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# Photocontrolled Cationic Polymerizations of Vinyl Ethers

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Photoinitiated cationic polymerizations are widely used in industrial processes. Importantly, obtaining photocontrol over chain growth would expand the utility of these methods and allow the synthesis of novel complex architectures. This presentation will detail the development of a cationic polymerization regulated by visible light.[1],[2] This polymerization proceeds under mild conditions and allows for the synthesis of various poly(vinyl ether)s with good control over molecular weight and dispersity. Additionally, combining this method with photocontrolled radical polymerizations enables switching of polymerization mechanism and, hence, monomer selectivity in situ with light to give control over polymer sequence and structure (Figure 1).[3]

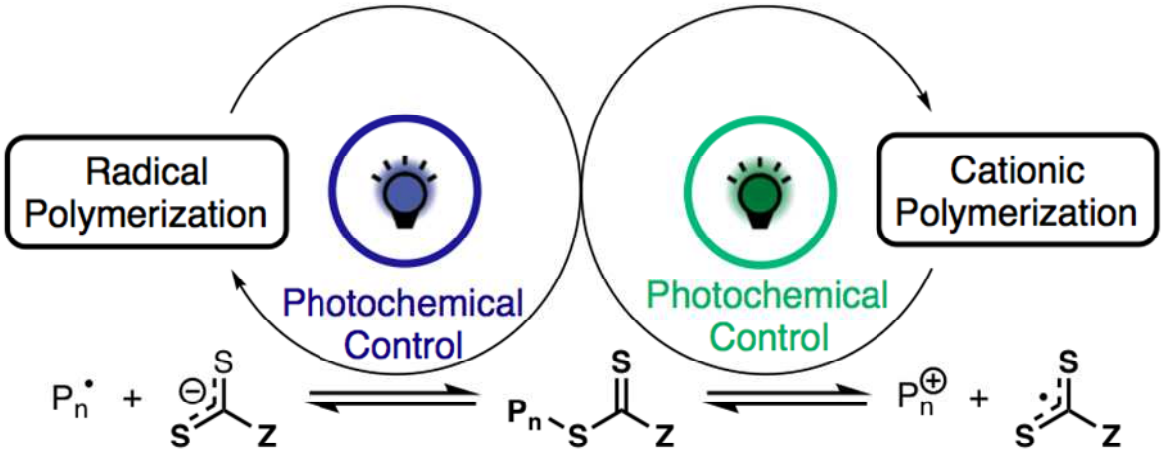


**Figure 1.** Switching between cationic and radical polymerization mechanisms in situ with light.

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# Thiol Catalyzed Radical Deuteration with $D_2O$: Mechanistic Insights

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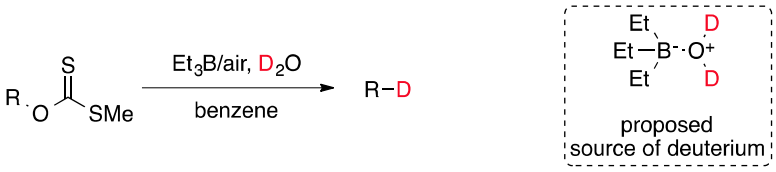
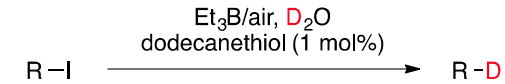
Recently, there has been a growing interest in the pharmaceutical industries to incorporate deuterium atomes in drugs candidates to improve their metabolism and pharmacokinetic properties. A significant number of deuterated drug candidates (heavy drugs) have been synthesized and forwarded to clinical trials[1], such as Deutetrabenazine (Austedo®, TEVA pharmaceuticals) which is the first deuterated drug on the market. However, preparation of organic compounds selectively labelled with deuterium atoms remains a challenging synthetic problem. Radical deuteration of alkyl halides is an efficient approach under mild conditions to perform this task. It is usually run using organotin deuterides[2] but this method has three major drawbacks: organotin deuterides are expensive, toxic[3] and lead to product contamination. Wood and co-workers reported a transition metal free method of deoxygenation/reduction employing $D_2O$ as source of deuterium[4]. The mechanism of the reaction was however puzzling.




Scheme 1: Deuteration of alkyl xanthates from Wood and co-workers

We report here a demystification of this process. We proved that the deoxygenation under Wood's conditions is in fact catalyzed by a tiny amount of thiol. We took then advantage of these findings to develop a method to deuterate alkyl iodides (Scheme 2)[5] using deuterated water as source of deuterium atom. The mechanism of this dehalogentation process as well as the scope and limitation of the reaction will be discussed.




Scheme 2: Deuteration of alkyl iodides catalyzed by thiols

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# Redox catalysis strategies for complex molecules

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Single electron transfer (SET) processes – frequently utilized by Nature to activate its substrates – significantly enhance the reactivity of organic molecules. These SET reactions provide facile access neutral radicals – reactive intermediates that are particularly attractive for use in complex settings as a consequence of their general lack of reactivity with polar functional groups. The use of redox catalysis (e.g. photocatalysis and electrocatalysis) furthers the benefits of SET processes enabling the reduction of stoichiometric waste byproducts and toxic or hazardous reagents compared with classical approaches. The development of methodologies involving organic free radicals underpinned on practicality and mechanistic understanding with demonstrated applications in complex molecule synthesis (pharmaceuticals and natural products) exploiting batch and flow reactor designs will be presented in this talk.

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# The Surprising Acidity of Radicals: Generality, Range and Applications

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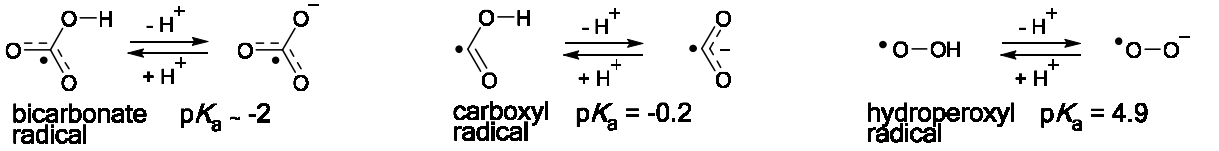
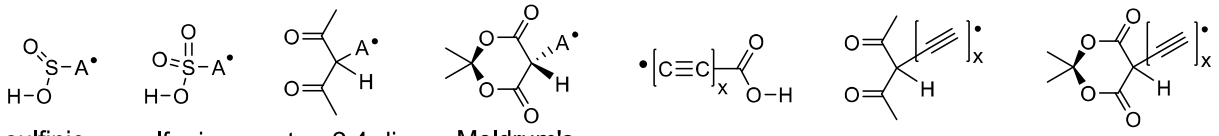
The bicarbonate buffer system maintains the p*H* of biological fluids within the range essential for enzymes to function. Several enzymes oxidize bicarbonate to the corresponding bicarbonate radical [HOC(=O)O•]; the fate of which is largely unknown. Oxime carbonates [ArC(R)=N-OC(=O)OR] readily release alkyl carbonate radicals [RO(C=O)O•] so those with R = H seemed potential precursors for the bicarbonate radical itself. This is still a work in progress, but it drew attention to the surprisingly high acidity of bicarbonate radicals. Other radicals were also found to be much more acidic than models with the unpaired electron replaced by H-atoms [1]:




It appeared that a radical centre could enhance the acidity of certain neighboring acid groups. This phenomenon had been noted in the literature but was little understood or exploited [2,3,4].

A DFT computational method of estimating $pK_a$s was developed and applied to a set of radicals designed to probe the phenomenon of Radical-Enhanced Deprotonation (RED-shift) and its underlying causes. This confirmed the intensified acidity of the above three radicals. Furthermore, the carboxy-ethynyl radical ($HO_2CC{\equiv}C^{\bullet}$) was identified as having enhanced acidity. The underlying cause was found to be extensive charge distribution away from the anionic O-atoms of the conjugate radical anions, coupled with spin density displaced towards these O-atoms [5].




The p$K_a$s for sulfinic, sulfonic, pentan-2,4-dione and Meldrum's acid species with adjacent radicals centred on C-, N- and O-atoms were computed. All series showed significant RED-shifts that increased with the electronegativity of the radical centre (A). The hugely negative p$K_a$ obtained for a Meldrum's acid with an alkoxyl radical substituent showed it to belong to the superacid class. Ethyne spacers, between the radical and H-donor centres, transmitted the effect extremely efficiently. Several families of potentially persistent radicals with enhanced acidity were identified [6].

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# Tailored microstructured hyperpolarizing matrices for optimal magnetic resonance imaging

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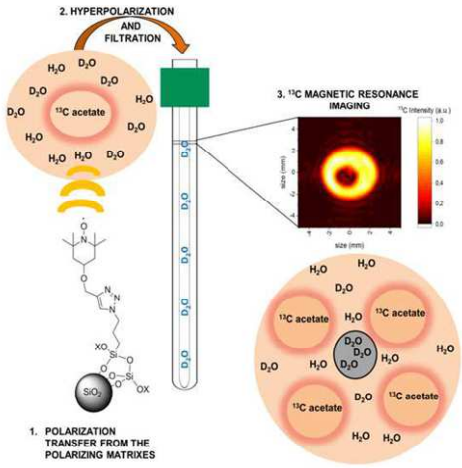
MRI is ubiquitous in our daily life with applications ranging from chemical engineering to *in vivo* MRI of tissues/target organs. However, NMR (or MRI) suffers from an intrinsic low sensitivity. This drawback can be circumvented by Dynamic Nuclear Polarization (DNP) which allows dramatic NMR signal enhancement *via* microwave-induced cross-polarization from highly thermally polarized electron spins to nuclear spins. Using DNP, dissolution DNP (d-DNP) set-ups have been developed to polarize a frozen sample at 1-4K, followed by a rapid dissolution of the sample to liquid state, yielding a hyperpolarized solution that is then transferred to a NMR spectrometer (or MRI scanner).[1] Unfortunately, as soon as the DNP sample becomes liquid, nuclear spin relaxation irreversibly tends to bring the nuclear polarization back to its thermal equilibrium very rapidly. This means that transfer and injection for *in vivo* applications have to be performed in a minimal time. There is also a need for DNP sample formulations that would avoid organic radicals and glassy agents for biocompatibility reasons. In this context, we have developed different silica-based materials containing TEMPO radicals, as polarization matrices for d-DNP applications.[2] We demonstrated that the physical features of such matrices have a dramatic impact on the polarization levels. After optimization, the resulting solids exhibit unprecedented performances in *d*-DNP and can be rapidly filtered to provide pure hyperpolarized solutions (free of radicals and without the need of glass-forming agents). The hyperpolarized solutions can be expelled from the porous solids, filtered and rapidly transferred a MRI system as demonstrated by the fast acquisition of a phantom image of a tube containing a $D_2O$-filled capillary and a hyperpolarized solution of sodium acetate. These results show that these solids are very promising as polarizing matrices for *in vivo* MRI applications.[3]




…. **Fig. 1** A phantom image by d-DNP using a solid matrix

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[3] Publication submitted

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# The neglected reductive catalytic cycle of nitroxides with hydroperoxyl radicals.

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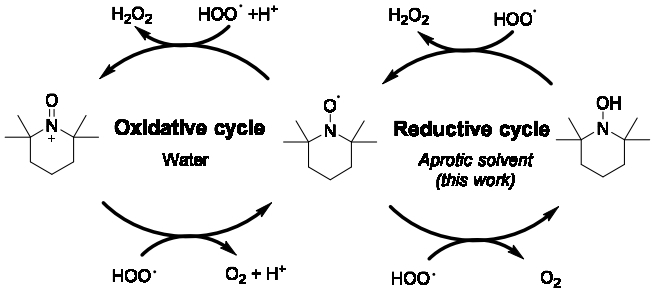
Nitroxides like TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) are reported to act as chemopreventive agents in a variety of oxidative-stress related conditions.[1] Their reaction with alkylperoxyl radicals ROO• requires an acid as the proton source.[2,3] Hence, this mechanism cannot be invoked in the many cases in which nitroxides reduce the extent of autoxidation in lipophilic environments such as the interior of membranes. Superoxide (HOO•/$O_2^{-}$) is the most abundant oxygen-centred radical in biological systems, being formed during mitochondrial respiratory chain, or by ROO• to HOO• chain-transfer during lipid peroxidation, in the presence of biologically relevant compounds like cyclohexadienes or 1,4-hydroquinones (e.g. ubiquinol), aliphatic amines or alcohols.[4] We demonstrate the occurrence of extremely fast reductive reaction TEMPO + HOO• →TEMPOH + $O_2$, and reoxidation TEMPOH + HOO• →TEMPO + $H_2O_2$. The two reactions compose a very efficient novel catalytic cycle that does not involve the formation of oxoammonium ions, being alternative to the cycle established in protic media (Scheme 1).[5] Such neglected cycle can provide dramatic protection from lipid peroxidation, outperforming Nature's best lipid soluble antioxidants like α-tocopherol.[5] The relevance and applications of this chemistry are discussed.




**Scheme 1.** Catalytic quenching of HOO• by TEMPO.

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## Tuesday, June 19, 2018/ Conference day 2

## MORNING SESSION

**Chairs :**

**Armido STUDER**
**University of Munster, Germany**
**Derek PRATT**
**University of Ottawa, Canada**

**Plenary lecture :**

**Cristina NEVADO**
**University of Zurich, Switzerland**

**EuCHeMS conference on Organic Free Radicals (ECOFR 2018)**
June 17-20, 2018 - Marseille (France)

# Harvesting Radicals to Functionalize π-Systems

A. García-Domínguez, Z. Li, W. Shu, X. Wei and C. Nevado*

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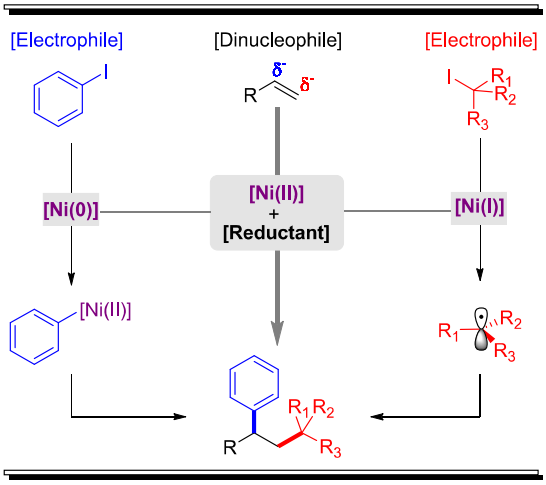
Addition of two functionalities across π-systems has been traditionally carried out using formally a nucleophilic and an electrophilic reaction partner[1]. The multiple bond is thus conceptually considered as a (+/-)-dipole, which justifies the extensive use of electronically biased substrates.[2] Procedures that can be applied to a wide range of substrates, regardless of their electronic bias, are still in high demand. Here, we will present examples of three-component difunctionalization reactions of alkenes and alkynes using readily available partners.[3]

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[2] For our previous contributions see: a) Z. Li, A. García-Domínguez, C. Nevado, *Angew. Chem. Int. Ed.* **2016,** *55*, 6938; b) Z. Li, A. García-Domínguez, C. Nevado, *J. Am. Chem. Soc.* **2015**, *137*, 11610.
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**EuCHeMS conference on Organic Free Radicals (ECOFR 2018)**
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# Organocobalt(III) based on $Co(acac)_2$ as a source of alkyl radicals under mild conditions: application to the precision synthesis of unprecedented copolymers

C. Detrembleur*,[a] D. Cordella,[a] J. Demarteau,[a] A. Kermagoret,[a,b] N. Patil,[a] P. Scholten,[a] C. Jerome,[a] A. Debuigne[a]

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[b]*current affiliation : Aix-Marseille Université , CNRS, Institut de Chimie Radicalaire, 13397 Marseille Cedex 20, France*

Organocobalt(III) complexes ($R\text{-}Co^{III}$), defined as cobalt complexes featuring a carbon-cobalt bond, produce radicals by homolytic cleavage of their C-Co bond. By modifying the type of ligand, the structure of the R group, the nature of the solvent or the mode of C-Co bond activation (by heating or by photoirradiation), the C-Co splitting can be easily tuned and consequently the reactivity of the entire system as well. $R\text{-}Co^{III}$ are therefore key compounds in cutting edge developments in the field of radical reactions. These last years, $R\text{-}Co^{III}$ received an incredible interest in polymer chemistry by enabling the production of unprecedented functional polymers by the control of the formation of radicals and of the growth of the polymer chains. More precisely, the controlled polymerization technique, named cobalt-mediated radical polymerization (CMRP), is based on the temporary deactivation of the propagating radical chains by the cobalt complex. The strength of the carbon-metal bond at the polymer chain-end is dictating the reactivity of the system. One of the most efficient CMRP process involves the commercially available $Co(acac)_2$. The facile modulation of the C-Co bond strength, and thus of its homolytic splitting, has enabled to control the polymerization of monomers of opposite reactivity, such as vinyl esters and acrylates, and to synthesize novel well-defined (co)polymers under very mild experimental conditions. The process is also compatible to aqueous media and to a large diversity of functional groups.[1-2]

In this talk, we will discuss some recent breakthroughs in the field that illustrate the utility of the weak C-Co bond for the controlled synthesis of unique functional macromolecules. We will first describe how these $R\text{-}Co(acac)_2$ can be produced by radical pathways.[3-4] Then, we will report how they can be implemented for the precision synthesis of unprecedented ethylene-based copolymers of tunable ethylene content,[5] and of novel perfluorinated copolymers,[6] all copolymers being produced under unusual mild experimental conditions. Additionally, we will demonstrate that this process is also highly active for the preparation of poly(ionic liquid)s[7-9] that have huge potential for battery applications[7,9,10] or advanced coatings.[9]

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**EuCHeMS conference on Organic Free Radicals (ECOFR 2018)**
June 17-20, 2018 - Marseille (France)

# A new water-compatible N-heterocyclic Carbenes-Borane: photopolymerization efficiency, relationship between structure and reactivity

**Bérengère Aubry**[a,b], **Daniel Subervie**[c,d], **Muriel Lansalot**[d], **Elodie Bourgeat-Lami**[d], **Bernadette Graff**[a,b], **Fabrice Morlet-Savary**[a,b], **Céline Dietlin**[a,b], **Jean-Pierre Fouassier**[a,b], **Emmanuel Lacôte**[c,d], **Jacques Lalevée**[a,b].

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N-heterocyclic carbene-boranes (NHC-Borane) were recently described as efficient co-initiators for the visible light photopolymerization of methacrylate resin in presence of both air and water. In this work, a new NHC-Borane: 2,4-dimethyl-1,2,4,5-tetrazol-3-ylidene borane – more watersoluble – has been synthesized and its efficiency in the three-component system (1. dye: Acridine Orange, 2 and 3. Co-initiators: disulfide and NHC-Boranes) for the methacrylate polymerization under visible light (LED@405 nm) has been studied. In fluid resin (0.053 Pa.s), this new photoinitiating system (PIS) gives better results to the previous studied (Figure 1.A). More important, this system is competitive with a well-know type II system : Camphorquinone/DMABN for methacrylate fluid resin polymerization. Next, hydrogels have been successfully synthesized under visible light thanks to NHC-Boranes systems (Figure 2). The excellent ability of the NHC-Boranes and especially the new one, to be used as photopolymerization co-initiators has been analyzed by Laser Flash Photolysis (LFP). Molecular calculations have well-explained the rate constants for elementary reactions of the three boranes (Figure 1.B) and its derived boryl radicals obtained by LFP. Photoinitiating systems based on NHC-Boranes are promising systems to overcome oxygen inhibition and for reactions in water.

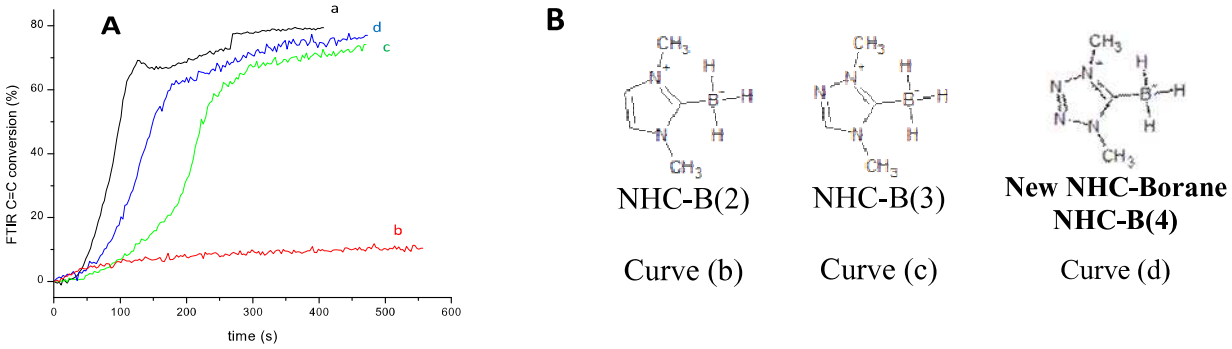


**Figure 1.A**: Photopolymerization profiles of a fluid methacrylate resin (conversion of the methacrylate function as function of time) under air, upon LED @405 nm, 1.4 mm thick samples for four photoinitiating systems: (a) CQ/DMABN (1/2 w/wt%), (b) AO/1/**NHCB(2)** (0.05/2/2 w/w/wt%), (c) AO/1/**NHCB(3)** (0.05/2/2 w/w/wt%), (d) AO/1/**NHCB(4)** (0.05/2/2 w/w/wt%) **B**. NHC-Boranes chemical structures

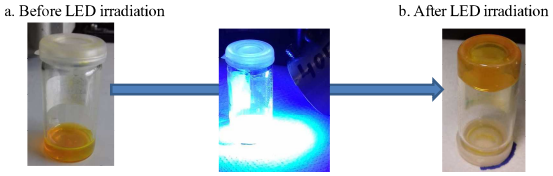


**Figure 2**: Hydrogel formation: polymerization of HEMA in water under LED@405 nm with NHC-Borane PIS.

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# Chemistry in living cells: covalent chemical capture for the discovery of new therapeutic targets

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[b]*Program in Chemical Biology, University of Michigan, Ann Arbor, MI USA*
**amapp@umich.edu*

It is abundantly clear that new targets are needed for drug discovery.[1] Misregulated transcription factors play prominent roles in human disease, but their dynamic protein-protein interaction network has long made the goal of transcription-targeted therapeutics impractical. The greatest challenge is that the complexes formed between transcriptional activators and coactivator complexes are structurally dynamic and transient. Thus the network of activator protein-protein interactions that underpin transcription initiation is poorly defined, particularly in the cellular context.[2] Here we demonstrate that the light-induced formation of radicals in a site-specific fashion in living cells allows for the discovery of new therapuetic targets. Through the coupling of *in vivo* covalent chemical capture and shotgun LC-MS (MudPIT) analysis, we discover that the prototypical activators Gal4 and VP16 directly target the Snf1 (AMPK) kinase complex via direct interactions with the core enzymatic subunit Snf1 and the exchangeable subunit Gal83. The covalent chemical capture-mass spectrometric analysis combination used here will be a powerful tool in discovering direct protein-protein interactions within other essential cellular networks that use similarly dynamic complexes. Additionally, we find that we can further enhance the covalente chemical capture yield through the incorporation of eléctron-withdrawing groups into unnatural amino acids.

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# KO*t*Bu as Facilitator in Electron Transfer Reactions

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**John.Murphy@strath.ac.uk*

Early reports of electron transfer by KO*t*Bu were made by Ashby *et al.*[1,2] However, it is really in more recent times that many papers have proposed this type of electron transfer as part of a reaction pathway. In 2014, we reported our examination[3] of a number of published claims and concluded that such cases are likely to be very rare, because the published oxidation potential of 0.10 V vs SCE[4] indicates that KO*t*Bu would be a very poor electron donor.
On the other hand, KO*t*Bu is very effective at facilitating indirect electron transfer through formation of electron donors with many types of organic molecules. But, can it do more? This presentation will describe new findings from our many-pronged search for ways in which KO*t*Bu can facilitate electron transfer reactions by either direct or indirect means.

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# Antiferromagnetic Ordering Based on Dispersion Forces in Amphiphilic TEMPO Ammonium Salts

J. Exner;[a] O. Janka;[b] C. Doerenkamp;[c] C. G. Daniliuc;[a] R. Pöttgen;[b,*] Eckert;[c,*] and A. Studer[a,*]

[a] *Institute of Organic Chemistry, Westfälische Wilhelms-University Münster, Germany*
[b] *Institute of Inorganic and Analytical Chemistry, Westfälische Wilhelms-Universität Münster, Germany*
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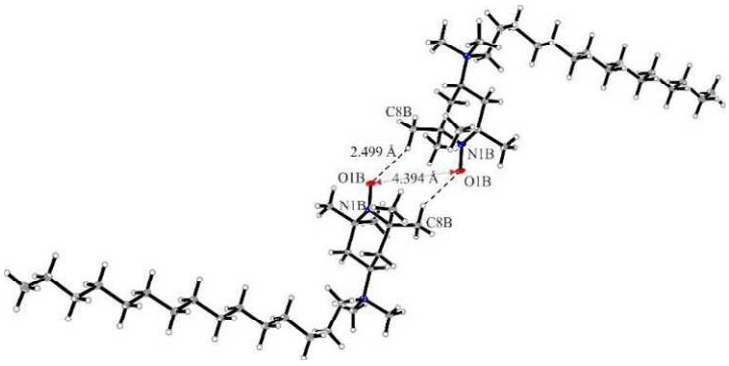
Due to their use as spin labels, spin traps and electronic, optical or magnetic materials, organic radicals are attracting much attention in the field of materials science.[1] These magnetic effects, i. e. antiferromagnetic or ferromagnetic, in fully organic materials originate and are highly dependent on the cooperative interaction between the unpaired electrons in the solid state and are therefore difficult to control.[2] An understanding of the relationship between the packing of the molecules in the crystal structure, tuned by hydrogen bond interactions, π-π stacking, dispersion forces or other interactions, and the resulting magnetic properties is of fundamental interest.

As a model compound class an amphiphilic system was designed, where the TEMPO radical is attached to a 4-dimethyl amino group bound to a linear alkyl chain with n C-atoms, forming a radical ammonium salt R-DMAT-n iodide ($R = C_nH_{2n+1}$; DMAT = dimethyl-amino-TEMPO). Such compounds have been studied before as spin probes and in fluorescence quenching studies.[3,4]




However, no investigations of their magnetic properties have been reported, except for R-DMAT-1, which shows antiferromagnetic ordering at low temperature ($T_N \sim 12$ K).[5] We will present the first systematic magnetic study of these radical cation salts, revealing that (1) the intermolecular dispersion interactions in these systems are indeed strong enough to induce cooperative magnetic behavior, and (2) the antiferromagnetic coupling strength shows a characteristic chain length dependence which can be additionally modified by the nature of the counter anion.

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# Site and Stereoselective Aliphatic C-H Oxidation with Biologically Inspired Catalysts.

Michela Milan,[a] Valeria Dantignana,[a] Anna Company,[a] Giorgio Olivo[a] Massimo Bietti[b,*] Miquel Costas,[a,*]

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Aliphatic C-H oxidation is a very powerful approach to functionalize hydrocarbon skeletons. The main challenge of this reaction is the control of site-selectivity, given the multiple C-H bonds present in any organic molecule. Natural enzymes elegantly solve this problem through the interplay of different interactions that geometrically orient the substrate to expose specific C-H bonds to the active unit, thus overriding intrinsic reactivity patterns.[1] A high valent metal-oxo species, generated via controlled lysis of the O-O bond of a peroxide is the common C-H cleaving agent, and the reaction proceeds via an initial hydrogen atom transfer reaction.[2] Coordination complexes based on iron and manganese can reproduce fundamental aspects of this chemistry; upon reaction with hydrogen peroxide, high valent metal-oxo species are formed that can engage in C-H oxidation reaction proceeding via short lived radical intermediates.[3] Control of the first and the second coordination sphere of the catalysts can be used to shape the place where the metal-oxo reactive center attacks the C-H bond, and this translates into site and stereoselective C-H oxidation reactions. Strategies pursued for the design of biologically inspired catalysts based on the manipulation of electronic and steric properties of the catalysts, and incorporation of substrate recognizing units via supramolecular effects will be discussed.[4] Insights into the nature of the C-H cleaving species will be provided.[5]

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# Stereoselectivity of the radical cyclisation of alpha-bromaluminium acetals: New developments and Strategies to access pyrrolidines, pyrrolizidines and tetrahydrothiophene derivatives

J.-C. Rouaud;[a] R. Bénéteau;[a] L. Arzel;[a] A. Boussonnière;[a] J. Lebreton[a] and F. Dénès*

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γ-Lactones represent an important class of compounds that are present in the skeleton of a large number of natural compounds. We have developed an efficient route to γ-lactols and methylene γ-lactols based upon an original Ueno-Stork-type radical cyclisation[1,2] using thermally labile α-bromoaluminium acetals as the radical precursors.[3] The resulting cyclic aluminium acetals proved to be suitable substrates for an oxidation reaction in the presence of aldehydes to give the corresponding γ-lactones[4] or γ-butenolides[5] and this methodology was successfully applied to the synthesis of several small natural compounds.[4,5] Our recent mechanistic study combining DFT calculations and low temperature $^{13}C$ INEPT-DOSY experiments gave us crucial information concerning the structure of the aluminium acetals and then new insights into the reaction mechanism of the overall process.[6]

A comprehensive study of the stereoselectivity of this radical cyclisation *in silico* was recently achieved and the results validated in batch reactions, highlighting stark differences between the cyclisation of α-bromoaluminium acetals and the classical Ueno-Stork reaction. Based on these results, the preparation of enantio-enriched, monoprotected 1,4,7-triols could be achieved from a simple precursor, using readily available enantiopur α-aminoacids as the source of chirality. These 1,4,7-triols are valuable precursors for the preparation of different classes of compounds such as pyrrolidine and tetrahydrothiophene derivatives. Our recent results in this field will be discussed here.

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## Tuesday, June 19, 2018/ Conference day 2

## AFTERNOON SESSION

**Chairs :**

**Denis CURRAN**
**University of Pittsburgh, USA**
**Michelle COOTE**
**Australian National University, Australia**

**Plenary lecture :**

**Armido STUDER**
**University of Munster, Germany**

**EuCHeMS conference on Organic Free Radicals (ECOFR 2018)**
June 17-20, 2018 - Marseille (France)

# Electron Catalysis

A. Studer

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Radical reactions are routinely considered in synthetic planning, and highly active research continues on new ways to make and use radicals. Because the products of radical-molecule reactions are again radicals, such processes are perfectly suited to be run as sequential reactions (cascades). Likewise, because radicals can be oxidized or reduced, radical-ionic crossover reactions can be implemented. Such cascade reactions serve well the goal of step economy in organic synthesis. As compared to non-radical processes, most radical reactions are very fast. Radical chain reactions require only a small amount of an initiator and addition of a catalyst is generally not necessary. Therefore, it is often difficult to catalyze radical transformations since background chain reactions are so fast.[1]

In the lecture the concept of using the electron as a catalyst will be discussed.[1,2] It will be shown that the electron is an efficient catalyst for conducting various types of radical cascade reactions that proceed via radical and radical ion intermediates. The "electron is a catalyst" paradigm unifies mechanistically an assortment of synthetic transformations that otherwise have little or no apparent relationship. Some recent examples on the use of the electron as a catalyst will be discussed.[3]

It will be emphasized how a negative charge can significantly weaken the neighbouring C–H bond and activate this bond towards H-atom transfer.[3e,j] Moreover, the activation of a C–H bond next to a C-radical towards deprotonation is a key point in the field of electron-catalysis. This issue will be addressed in the lecture. Extending that concept, the use of a negative charge to activate a C–C sigma-bond towards homolysis is also discussed.[3i,k] For example, electron catalyzed transition metal-free β-alkenylation-α-perfluoroalkylation of unactivated alkenes via radical 1,4 or 1,5-alkenyl migration will be presented.

It will be further shown, that readily generated vinyl boron ate complexes, generally used as substrates in the Suzuki-Miaura coupling, are efficient radical acceptors to conduct electron-catalyzed modular synthesis comprising a radical polar cross over step.[3h] This approach has recently been successfully applied to the development of a novel method for the preparation of highly enantioenriched α-chiral ketones.[3l]

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# Metalloradical Catalysis for Stereoselective Radical Chemistry

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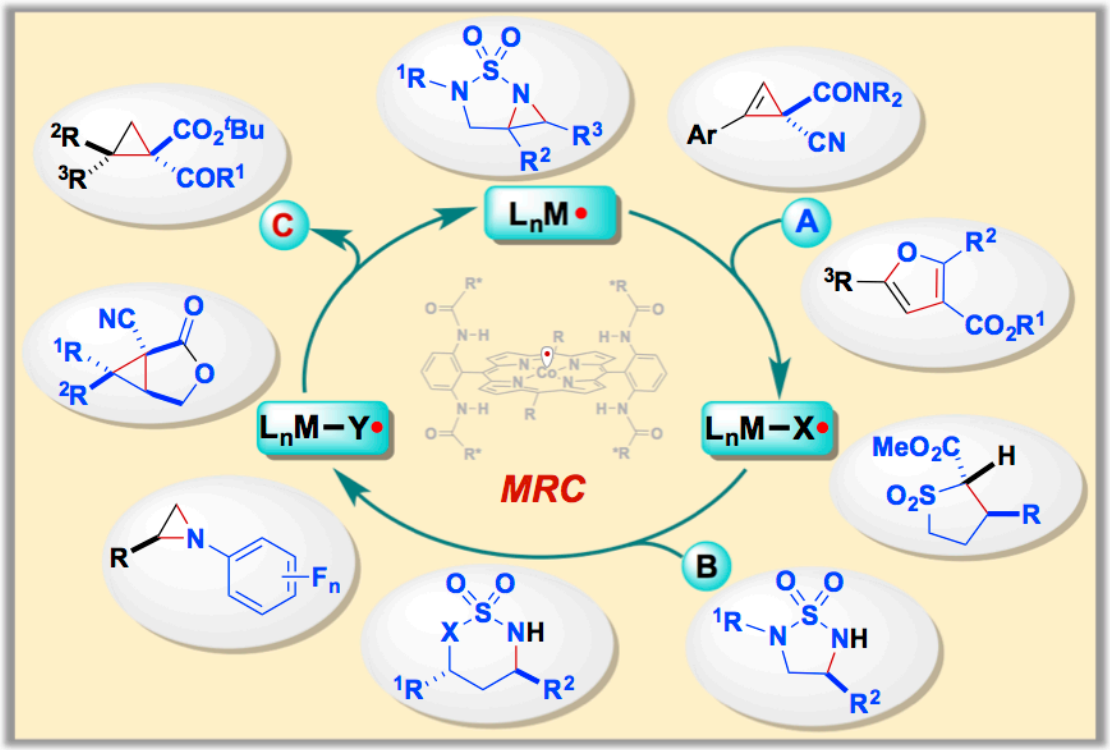
Organic synthesis has been dominated by chemical reactions that are based on two-electron ionic processes, either stoichiometrically or in catalytic fashion. While one-electron radical chemistry is equally rich and has been demonstrated with a number of unique features, its application in organic synthesis has been hampered by several enduring challenges. Over the past decade, my laboratory has been in the process of formulating "Metalloradical Catalysis" (MRC) as a general concept to guide the development of fundamentally new approaches for controlling both reactivity and stereoselectivity of radical reactions. In essence, metalloradical catalysis aims for the development of metalloradical-based systems for catalytic generation of carbon- and nitrogen-centered radicals from common organic compounds without the need of radical initiators or the use of light. The subsequent reactions of the resulting organic radical intermediates, which remain covalently bonded to the metal center, can be selectively controlled by the catalyst. For achieving enantioselective radical reactions via MRC, we have developed a family of unique chiral metalloradical catalysts based on structurally well-defined Co(II) complexes of $D_2$-symmetric chiral porphyrins with tunable electronic, steric, and chiral environments. These Co(II)-based metalloradical catalysts have been shown to be highly effective for a wide range of stereoselective organic reactions, including olefin cyclopropanation, olefin aziridination, C–H alkylation and C–H amination. Due to their distinctive radical mechanisms that involve unprecedented α-metalloalkyl and α-metalloaminyl radical intermediates, the Co(II)-based metalloradical systems enable addressing some long-standing problems in these important organic transformations.



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# Structural basis for semiquinone radical reactivity in bioenergetics enzymes: New insights from EPR spectroscopy, isotopic labeling and DFT calculations

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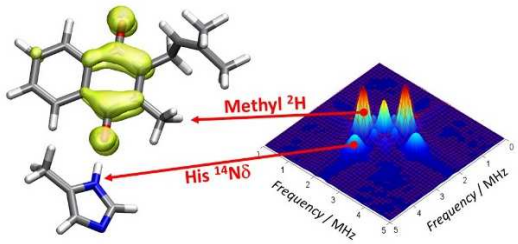
Isoprenoid quinones are small liposoluble molecules present in energy-transducing membranes of most living organisms. They play essential role in energy conversion mechanisms by shuttling electrons and protons between redox enzymes involved in bioenergetic processes. Their interaction with membrane-bound enzymes occurs at specific sites and leads to the transient generation of EPR-detectable semiquinone intermediates. The stability of these radical intermediates is strongly dependent on their chemical surrounding within binding sites and can have a major influence on the Reactive Oxygen Species production during respiratory processes. Due to their lability, the quinones are generally lost during the purification of membrane-bound enzymes and the crystallographic data on their binding site are extremely scarce.

To overcome this issue and decipher the influence of the protein environment in tuning quinone reactivity, we have developed an approach based on the combination of selective isotope labelling, high resolution EPR spectroscopy and DFT calculations. We used nitrate reductase A (NarGHI) from *E. coli* as a model system. Surprisingly, we shown that this membrane-bound respiratory enzyme is able to function with quinones of low (menaquinone, demethylmenaquinone) and high (ubiquinone) redox potential, stabilizing in the three cases a semiquinone radical intermediate [1-3].

The analysis of their $^{14,\ 15}$N and $^{1,\ 2}$H hyperfine couplings by multifrequency ESEEM/HYSCORE spectroscopy and DFT modeling enabled a detailed characterization of the electronic structure of these radicals and the identification of a unique common binding site. Our results point clearly to a strongly asymmetric binding mode of these semiquinones to the axial Histidine ligand of a heme group of the NarI subunit [3, 4]. They also underline the peculiar role of the quinone ring substituents in tuning the conformation of the isoprenoid side chain within a unique binding site.




*Does a high stability correlate with a high asymmetry?*

Our study provides the first spectroscopic evidence to adress at the molecular level the question of the bacterial adaptation to the transition between anoxygenic to oxygenic conditions

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# Successful combination of RAFT and emulsion polymerization: from the formation of amphiphilic block copolymer particles to the synthesis of surfactant-free latexes

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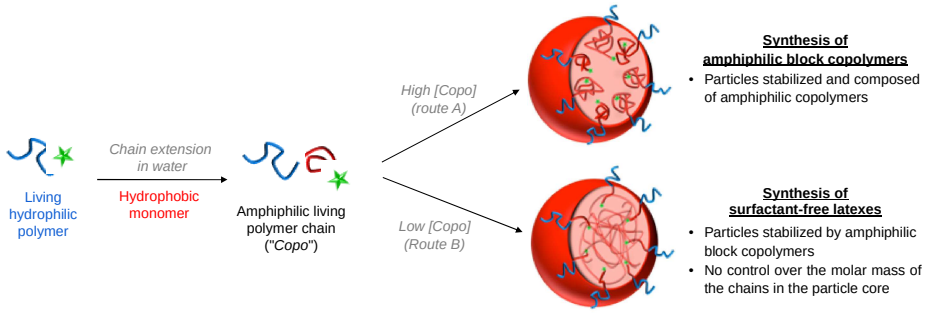
Recently, an original strategy combining emulsion polymerization and reversible-deactivation radical polymerization (RDRP) has been developed to produce, directly in water, amphiphilic block copolymers that self-assemble *in situ* to form self-stabilized particles.[1] The process, coined polymerization-induced self-assembly (PISA), requires the synthesis by RDRP of hydrophilic polymer chains followed by their chain extension with a hydrophobic monomer in water leading to the formation of amphiphilic block copolymers with predefined and narrowly distributed molar masses (Scheme 1, route A).[2] Alternatively, the use of very low amount of these living hydrophilic chains can lead to the *in situ* formation of amphiphilic block copolymers that can further act as efficient stabilizers for the particles produced simultaneously by emulsion polymerization, without seeking control on the molar mass in the particle core (Scheme 1, route B).[3] This second approach consists in an interesting alternative to avoid the use of low molar mass surfactants. Indeed, when emulsion polymers undergo film formation, these hydrophilic species are prone to migration and segregation at film interfaces, negatively impacting properties such as water sorption, permeability and adhesion to a substrate. The PISA process therefore not only provides a powerful mean for the production of amphiphilic block copolymers directly in water, but also a valuable new pathway of performing surfactant-free emulsion polymerizations considering the living hydrophilic polymer chains as reactive surfactants. The present paper will cover our latest developments of the PISA approach for the production of amphiphilic block copolymer particles and surfactant-free polymer latexes using RAFT (reversible addition-fragmentation chain transfer), one of the most versatile RDRP processes.




**Scheme 1**. Particle synthesis using living/reactivatable polymer chains in emulsion polymerization

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# Homogeneous aerobic oxidation catalyzed by NHPI dervivatives: Co-solvent or not co-solvent, that is the question.

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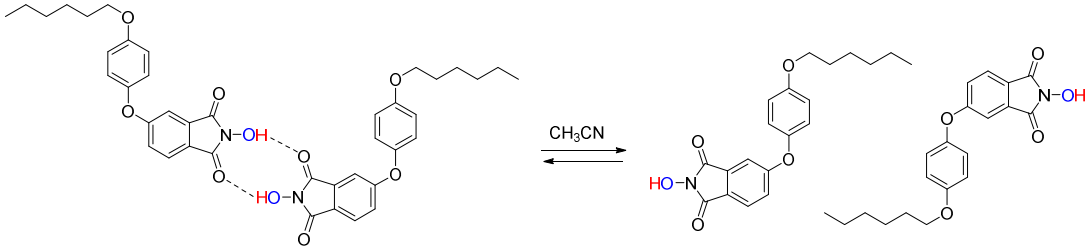
The liquid phase aerobic oxidation catalysis by *N*-hydroxyphthalimide (NHPI) has always been performed in polar solvents to guarantee the complete solubilization of the polar catalyst, especially at room temperature [1,2]. As a consequence, the reactivity of this organocatalyst in apolar mediums was unknown.

Moreover, economic and environmental sustainability of large-scale oxidations of intermediates makes the development of solvent-free processes mandatory [3].

To overcome this issue, we designed and synthesized a new class of lipophilic NHPI-catalysts completely soluble in alkyl aromatics. The design focused on the introduction lipophilic chains on the NHPI aromatic ring, via insertion of proper functional groups which, at mean tine, do not interfere with the thermodynamic and the kinetic of the catalytic cycle [4].

First attempts to conduct the selective oxidation catalyzed by these new derivatives in neat cumene afforded poor results in terms of conversion. Indeed, the potentials of new lipophilic catalysts were exploited by adding small amounts of acetonitrile. In this way, it was possible to prevent the hydrogen-bond (HB) driven aggregation of lipophilic NHPI units in apolar mediums, fully promoting the hydrogen atom transfer (HAT) process [5].

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# Synthesis of Structurally Controlled Dendritic Hyperbranched Polymers by Radical Polymerization

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Hyper-branched polymers (HBPs) have attracted significant attention because of their characteristic topological structure associated with their unique physical properties compared to linear polymers.[1] Control over the three-dimensional (3D) structure of HBPs, i.e., molecular weight, dispersity, number of branching points, branching density, and chain-end functionalities would significantly improve and modify polymer properties and contribute to the design and synthesis of new polymer materials. However, there is no practical and effective method to synthesize structurally well controlled HBPs.

We report here the controlled synthesis of dendritic HBPs by the copolymerization of vinyltelluride **1** and acrylate monomer in the presence of organotellurium chain transfer agent **2** (Scheme 1).[2] Vinyl telluride **1** serves as a branching point after it's vinyl moiety has reacted, and HBPs with controlled 3D structure are formed. The 3D structure was easily controlled by changing the relative amounts of the **1**, **2**, and acrylate monomers.[3]

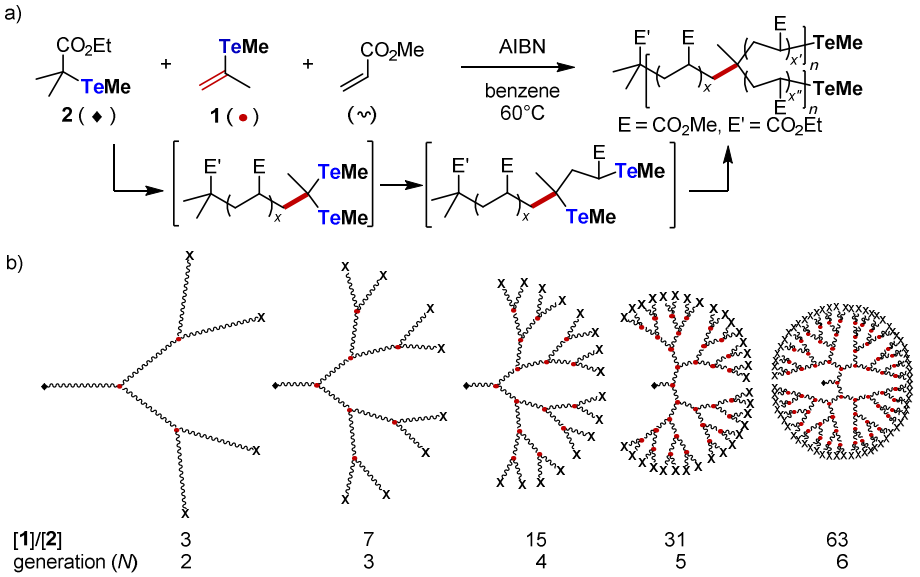


**Figure 1.** a) Synthesis of dendritic HPBs by the copolymerization of **1** and acrylate monomer, and b) schematic structures of ideal polymer products (X = TeMe).

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# Kinetic Studies on the Effect of Metal Ions on Hydrogen Atom Transfer from Alkanols and Alkanediols to the Cumyloxyl Radical

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Hydrogen atom transfer (HAT) reactions are one of the most common chemical transformations, and are involved in many different processes such as the radical-induced oxidative damage to biomolecules and polymers,[1] the mechanism of action of radical scavenging antioxidants,[2] enzymatic and biomimetic reactions,[3] and a large number of synthetically useful C-H bond functionalization procedures.[4] Among the reactive species that take part in these processes, alkoxyl radicals have gained major attention, and our research group has devoted much effort to elucidate the factors underlying HAT reactivity and selectivity employing a representative radical such as cumyloxyl ($PhC(CH_3)_2O^{\bullet}$, $CumO^{\bullet}$).[5] $CumO^{\bullet}$ can be easily generated by UV photolysis from commercially available dicumyl peroxide, can tolerate a wide range of experimental conditions and is characterized by a visible adsorption band and a lifetime in the microsecond time regime. Taken together, these features make the direct measurement of rate constants for HAT to $CumO^{\bullet}$ by means of the laser flash photolysis technique particularly convenient. Among the different aspects studied in our laboratory, recent studies have shown how Lewis acid-base interactions can be used to promote aliphatic C-H bond deactivation of ether, amine and amide substrates towards HAT, through the addition of alkali and alkaline earth metal ion salts.[5,6]

Within this framework, and being hydroxyl functional groups a common structural motif of organic substrates, we have carried out a detailed time-resolved kinetic study on the reactions of $CumO^{\bullet}$ with an extended series of alcohols and diols. The effect of substrate structure and of added alkali and alkaline earth metal ion perchlorates on the HAT reactivity and selectivity will be discussed, highlighting in particular the important role played by electronic, torsional and medium effects on these reactions.

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# New Transformations in Synthesis Enabled by Organic Photoredox Catalysis

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Single electron pathways are prevalent in numerous biosynthetic pathways that are crucial to life on our planet. As synthetic chemists, we seek to harness the power of these open-shell processes to achieve uncommon but valuable chemical reactivity. To this end, my laboratory is interested in accessing single electron pathways via the use of organic photoredox catalysis. This seminar will highlight the recent synthetic methods developed by my laboratory, including anti-Markovnikov hydrofunctionalization reactions of olefins,[1] C–H functionalization reactions of aromatic[2] and aliphatic compounds and acceleration of the venerable nucleophilic aromatic substitution reaction using, for the first time, methoxyarenes. Where applicable, discussion of mechanistic studies will be presented.[3]

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# Synthesis of Heterocycles through Electrochemical Dehydrogenative Cyclization and Annulation Reactions

Z.-W. Hou, H.-B. Zhao and H-.C. Xu*

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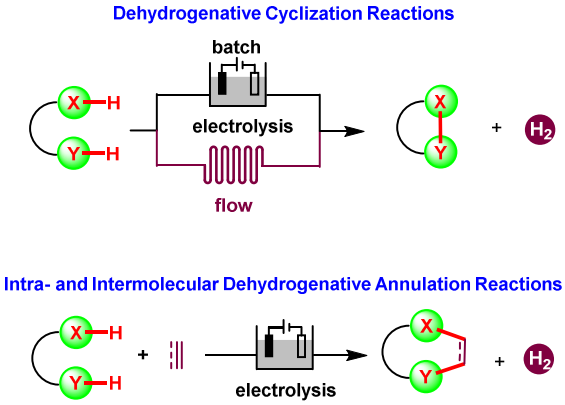
Heterocyclic structural moieties are prevalent in natural products, pharmaceuticals, agrochemicals and organic materials. As a result, the preparation of heterocycles is one of the major focuses of organic chemistry. We have been involved in the preparation of heterocycles through electrochemical dehydrogenative cyclization and annulation reactions. In the lecture, our recent progress on the electrochemical generation of radical intermediates and their synthetic applications in dehydrogenative cyclization and annulation reactions will be discussed.[1] The use of electric current as a driving force for the conversions obviates the need for oxidizing reagents.

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## Wednesday, June 20, 2018/ Conference day 3

## MORNING SESSION

**Chairs :**

**Jacques LALEVEE**
**University of Haute Alsace, France**
**Philippe RENAUD**
**University of Bern, Switzerland**

**Plenary lecture :**

**Yusuf YAGCI**
**Istanbul Technical University, Turkey**

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# Photochemically Generated Radicals for Coupling, Functionalization and Polymerization Processes

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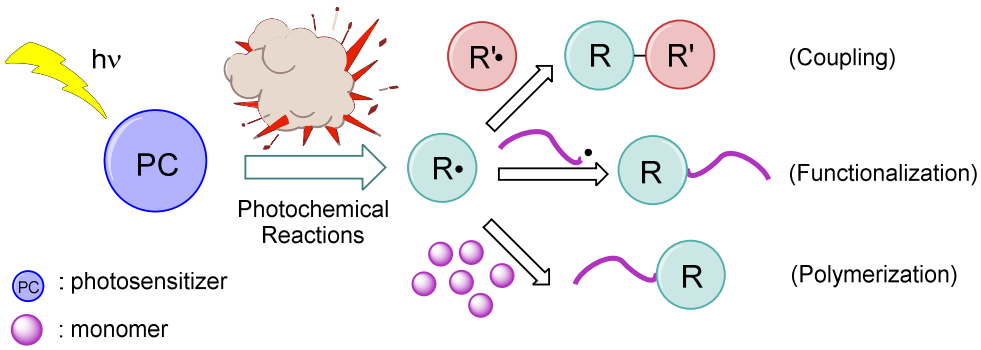
Photochemical strategies have distinctive advantages in comparison to conventional methodologies in terms of mild reaction conditions, low energy requirements and temporal and dimensional control.[1] After such benefits have been realized by the synthetic polymer community, photochemical reactions have been employed to a wide range of organic reactions, functionalization and polymerization processes. Specifically, photochemical radical generation is the most commonly applied strategy as the reactive nature of radicals make them useful not only for traditional polymerizations[2] but also for controlled/living polymerizations. [3-7] In addition, they can be utilized for the simultaneous generation of specific compounds, which can mediate various coupling reactions including click processes.[8] This make them applicable to modification of polymers and syntheses of complex macromolecular structures such as telechelics, block and hyperbranched polymers.[8-10] Below is the schematic representation of photoinduced radical generation and its applications to polymer chemistry.




**Scheme 1.** Photoinduced radical generation and its applications to polymer chemistry

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# New radical cyclizations mediated by $SmI_2$

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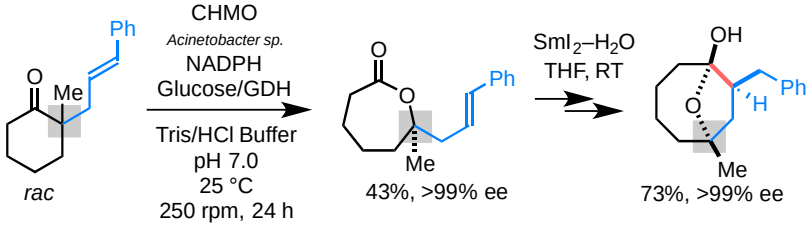
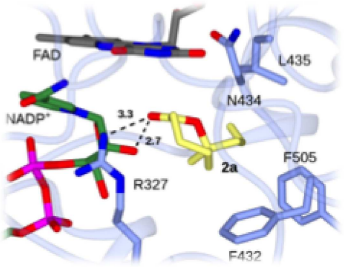
New cyclizations and cyclization cascades have been developed that involve reductive electron transfer from $SmI_2$[1]. The talk will describe the use of ester carbonyl-alkene radical cyclizations[2] in conjunction with biocatalytic oxidation in an enantioselective approach to medium-sized carbocycles (see Scheme),[3] urea carbonyl-alkene radical cyclizations,[4] and the first chiral ligand-controlled enantioselective cyclizations mediated by $SmI_2$.[4,5]




■ combined biocatalytic-radical cyclization approach to medium-sized cycloalkanols




Model of $CHMO_{Actineto}$ in complex with an *(R)*-lactone product

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# Charge-Transfer Complexes as a Linchpin for Transition Metal-Free Solar Light Assisted Synthesis

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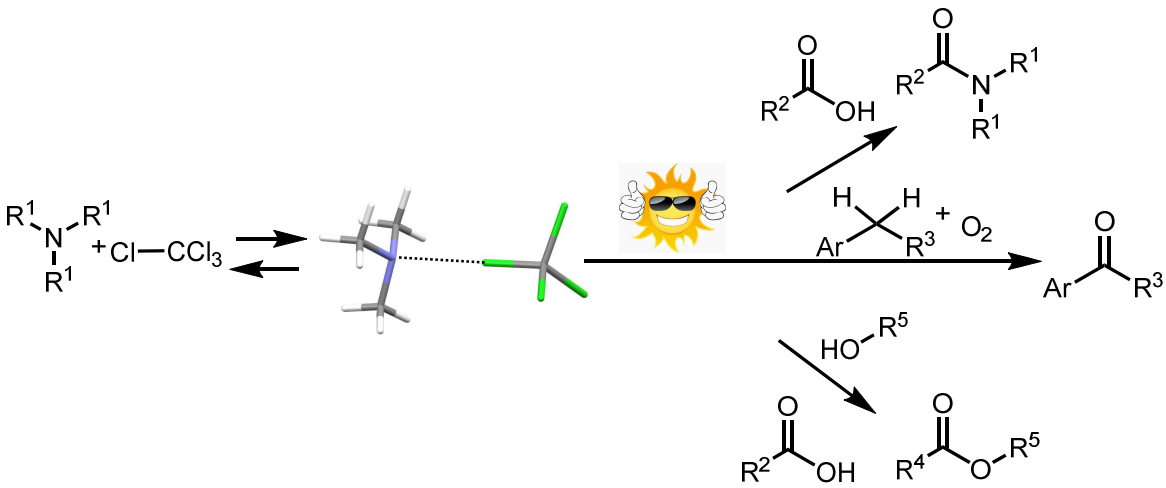
Trialkyl amines form charge transfer complexes with tetrachloromethane and tetrabromomethane.[1-2] We have characterized and studied amine $CCl_4$ complexes computationally and crystallographically.[3] When subjected to visible light these complexes form radicals and eventually other reactive species that may be utilized in photo-redox synthetic reactions. Advantages of this mode of activation are that no transition metal catalysts are needed and the wide range of possible reactions that may be linked to this linchpin. As proof of concept we have developed a dealkylative amide forming reaction of trialkyl amines and carboxylic acids,[4] a esterification reaction.[5] and a C-H functionalization reaction.[6] While these reaction necessarily have widely different mechanisms they are all initiated by the visible light activation of an amine-tetrahalomethane charge transfer complex. The mechanistic intricacies of this divergent reactivity will be discussed.

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# Recent Advances in Site-Selective C($sp^3$)-H Functionalization by Radicals

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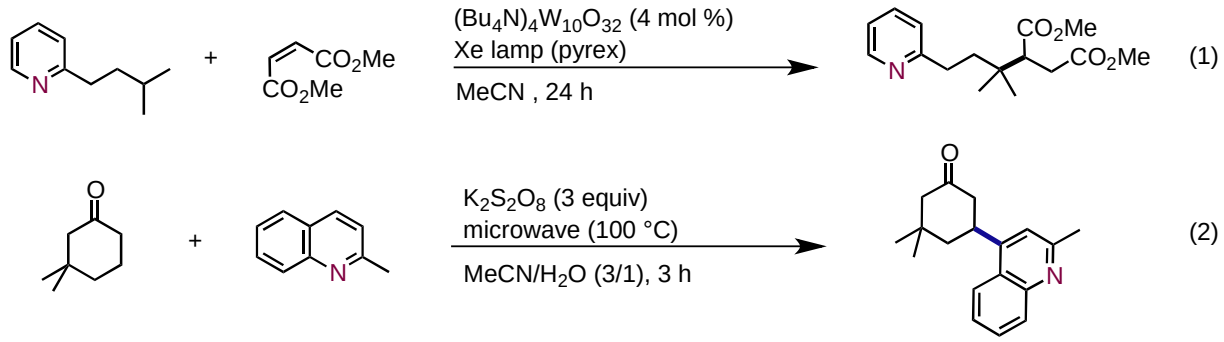
Development of new strategies to realize site-selective functionalization of C($sp^3$)-H bonds is at the forefront of synthetic organic chemistry. Oxygen-centered radicals have excellent potentials to abstract hydrogen from C($sp^3$)-H bonds to generate alkyl radicals and we are particularly interested in the synergistic control of the $S_H2$ transition states of hydrogen abstraction by polar and steric effects in achieving site-selective C($sp^3$)-H functionalization. Under decatungstate anion photocatalysis,[1,2] the applications of the strategy expanded to a wide range of functionalizaed compounds involving cyanoalkanes, lactones, cyclic ketones, and pyridylalkanes (eq 1).[3] This lecture also focuses on the site-selective functionalization of C($sp^3$)-H bonds by diferente types of oxygen-centered radicals. For example, the microwave assisted Minisci type reaction of 3,3-dimethylcyclohexanone with 2-methylquinoline proceeded via site-selective H-abstraction by sulfate radicals to give 4-substituted 2-methylquinoline (eq 2).

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# Taming $CO_2$ reduction to methane. Fe based molecular complexes as catalysts, radicals (ions) as intermediates

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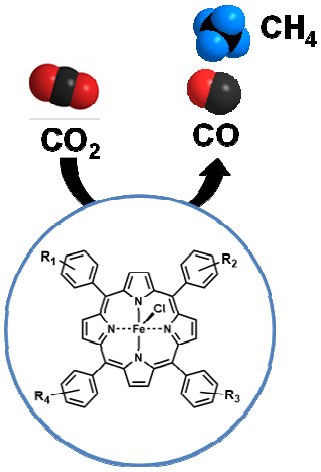
Recent attention aroused by the reduction of carbon dioxide has as main objective the production of useful organic compounds and fuels – the "solar fuels" – in which solar energy would be stored.[1] One route to this goal consists in first converting sunlight energy into electricity than could be further used to reduce $CO_2$ electrochemically.[1-4] Another approach is to directly use the visible photons and photocatalyze the reduction of the gas in the presence (or not) of an appropriate sensitizer and of a sacrificial electron donor. [5-9] In all of these cases, radicals are key intermediates. By using Fe based molecular complexes (including substituted tetraphenyl porphyrins and quaterpyridine complexes) we have recently found that it was possible to selectively and efficiently convert $CO_2$ with 2 electrons into CO [2-7], both in organic solvent and in pure water. Recently, we have discovered that the carbon dioxide could be reduced with 8 electrons to methane with a single molecular porphyrin catalyst. [8,9] Our most recent results will be presented and discussed.

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# Synthesis of alkylsulfonyl cyanides:

# Tin-free radical carbo- and sulfonyl-cyanation of olefins

V. Pirenne;[a] G. Kurtay;[a] F. Robert;[a] D. Bassani[a] and Y. Landais[a,]*

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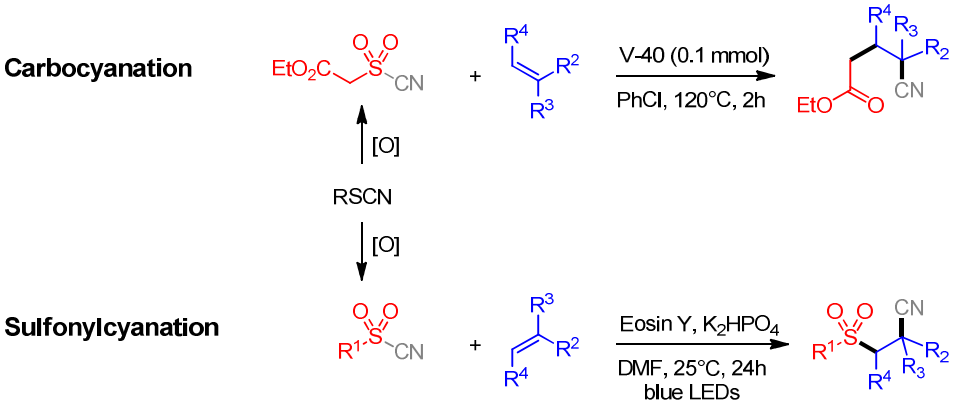
In the course of our ongoing research on the functionalisation of olefins, we anticipated that the introduction of a nitrile onto the olefin backbone in a free-radical manner would lead to useful intermediates for the total synthesis of natural products including indole alkaloids. During our efforts directed toward the total synthesis of Leucophyllidine, a bis-indole alkaloid, the free-radical carbo-cyanation of olefins was investigated. With the aim of developing a tin-free version, new alkylsulfonyl cyanides were synthesized as radical traps through oxidation of the corresponding thiocyanates. Results on this new oxidation reaction and the tin-free carbo-cyanation reaction of olefins will be presented. This methodology, where $SO_2$ is the unique by-product, leads to the desired adduct in high yield and is compatible with various functional groups.[1]

In line with this study and keeping in mind the importance of sulfones in pharmaceutical and agrochemical industries,[2] the photocatalysed sulfonyl-cyanation of olefins was also envisioned. In this case, the mild conditions of photo-redox processes were required to avoid the desufonylation occurring at high temperature. Here, we will present the Eosin-mediated sulfonyl-cyanation of olefins occurring at room temperature using LEDs as a visible light source. This reaction showed a broad applicability and a remarkable compatibility with many functional groups both on the olefinic partner and on the starting sulfonyl cyanide. The utility of this methodology was demonstrated by a short synthesis of a metalloproteinase inhibitor. Finally, an unprecedented mechanism is proposed.[3]

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# Organic radicals in metallic complexes: cooperative catalysis with redox-active ligands

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[b] *Sorbonne Universités, IPCM, UPMC Paris 06, UMR 8232, 75005, Paris (France)*
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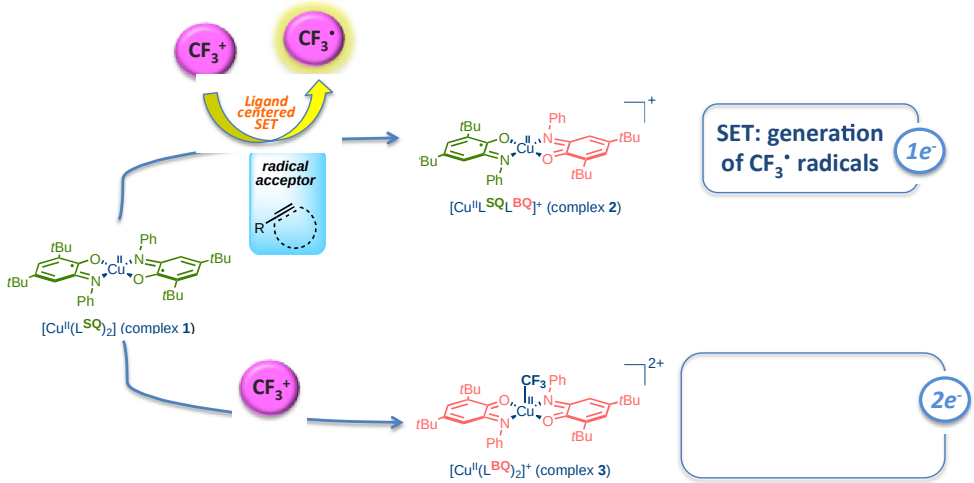
Increasing concerns regarding sustainability and cost-related issues of noble metals are driving chemists to revisit the chemistry of first-row early transition metals (Fe, Co, Ni, Cu). Although widely used, these metals tend to be limited by their electronic structure, which makes them prone to mono-electronic transfers and can limit their efficiency and selectivity. An emerging area in catalysis is the use of redox non-innocent ligands, which can act as a storage and supply unit of electrons, allowing the metal to perform reactions once forbidden and broadening the scope of their synthetic applications.[1]

We have been focusing on redox-active iminosemiquinone ligands in copper and nickel complexes in order to foster alternative pathways in conventional reactivities, or unconventional behaviors altogether. Progress made in trifluoromethylation,[2] formation of C–N bonds through the implication of masked high-valent species[3] and aziridination[4] will be presented.

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# Visible-Light-Mediated Photoredox-Catalyzed *N*-Arylation of *NH*-Sulfoximines with Electron-Rich Arenes

A. Wimmer[a] and B. Koenig[a,*]

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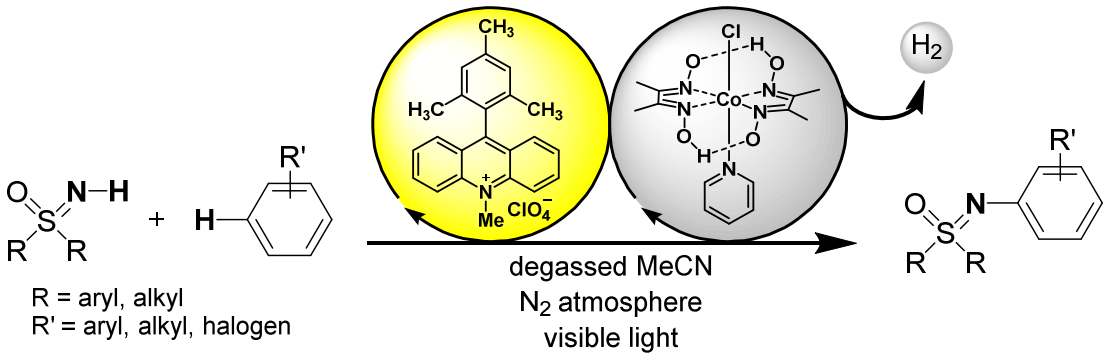
Sulfoximines, the monoaza analogues of sulfones, are a rather uncommon class of substrates to many chemists, although their discovery goes back into the early 1950s.[1] Due to their chemical and configurational stability, first applications mainly focused on asymmetric reactions or catalysis where they act as chiral auxiliaries or ligands.[2] Only recently, it was realized that the diverse structure of sulfoximines has much more to offer, especially in medicinal chemistry and the pharmaceutical industry. Recent reports attest sulfoximines to be relevant bioactive structures, which display desirable metabolic stability and physicochemical properties in combination with hydrogen-bond acceptor/donor functionalities.[3]

We realized the direct C-H/N-H dehydrogenative cross-coupling of *NH*-sulfoximines with electron-rich arenes by oxidative visible-light photoredox catalysis, applying 9-mesityl-10-methylacridinium perchlorate as an organic photocatalyst. Our reaction proceeds without sacrificial oxidant, at room temperature and is highly selective for the C-N bond forming reaction. The scope of the reaction includes mono- and multi-alkylated and halogenated arenes, which are reacted with aromatic and aliphatic electron-rich and electron-poor *NH*-sulfoximines, giving moderate to excellent yields of the *N*-arylated sulfoximines. In addition, we successfully conducted the developed reaction on a gram scale (1.5 g). Mechanistic investigations show that both arene and *NH*-sulfoximine interact with the excited-state of the photocatalyst. We propose a radical-based mechanism, where both the arene and the *NH*-sulfoximine are photo-oxidized to their respective radical intermediates. Radical-radical cross-coupling subsequently leads to the *N*-arylated sulfoximine. Two electrons and two protons are released during the reaction and are subsequently converted into $H_2$ by a proton-reducing cobalt-catalyst.

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## Wednesday, June 20, 2018/ Conference day 3

## AFTERNOON SESSION

**Chairs :**

**Cristina NEVADO**
**University of Zurich, Switzerland**
**Emmanuel LACOTE**
**CNRS, Université de Lyon, France**

**Plenary lecture :**

**Michelle COOTE**
**Australian National University, Australia**

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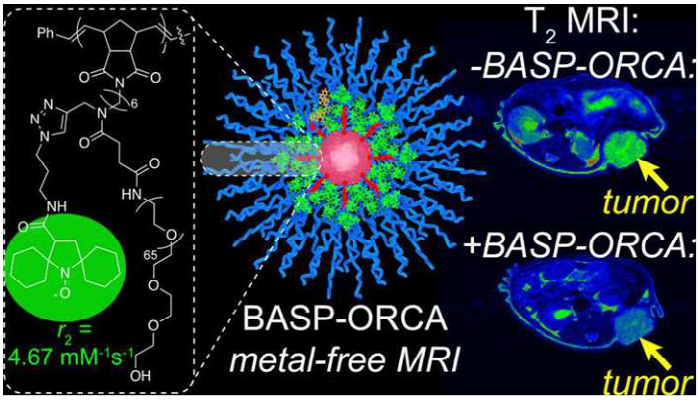
# New Macromolecular Designs for Nitroxide-Based MRI Contrast Agents: Enabling Metal-Free Tumor Imaging *In Vivo*

J. A. Johnson;[a,*]

[a]*MIT Department of Chemistry, Program in Polymers and Soft Matter, Koch Institute for Integrative Cancer Research, Cambridge, MA, U.S.A.*
**jaj2109@mit.edu*

Metal-free magnetic resonance imaging (MRI) agents could overcome the established toxicity of metal-based agents in some patient populations and enable new modes of functional MR imaging *in vivo*. We have developed nitroxide-functionalized bottlebrush and brush-arm star polymer organic radical contrast agents (BASP-ORCAs, see Figure) that overcome the low contrast and poor *in vivo* stability associated with nitroxide-based MRI contrast agents. As a consequence of their unique macromolecular architectures, these materials possess per-nitroxide transverse relaxivities up to ~44-fold greater than common nitroxides, exceptional stability in highly reducing environments, and low toxicity. These features combine to enable longitudinal imaging of tumors in mice using clinical high-field $^{1}$H MRI techniques.



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# Functionalization of Olefins with Organic Radicals

Shunsuke Chiba[a]

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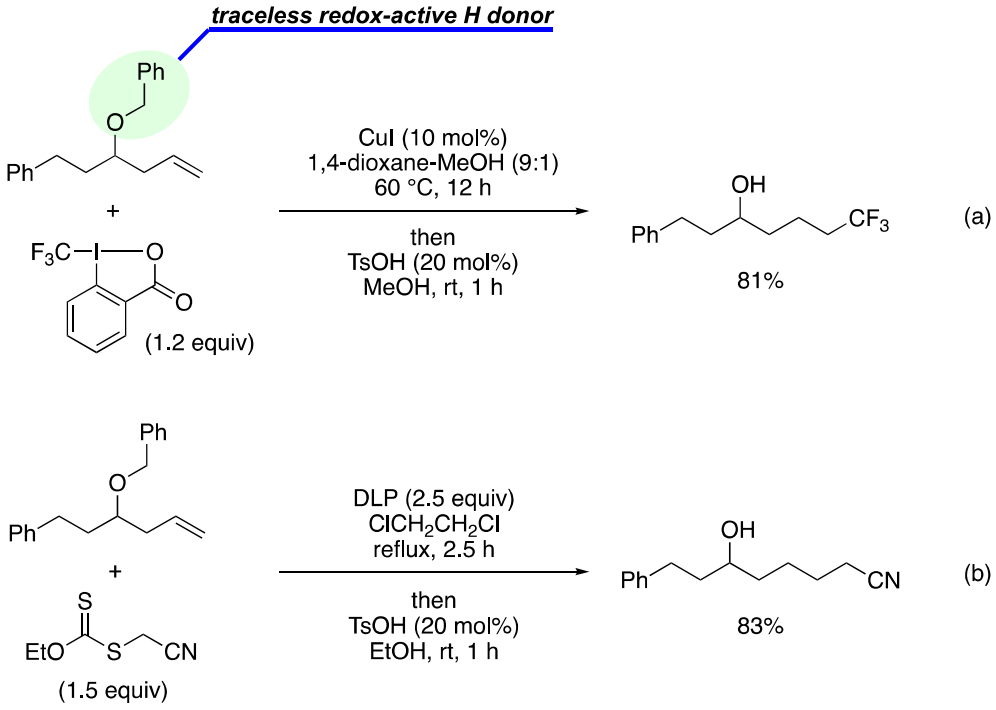
This talk will describe the development of new protocols to functinoalize olefines using a benzyl ether as a traceless redox-active hydrogen donor.[1] Under copper catalysis and in the presence of $CF_3$- or $N_3$-containing hypervalent iodine reagents, a series of homoallylic alcohol derivatives could be regioselectiviely hydrofunctionalized (Eq. a). Use of xanthates in the presence of lauroyl peroxides as a radical initiator and a stoichiometric oxidant enabled hydrofunctionalization of olefins under transition-metal-free fashion (Eq. b).

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# Boosting NMR sensitivity: free radicals at work

G. Casano,[a] G. Karthikeyan,[a] H. Karoui;[a] D. Wisser,[b] D. Kubicki,[c] M. Lelli,[d] M. Yulikov,[e] G. Jeschke,[e] C. Copéret,[e] F. Aussenac,[f] M. Rosay,[f] A. Lesage,[b] L. Emsley[c] and O. Ouari[a,*]

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Dynamic Nuclear Polarization (DNP) is one of the most promising approaches to overcome the sensitivity limitations of solid-state NMR, opening new possibilities and applications in materials and life sciences. The recent advances result from significant developments in DNP instrumentation, in the introduction of new methodological concepts and in the design of ever more efficient polarization sources. In a DNP experiment, the larger polarization of unpaired electrons (usually from a stable free radicals) is transferred to surrounding nuclei by microwave irradiation at or close to the EPR Larmor frequency, providing maximum theoretical signal enhancements of a factor 658 for $^{1}H$ and 2620 for $^{13}C$. The improvement in the understanding of the polarization mechanisms and the rational design of polarizing agents by optimizing their structural and magnetic properties have contributed to the success of the technique. Signal enhancements ($\varepsilon$) of 50-200 are routinely obtained today at 9.4 T and 100 K, allowing the investigation (not feasible without DNP) of an ever broader range of molecular and macromolecular systems including biomolecules, hybrid materials, mesoporous silica, metal oxides, polymers, nanoparticles and microcrystals. However, the enhancement factors are still far from the predicted maximum values, notably at high-field. Indeed, the development of ideal polarizing agents is not trivial due to the multidimensional optimization problem. We will report our recent efforts on the design, synthesis and characterization of improved dinitroxide polarizing agents, notably by discussing the role of parameters such as the magnetic dipolar interaction, the electron relaxation and the glassy matrix.[1-3]

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# Oxidative NHC-organocatalysis: what are the radical intermediates?

David Martin

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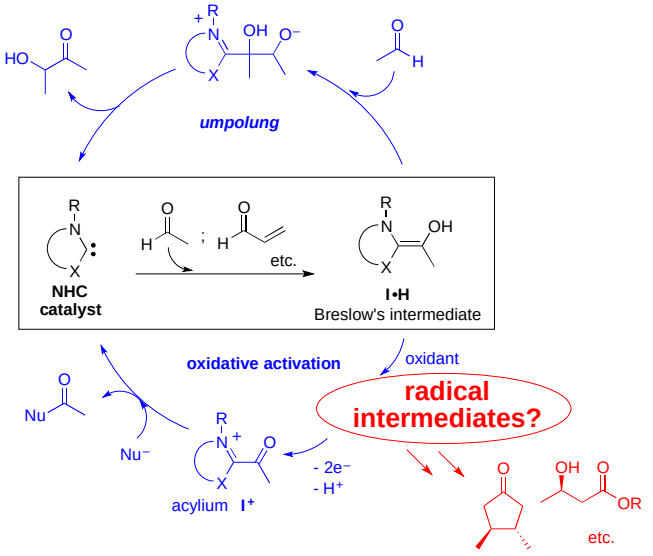
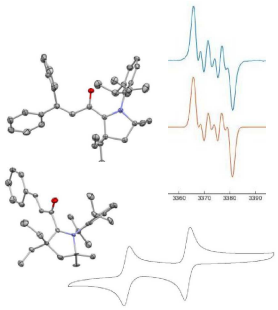
N-heterocyclic carbenes (NHC) allow for the catalytic *umpolung* of α,β-unsaturated aldehydes, through the formation of enaminols **I•H**, so-called Breslow intermediates. The scope of this chemistry can be extended further with oxidative conditions, not only through the formation of acylium intermediates $\mathbf{I}^+$, but also by enabling radical pathways through one-electron oxidations, as in recently reported enantioselective oxidative NHC-catalyzed transformations of enals into β-hydroxyester,[1-2] cyclopentanones[3] and spirocyclic-γ-lactones.[4] For these reactions, a SET from **I•H** to a mild one-electron oxidant is usually proposed as the key step of the catalytic cycle. However, the genuine mechanism is unclear, due to the lack of experimental data on the radical intermediates. Taking advantage of our previous experience in the study on stable capto-dative radicals,[5-8] we attempted to assess the key intermediates in the oxidative NHC-catalyzed radical reactions of enals. In particular, we show that the usually hypothesized direct SET from **I•H** is unlikely, and propose isolable models for more relevant radical intermediates.



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# The redox activity of nitroxides and their derivatives

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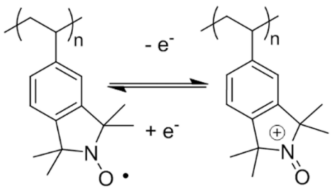
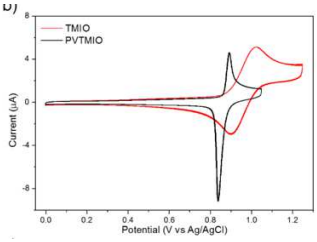
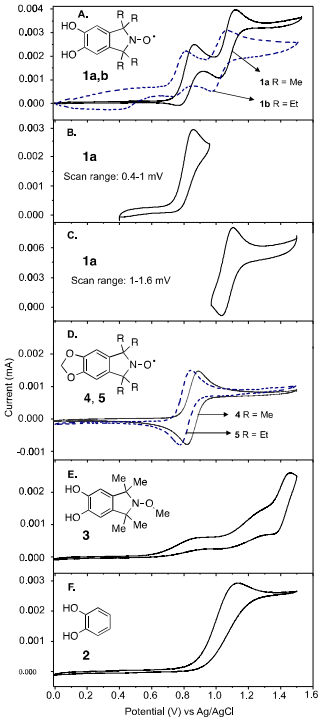
Nitroxides are highly versatile EPR probes, powerful antioxidants and very efficient scavengers of free radicals. They are also remarkable in that they can be both oxidised (to the oxoammonium ion) or reduced (to the hydroxylamine). When incorporated within polymers, nitroxides provide important electroactive components in organic radical batteries (ORB).[1] The redox chemistry of nitroxides also forms the basis of new developments in redox flow batteries,[2,3] as new fluorescent probes for radicals and as catalytic antioxidants in biological systems.[4]




Herein we discuss the synthesis and electrochemical properties of some novel nitroxides, as well as some related analogues and derivatives. Of particular interest is the oxidation of a novel catechol-based nitroxide and the non-radical methoxyamine which may prove to have value as a biological antioxidant, or as a charge carrier in redox flow batteries and other electroactive materials.

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# Electrostatic Catalysis of Radical Reactions

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Chemists appreciate that the rate of redox reactions can be manipulated by means of an electrical potential gradient. However, it was only in 2016 that it was shown that an external electric field can also be used to catalyse non-redox reactions, thereby opening up a new dimension to chemical catalysis [1]. So-called electrostatic catalysis arises because most chemical species have some degree of polarity and so can be stabilized by an appropriately aligned electric field; when this occurs to a greater extent in transition states compared with reactants, reactions are catalyzed [2]. However, by their nature such effects are highly directional and so implementing them in practical chemical systems is problematic. We have been using a combination of theory and experiment to explore various solutions to this problem. The first is using surface chemistry techniques, in conjunction with the break-junction technique in scanning tunnelling microscopy [1]. This allows us to detect chemical reaction events at the single molecule level, whilst delivering an oriented electrical field-stimulus across the approaching reactants. The second is making use of the electric fields within the double layers of electrochemical cells to manipulate both redox and non-redox unimolecular reactions. Here we find that molecules actually self-align and interact with electrolyte ions to facilitate catalysis [3]. Finally, in an approach that is truly scalable, we have instead addressed problem of orientation of the electric field by making use of appropriately placed charged functional groups to provide the electrostatic stabilization for solution-phase reactions [4]. In this way, the direction of the local field experienced by the reaction centre is fixed, and by associating the stabilization or destabilization with the protonation state of an acid or base group, it has the advantage of providing a convenient pH switch. In this talk our experimental and theoretical results will be presented and the prospects for electrostatic catalysis discussed. Our particular emphasis will be on prospects for radical chemistry, where we have been harnessing both external fields and charged groups for low temperature alkoxyamine cleavage [3d,4b] and harnessing the electrostatic effects of Lewis acids for propagation catalysis of radical polymerization [5].

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# *Abstracts of Posters*

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# Revising the Mechanism of Autoxidation

H. M. Aitken,[a] R. Lee,[a] G. Gryn'ova,[a] L. Smith,[a] L. de Keer,[b] P. van Steenberg,[b] G. Desmet,[b] M. F. Reyniers[b] and M. L. Coote[a,*]

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The basic scheme for autoxidation of polymers was originally developed by Bolland, Gee and co-workers for rubbers and lipids.[1] These days, it has come to be the accepted scheme for all polymeric materials. Yet, for this process to be autocatalytic, the propagation reaction must occur as hydrogen abstraction from the next substrate by the peroxyl radical (ROO· + RH → ROOH + R·).[2] Unless the hydrogen transfer process forms highly stabilized R• radicals (e.g. with allylic double bonds), this reaction is highly thermodynamically disfavored.

In attempting to elucidate the scheme for autoxidation of polymers when highly stabilized R• radicals are not formed by hydrogen abstraction (unlike rubbers and lipids) a number of questions must be answered: Is the transfer step still driven kinetically? If not, what is the fate of the peroxyl radical?[3] What is the role of oxygen? What is the role of defect structures in the polymer? What other species contribute to polymer degredation?[4]

This presentation will outline our progress towards solving these questions using a combination of quantum chemical calculations and kinetic modelling, with a view towards improved polymer and antioxidant design.

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# Generating Superoxide Ion from Biologically-Relevant Compounds

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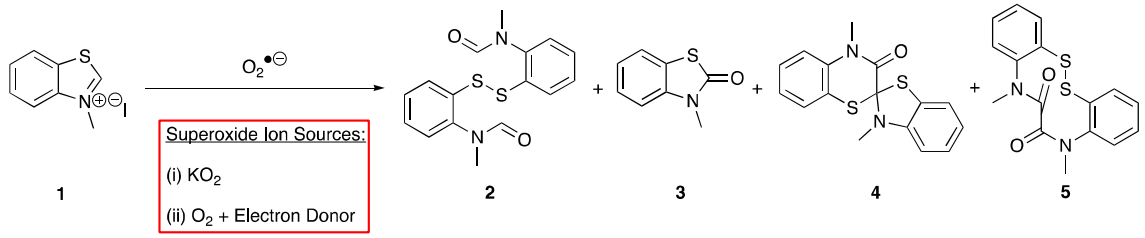
In this work, we explore the possibility of generating superoxide ion *via* the reduction of molecular oxygen ($O_2$) using several biologically-relevant compounds, which can act as precursors to electron donors. In order to do so, we tested and compared various superoxide ion detectors from which 3-methylbenzothiazolium iodide **1** was both the most selective and sensitive for our studies.[1,2] **1** in the presence of a superoxide ion source such as potassium superoxide ($KO_2$) forms products **2-5**. Using this, an array of biologically-relevant compounds (in the presence of $O_2$) were probed.




**Scheme 1** 3-Methylbenzothiazolium iodide as a superoxide ion detector.[1,2]

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# Enzymatically activated nitroxides as selective probes for Overhauser-enhanced Magnetic Resonance Imaging

G. Audran[a,*], S. Jacoutot[a], I. Duttagupta[a], S.R.A. Marque[a], N. Jugniot[b], P. Massot[b], E. Thiaudiere[b] and P. Mellet[b]

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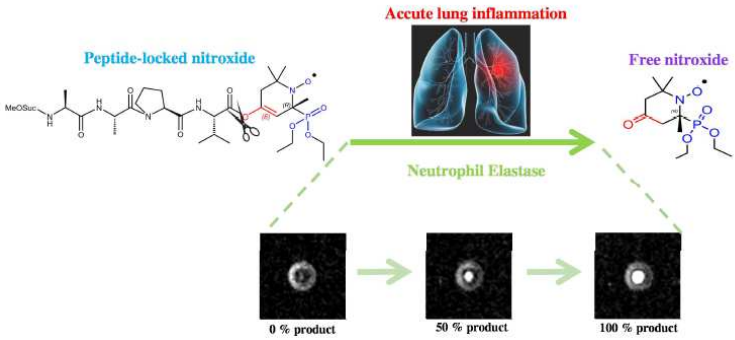
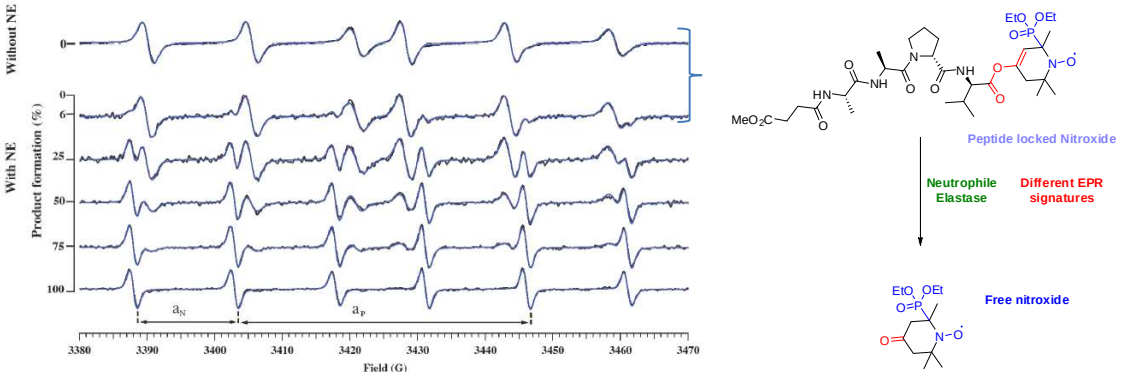
Pulmonary inflammatory diseases like cystic fibrosis (CF), chronic obstructive pulmonary disorder (COPD) are a major health concern worldwide. Those inflammations result in an influx of neutrophils leading to the overexpression of elastases. Neutrophile elastases are responsible of the degradation of lung's structure via elastin fragmentation. Development of new methods for the early detection of those inflammations by monitoring the protease-inhibitor balance would be an efficient diagnostic tool.

Herein, we present the **synthesis of a nitroxide probe** MeO-Suc-$(Ala)_2$-Val-Pro-Nitroxide.[1] As shown in the scheme, this probe is **selective** for **neutrophile elastases** and is suitable for **EPR imaging** and **OMRI**. Efficacy and selectivity of substrates were assessed with broncho alveolar lavages derived from a mouse model of pneumonia.




Moreover, **selective irradiation** and **quantification** of one of the nitroxide is possible owing the difference in respective EPR signatures of peptide locked nitroxide and the free nitroxide. Monitoring the product formation (free nitroxide) allows to direct **access to the protease-inhibitor balance**.




Further development along these results can lead to the development of **selective probes for proteases**, using their natural selectivity for specific peptide sequences. Similar probes are being designed with enhanced water solubility in order to provide new preclinical *in vivo* OMRI diagnostic methods.

**Acknowledgments**: This study was achieved within the context of the ANR PULMOZYMAGE (ANR-15-CE18-0012-01).

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# Nanoconfinement Effect on Phenoxyl Radical Lifetime in Nanostructured Silica

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Organic radicals and materials have already a long common history. Organic radical precursors have been adsorbed in zeolites, grafted onto silicas and onto nanostructured silicas. In these previous studies the organic radical precursor was introduced in the material by simple adsorption or by post-grafting, in other words with no means to control the distribution of the radical precursor in the inorganic material.
Recently, our group focused his attention on the effect of nano-structuration on the behavior of transient radical. [1],[2]

In this study, we report the effect of nanoconfinement on phenoxyl radical properties when a radical precursor was wittingly located in the wall or in the pores of a nanostructured silica. Several phenoxyl radical precursors[3] were considered as well as various substitution.

This nanoconfinement enables to a transient phenoxyl radical to become persistent and thus facilitates the determination of spectroscopic properties. The influence of the radical precursor and the substitution on the radical lifetime will be presented.

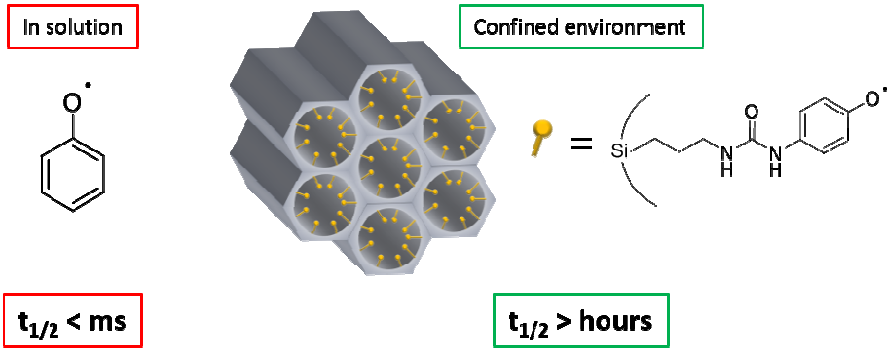


*Figure 1 : Influence of nanoconfinement on radical lifetime*

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# NOVEL ACCESS TO COMPOSITE BY POLYMERIZATION OF METHACRYLATES USING NEW PHOTOINITIATING SYSTEMS UPON NIR LIGHT

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Photopolymerization under near infrared (NIR) light is challenging due to the low energy of the absorbed photon, but if successful, presents significant advantages. For example, this lower energy wavelength is safer than UV-light that is currently the standard photocuring light source [1]. Also, NIR allows for a deeper light penetration within the material and therefore resulting in a more complete curing of thicker materials containing fillers for access to composites. In this study, we report the use of three-component systems for the NIR photopolymerization of methacrylates. 1) a dye used as a photosensitizer in the NIR range, 2) a iodonium salt as a photoinitiator for the free radical polymerization of the (meth)acrylates and 3) a phosphine to prevent polymerization inhibition due to the oxygen and to regenerate the dye upon irradiation [2]. Several NIR absorbing dyes such as a cyanine borate and a silicon-phthalocyanine are presented and studied. Systems using borate dyes resulted in methacrylate monomer conversion over 80% in air. We report three types of irradiation system: low power LED @660 nm and @780 nm as well as a higher power laser diode @785 nm. The excellent performance reported in this work is due to the crucial role of the added phosphine.

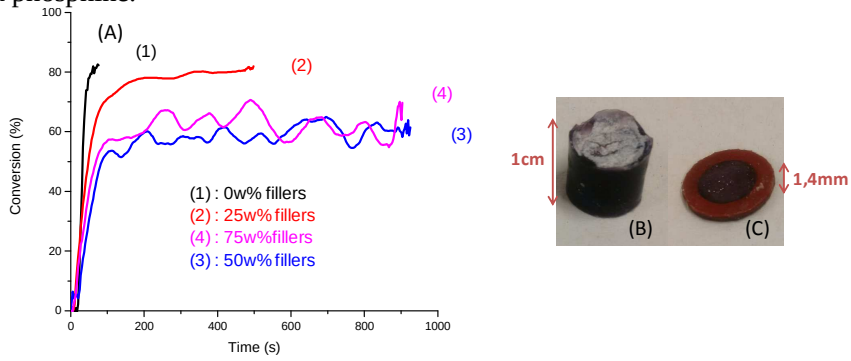


**Figure 1** – Photopolymerization of methacrylate under air with different fillers contents (up to 75w%) upon irradiation to NIR light @785nm (A) profiles (methacrylate functions conversion vs. irradiation time) (B) and (C) Example of composite produced under NIR light with 75w% fillers

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# Chemical modifications of imidazole-containing alkoxyamines increase C–ON bond homolysis rate: effects on cytotoxic properties in glioblastoma cells

Toshihide Yamasaki,[a] Duje Buric,[b] Christine Chacon,[b] Gérard Audran,[a] Diane Braguer,[b,c] Sylvain R. A. Marque,[a,d] Manon Carré[b,*] and Paul Brémond[a,e,*]

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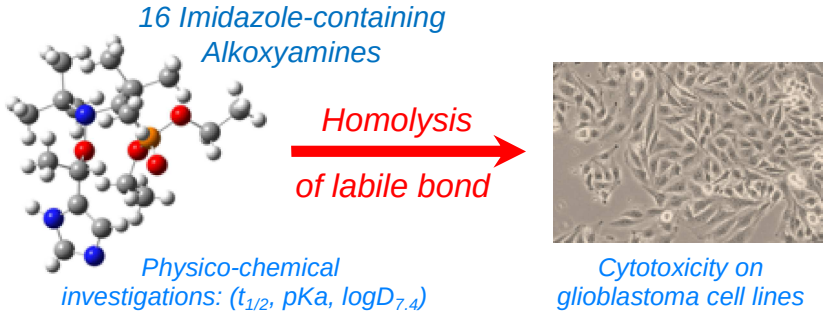
Previously, we described alkoxyamines $R^1R^2NO–R^3$ as new pro-drugs with low molecular weights and theranostic activity. Alkoxyamines, upon chemical stimulus, can be activated to release free radicals: i) a nitroxide $R^1R^2NO•$ which can, reportedly, enhance magnetic resonance imaging and ii) an alkyl radical $•R^3$ able to trigger cancer cell death.

We recently investigated the synthesis and the anti-cancer activity of novel alkoxyamines containing an imidazole ring. Activation of the homolysis was conducted by protonation and/or methylation. These new molecules displayed cytotoxic activities towards human glioblastoma cell lines, including in U251-MG cells that are highly resistant to the conventional chemotherapeutic agent Temozolomide.

We further highlighted that the biological activities of the alkoxyamines were not only related to their half-life times of homolysis. However, their favorable $logD_{7.4}$ and $pK_a$ values as well as a strong probability of not being a substrate for efflux transporters makes them robust candidates for blood-brain barrier penetrating therapeutics against brain neoplasia.

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# Anionic Polymerization Initiated By Organic Electron Donors

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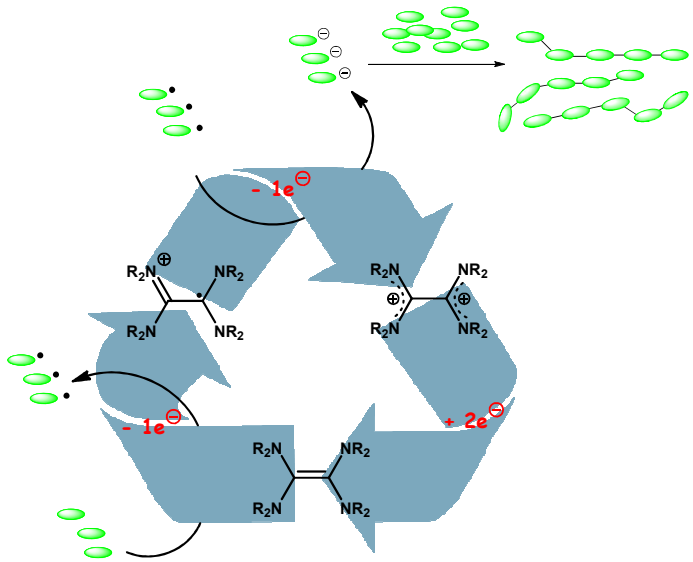
Organic electron donors (OEDs) with exceptionally negative redox potentials showed their potency and chemoselectivity in the reduction of challenging substrates.[1-3] They promote the formation of radical or anionic intermediates by single- or double-electron transfers. These strong reducing agents are now attracting more and more the interest for original applications in diverse domains (coupling partners, redox switches, greenhouse gas reduction).

To further study the potential of OEDs, we decided to tackle the reduction of uninvestigated functional groups and the exploitation of the resulting active species in the initiation of chain-growth polymerizations. Organic electron donors revealed to be remarkable polymerization initiators, allowing the development of an efficient, simple and room temperature process, responding to energy-friendly, cost-efficient and secure technical specifications. Their high group tolerance makes them fully compatible with the synthesis of a large range of polymers and bio-polymers of wide industrial importance. Our mechanistic considerations support both the initiation through electron transfer and the anionic chain propagation.

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# Decarboxylation of Glutamic Acid Derivatives-Synthesis of Homoprolin Analogs

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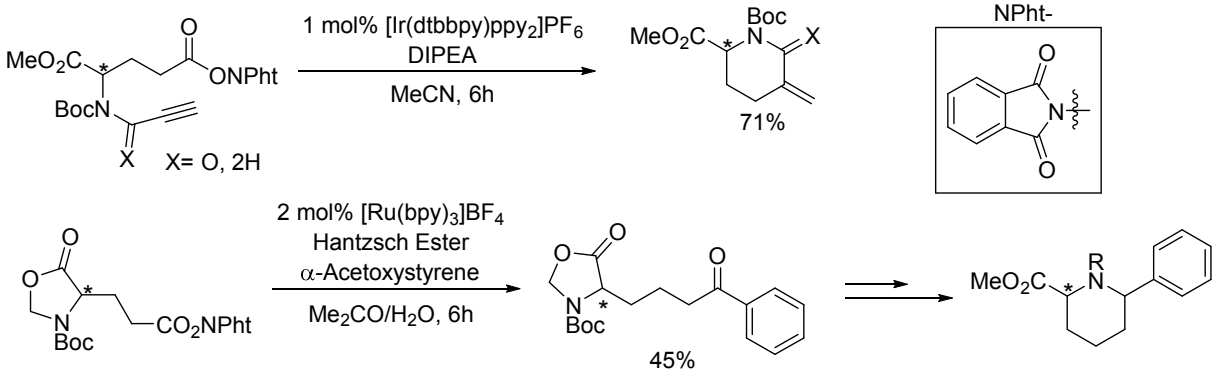
The visible light mediated decarboxylation of carboxylic acids represents an important technique to generate organic radicals.[1] Primary, unactivated carboxylic acids can easily be transformed to N-acyloxyphthalimides, which undergo decarboxylation upon visible light irradiation in the presence of a catalyst and a sacrificial electron donor.[2] Upon release of neutral phthalimide and $CO_2$, the generated radical can undergo intra- and intermolecular reactions, such as addition to double or triple bonds.
Glutamic acid is used as an inexpensive starting material, which can be transformed to different amino acids, retaining the stereocenter in α-position. Therefore, the α-carboxyl group is adequately protected as ester or oxazolidinone[3]. Then, either a propargyl or propiolate group is introduced, allowing for intramolecular cyclization, or addition to α-acetoxystyrenes[4] takes place upon decarboxylation of the γ-carboxyl group (Scheme 1). The intramolecular cyclization leads to pipecolic acid derivatives [5] exhibiting an exo-methylene group, which constitutes an excellent site for further functionalization.




**Scheme 1**: Intra- and intermolecular reactions of Glu-derivatives leading to pipecolic acid analoges.

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# Immobilization of Photocatalysts on Solid Supports *via* Electrostatic Interactions

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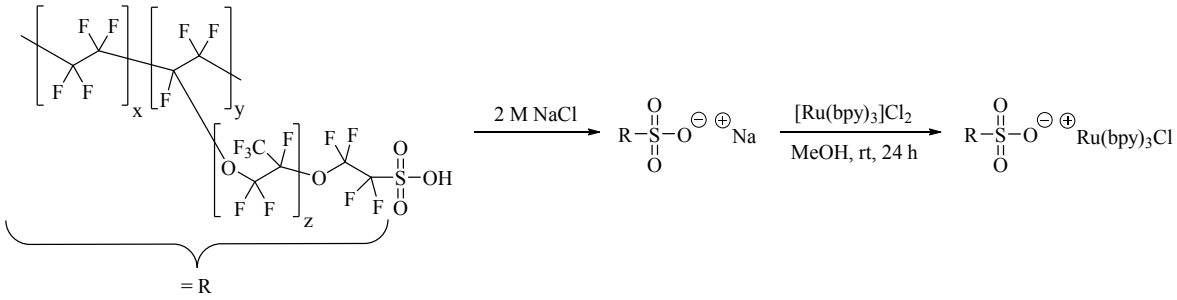
In recent years many discoveries were made in the field of photochemistry mediated by visible light which is inexpensive and readily available, not polluting the environment and able to transfer energy under mild reaction conditions. Since most of the organic compounds are not able to absorb light in the visible light range, a number of photosensitizers and photocatalysts were discovered absorbing the visible light and delivering the absorbed energy for the substrate molecules. Often very costly Ru an Ir complexes are employed for this purpose, however, their homogeneous nature makes it difficult to recover the catalyst after a reaction.[1, 2]
The immobilization of transition metal photocatalysts on solid supports, e.g. Nafion®/silica nanocomposites, *via* electrostatic interactions promises a broad range of easy accessible heterogeneous photocatalysts. Within only two steps different positive charged transition metal photocatalysts, e.g. $[Ru(bpy)_3]Cl_2$, can be attached to Nafion® *via* an ionic exchange (Scheme 1).[3, 4]




**Scheme 1**: Immobilization of $[Ru(bpy)_3]Cl_2$ onto Nafion *via* electrostatic interactions.

The heterogeneous nature of the catalysts enables the recycling by centrifugation and its subsequent reusability in visible-light mediated reactions. Depending on the choice of solvents and reaction additives, only slight decrease in catalytic efficiency within several runs is observed.

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## Radical Remote C–H Arylation of Unactivated Aliphatics

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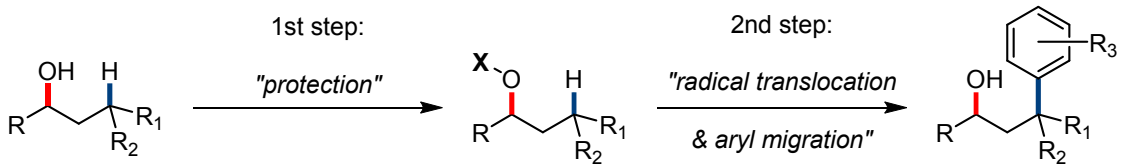
Due to the inherently high bond-dissociation energy of unactivated C($sp_3$)–H bond, its selective chemical functionalization sets one of the greatest synthetic challenges and has received much research attention for decades. Recent successful studies of the functionalization of primary and secondary aliphatic C–H sites mostly focus on the use of transition metal catalysis in combination with substrates bearing directing groups to overcome selectivity and reactivity issues. [1]

In contrast, the functionalization of tertiary C–H bonds is often enabled by homolytic bond cleavage introducing the chemistry of free radicals as a complementary approach. Intramolecular hydrogen atom transfer processes have been established to address otherwise mostly unreactive remote C($sp_3$) –H sites with the well-known Barton and Hofmann-Löffler-Freytag reactions being early examples of distal C–H functionalization [2-4]. This concept was widely adapted by many groups recently, yet not addressing the remote arylation reaction of aliphatic carbon chains mediated by free radicals.

***Concept for Remote C–H Arylation:***




**X**: "*radical translocation arylation group*"

Herein we present a novel approach for the γ-arylation of aliphatic alcohols introducing designed "radical translocating arylating groups" [5, 6]. These functional groups offer both the source of a remotely generated radical and a migrating aryl moiety. Moderate to good yields are obtained, remote C–H arylation occurs with excellent regioselectivity and for secondary C($sp_3$) –H bonds good to excellent stereoselectivity is achieved. The experimental findings let to a mechanistic proposal that is broadly supported by detailed DFT studies.

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# Metal Acetylacetonate –Bidentate Ligand Interaction (MABLI) as Highly Efficient Free Radical Generating Systems for Polymer Synthesis

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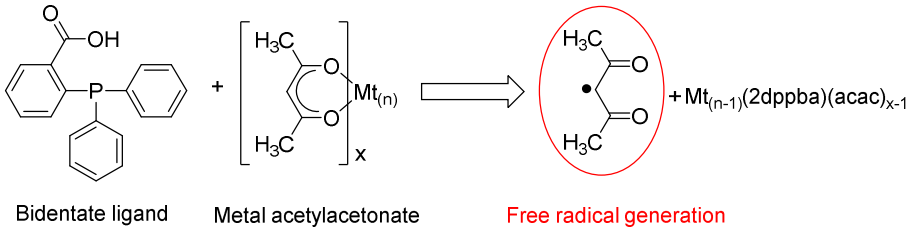
Nowadays, roughly 45 wt% of the polymers are produced thanks to free radical polymerization (**FRP**) processes. At room temperature, under air (oxygen inhibition), without energetic consumptions (thermal or radiatives) and without distillation of the vinylic monomers, FRP initiating systems have to be outsandingly efficients. We propose in the present communication the "Metal Acetylacetonate –Bidentate Ligand Interaction" (MABLI[1]) as a new two-component FRP initiating strategy for (meth)acrylates polymerization. Elegantly, **MABLI initiating systems avoid the use of hazardous peroxides** (or other O-O or S-S weak bond containing compounds) or carcinogenic amines that are currently proposed in redox initiating systems. Indeed, in a MABLI approach (Scheme 1), bidentate ligand chelate metal acetylacetonates with simultaneous: i) change of oxidation degree for the metal (n to n-1) and ii) release of acetylacetonate-like radicals. These latter can find use for the initiation of FRP; doing so they are competitive with redox FRP references such as 4-*N*,*N* trimethylaniline/dibenzoyl peroxide systems. **The chemical mechanisms involved will be studied exhaustively** thanks to ESR, ESR spin trapping, HR-ESI-MS, NMR, UV-vis spectrometry, molecular modeling, cyclic voltammetry, FRP followed by optical pyrometry and Raman confocal microscopy.




**Scheme 1.** Metal Acetylacetonates – Bidentate Ligand Interaction (MABLI) for free radicals initiating systems[1].

As a perspective for the present communication, we will also demonstrate: i) near infrared **(NIR) photoactivation** of MABLI processes and ii) possible ***grafting from* polymerization** using stable copper methacryloyloxyethylacetoacetate ($Cu(AAEMA)_2$ under mild conditions.

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# Exploring the Reactivity of Vinyl and Dienyl Boron Ate Complexes in Radical-Polar Crossover Reactions

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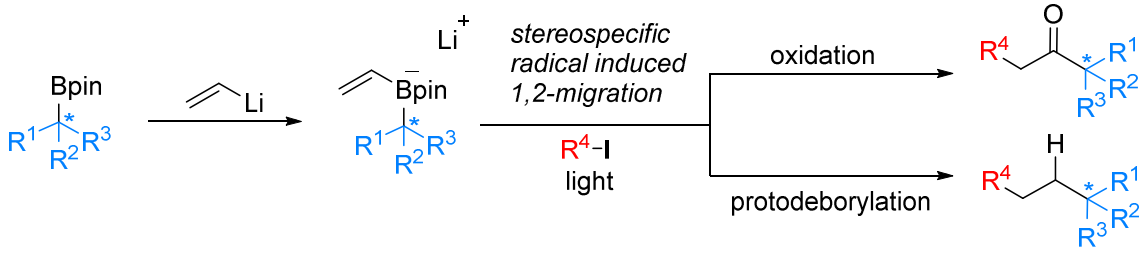
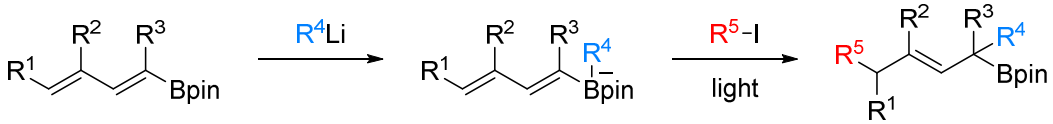
Vinyl boronic esters and their corresponding ate complexes are highly valuable substrates in organic synthesis. Besides their use in *Suzuki Miyaura* couplings[1] they are known to undergo 1,2-migration promoted by electrophilic halogenation[2] or palladation.[3] As recently demonstrated, vinyl boron ate complexes also act as efficient radical acceptors and the corresponding radical anions undergo a radical-polar cross over reaction allowing the synthesis of secondary and tertiary alkyl boronic esters.[4]

Along these lines, we will show that chiral vinyl boron ate complexes of enantioenriched secondary alkyl boronic esters undergo a stereospecific radical-induced 1,2-migration in a radical-polar cross over reaction. Various alkyl iodides can be used as radical precursors in this light initiated chain process. Subsequent oxidation of the intermediate boronic esters offers a new route to α-chiral ketones and β-fluorinated enones, while protodeborylation provides chiral alkanes. The products are isolated in moderate to good overall yields and excellent stereospecificity.[5]




In addition, the strategy was applied to the synthesis of synthetically useful allylic boronic esters. To this end dienyl boronic esters were used as starting materials and radical addition occurred at the vinylogous position. The following 1,2-migration provided the desired products in good yields.[6]
Notably, both protocols presented proceed without the need of a transition metal and allow facile modular construction of versatile, valuable compounds via formation of two C-C bonds using three components - pinacolboronic esters, lithium reagents and commercial iodides as radical precursors.

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# Synthesis of arylated nucleobases by visible light photoredox catalysis

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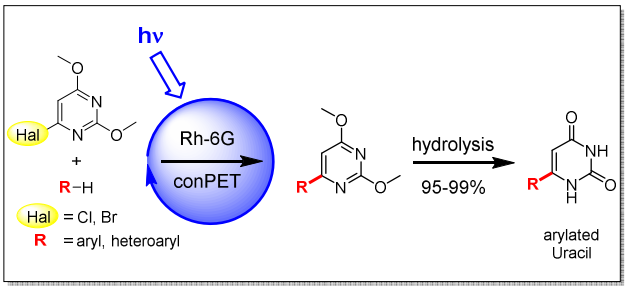


Arylated nucleobases were synthesized by visible light photocatalysis using rhodamine 6G as photoredox catalyst and *N*,*N*-diisopropylethylamine as sacrificial electron donor. The high redox potential of this catalyst system is achieved by a consecutive photoinduced electron transfer process (conPET)[1] and allows the room temperature conversion of brominated and chlorinated nucleobases or nucleobase precursors as starting materials. In contrast to many transition-metal-based syntheses, a direct C−H arylation of nitrogen-containing halogenated heterocycles is possible without protection of the N−H groups.[2] The method provides a simple, metal-free alternative for the synthesis of biologically interesting arylated heterocycles under mild conditions.

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# Photochemical derivatization of helicenes

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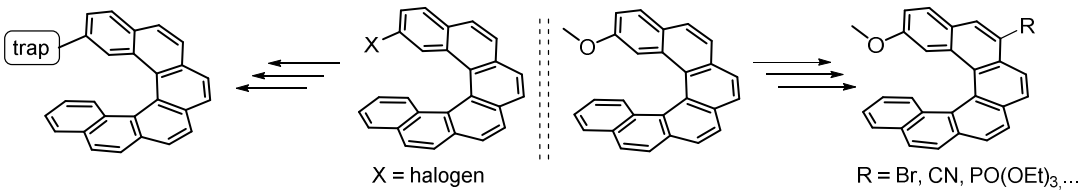
Helicenes are chiral polyaromatic compounds of great potential in many fields, such as asymmetric catalysis, optoelectronics, or material sciences[1]. The most commonly used methods of preparation of helicenes – photocyclization and [2+2+2] cycloaddition – can be both successfully used for incorporation of different functional groups into the helicene structure, however the scope of functional groups can be limited and/or requires time consuming multistep procedures[2]. This obstacle can be overcome by derivatization of simple helicene derivatives. Several articles discussing late-stage derivatization of helicenes were published in the last few years[3-4].

This work is focused on the use of simple helicene derivatives as substrates for modern photochemical methods. Halogen containing substrates are transformed in the reductive pathway to helicenyl radicals, before being trapped by different radical traps. In the oxidative pathway, activated alkoxyhelicenes undergo photoredox catalyzed reactions, yielding various carbon-carbon, as well as carbon-heteroatom containing compounds.




**Scheme 1:** Derivatization of helicenes.

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# Advanced photopolymers materials and photoinitiating systems for 3D printings

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Three-dimensional (3D) printing is an additive manufacturing technology that allows fabrication of 3D objects by adding successive layers of materials (e.g. photopolymers) on top of each other. In the last few years, this promising technology has developed rapidly and has found numerous applications in various fields (e.g. electrical components, dentistry, food industry, surgery and biomaterials implants).
This project is a collaboration between an industrial partner and an academic laboratory aims to develop new photosensitive resins outside usual acrylate and epoxy systems for our study. With this approach, the production of new polymer products that can be designed in a short time and for a low price in industrial 3D additive manufacturing will be presented. These photosensitive resins consist of bio-based polymers. Today, faced with the growing scarcity of non-renewable raw materials, the development of bio-based products is a priority for the industry. This chemistry has a very important advantage in particular by limiting greenhouse gas emissions and all environmental impacts (toxicity, waste). All the components of the resin (photoinitiators and monomers/oligomers) have been developed for a specification towards the use of: visible light irradiation 'light-emitting diode LED', low intensity, low viscosity and writing fast speed.

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# Silyl Glyoxylates as a New Class of Photoinitiators for Blue LED Induced Polymerization

Julie Kirschner;[a] Mariem Bouzrati-Zerelli;[a] Christoph P. Fick;[c] Maximilian Maier; [b] Céline Dietlin; [a]

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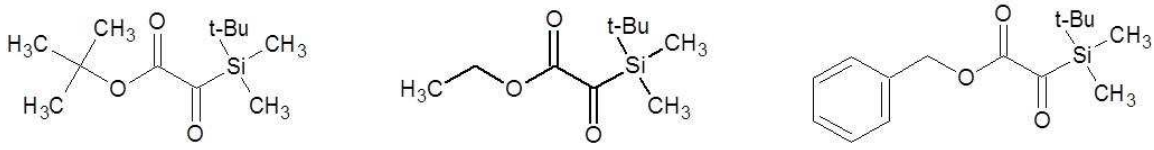
Silyl glyoxylates (e.g., DKSi, Et-DKSi and Bn-DKSi in Scheme 1) are proposed as a new class of high performance photoinitiators for the free radical polymerization of methacrylates upon near-UV or blue light emitting diodes (LEDs).

Three silyl glyoxylates (Scheme 1) have been synthesized and checked as novel photoinitiating systems for the radical polymerization of thick samples of a urethane dimethacrylate (UDMA) upon exposure to a blue LED (477 nm) under air. The modification of the ester group has been investigated in order to check the relationship between the nature of the substituent and the reactivity of the derivative. Remarkably, silyl glyoxylates can operate alone due to their Type I character or they can be used in presence of an amine (Type II behavior). Thick samples (1.4 mm), tack-free polymers as well as the access to composites can be easily obtained.

The silyl glyoxylates-based photoinitiating systems exhibit excellent polymerization performance under blue LED (477nm) with exceptional bleaching properties compared to CQ systems.




Scheme 1. Structures of DKSi, Et-DKSi and Bn-DKSi.

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# Photosensitive Alkoxyamine: Mechanistic Insights

A. Lin[a*] ; J. C. Morris[a] ; J.-L. Clément[a] ; Y. Guillaneuf[a] ; S. Bottle[b] ; K. Fairfull-Smith[b] ; D. Gigmes[a]

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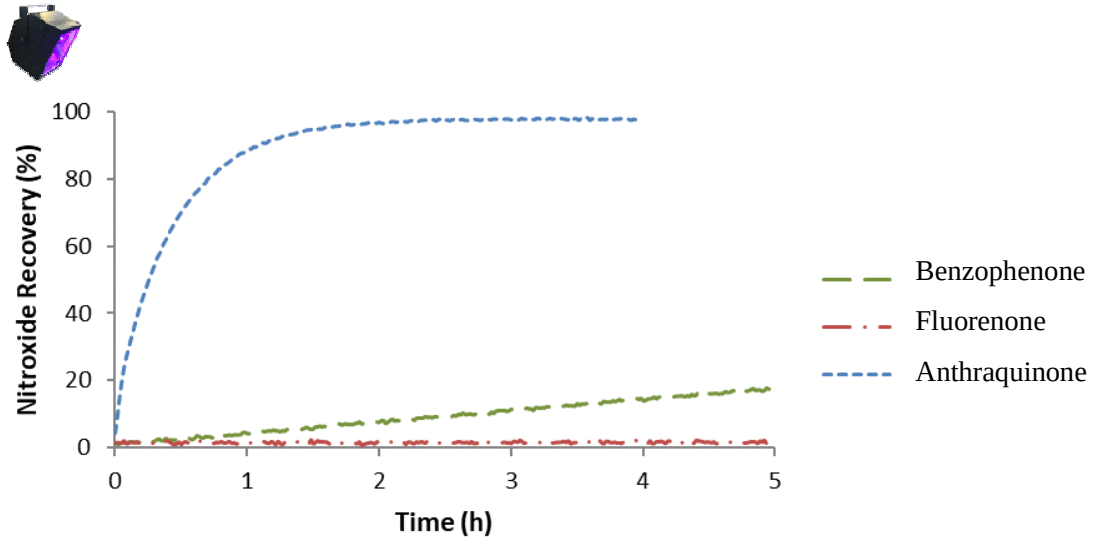
Photosensitive alkoxyamines are comprised of a chromophore covalently linked to an alkoxyamine moiety, which, under electromagnetic irradiation, cleave to generate alkyl and nitroxide radicals. This process provides special and temporal control over the release of nitroxides, which underscores their interest in nitroxide-mediated photopolymerization.
The quintessential feature of photosensitive alkoxyamines is the translation of electromagnetic energy into chemical energy to facilitate alkoxyamine bond homolysis. Despite the importance of this process, the mechanism of energy transfer from the excited state chromophore to the pendant alkoxyamine moiety has not been established. Recently however, Rotllant et al. used quantum mechanical calculations to propose that under UV irradiation, alkoxyamine bond homolysis proceeds through photoinduced electron transfer- (PET) type processes. [1]
To investigate the potential role of PET processes in the photo-dissociation of photosensitive alkoxyamines, novel fluorenone-, benzophenone- and anthraquinone-based photosensitive alkoxyamines were examined. Photochemical investigation of the examined photosensitive alkoxyamines demonstrated that the photo-dissociation efficiencies followed a trend predicted by the excited state reduction potential of the chromophore (fluorenone < benzophenone < anthraquinone), supporting the involvement of PET processes in the photo-dissociation of alkoxyamines.

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# Electrochemically initiated Trifluoromethylation of Biaryl Isonitriles

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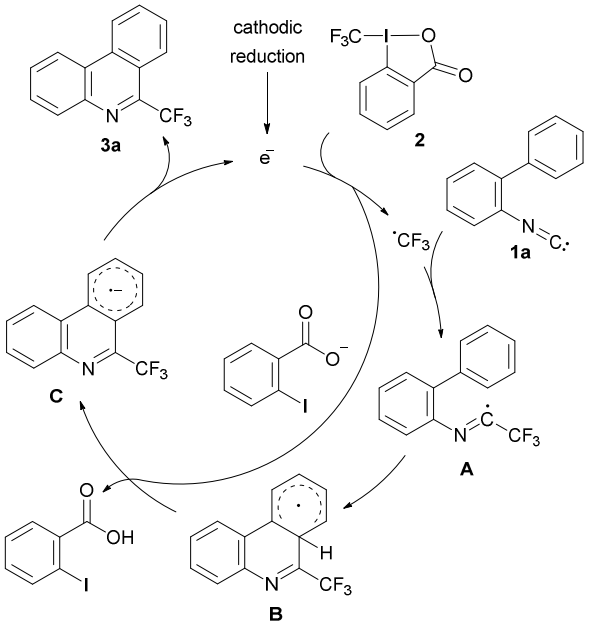
The efficient synthesis of phenanthridines via electrochemically initiated trifluoromethylation of biaryl isonitriles is presented.[1] The catalytic amount of electric charge verifies the electron's catalytic character, which was proposed previously for this reaction.[2] Turnover numbers up to 49 are reached. Considering the background current, turnover numbers up to 300 are reasonable.
The trifluoromethylation proceeds via cathodic reduction of the employed Togni reagent **2**, generating a trifluoromethyl radical that can add to the isonitrile functionality of substrate **1a**. The formed imidoyl radical **A** undergoes an intramolecular cyclization forming a highly acidic cyclohexadienyl radical **B**. Deprotonation is facilitated by the ortho-iodobenzoate that is formed as a byproduct during the reduction. The resulting radical anion **C** can sustain the catalytic cycle by transferring an electron to another Togni reagent molecule, yielding the desired 6-(trifluoromethyl)phenanthridine.




After initiation with an electric charge of 0.075 faraday/mol, yields between 63% and 80% were obtained for 13 further substrates. The applicability of the reaction in 4 mmol scale was shown. Cyclic voltammetry experiments support the suggested mechanism.

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# Radical Cascades Triggered by Alkoxyl Radicals in Cyclodextrin Frameworks

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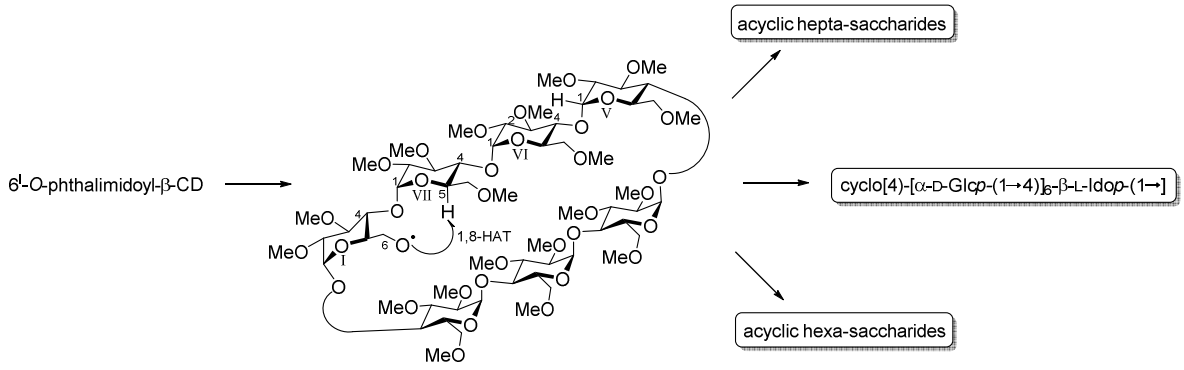
In the last decades, cyclodextrins (CDs) and their derivatives have widely investigated due to their ability to encapsulate biomolecules in their internal cavity and being potential nanocarriers. Hence, an intense research to modify their structure and modulate their properties through chemical transformations has developed, being the radical method practically unknown in these macromolecules.[1]
In previous papers we have described an novel intramolecular 1,8-hydrogen atom transfer (1,8-HAT) reaction between the two pyranose units in Hex*p*(1→4)-Hex*p* disaccharides systems (e.g., D-(+)-maltose),[2] promoted by alkoxyl radicals, that allows a remote C-H functionalization in the vicinal units. Herein, we will present our most recent work by extension of this methodology to more complex carbohydrates such as CDs.[3] The well-suited disposition of the glucose units in these macrostructures favors that $6^{I}$-*O*-yl radical can get involved into a radical cascade process: the initial 1,8-abstraction of the H5 of the contigous sugar generate a C5-radical which can move through the saccharide skeleton and reach the anomeric hydrogen three sugar units ahead. Moreover, the cascade can selectively stop at different carbons, simply by choosing the proper reagent, to produce interesting cyclic and acyclic saccharides with different terminal residues.

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# Copper Photoredox Catalyst "G1" as New Class of Photoinitiator under Soft Irradiation Conditions: Access to Composite Materials and LED 3D printing Technology

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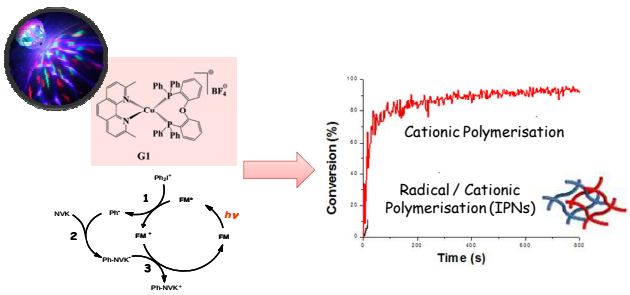
A novel photoinitiating system operating under LEDs for the radiation curing market is proposed. It is usable in industrial processes for coating applications (cationic polymerization of epoxide based resins), the manufacture of Interpenetrating Polymer Networks (IPNs) (polymerization of acrylate/epoxy blends) and the production of thick epoxy/glass fibres composites. Our approach relates to the use of a photoredox catalyst as no photoredox catalyst is commercially available yet. Here, the promising copper complex called G1, disclosed in [1], is investigated as a high performance photoinitiator PI upon irradiation with near UV or visible Light Emitting Diodes (LEDs) exposure. It allows the design of very efficient photoinitiating systems (G1/iodonium salt [Iod]/N-vinylcarbazole [NVK] (Scheme 1)). The effects of resin, light source (LED at 375, 395, 405 nm, halogen lamp), G1 concentration, coating thickness (25µm, 1.4 mm), water content, formulation stability and the hydrolytic stability of the cured coatings were investigated. Remarkably, in the different studied applications, the G1/Iod/NVK system is much better than BAPO/Iod/NVK used as a reference system, which is already characterized by a good reactivity in the 365-420 nm range. Owing to the excellent catalytic behaviour of G1, very low loadings of G1 are required compared to BAPO. The use of G1 based system in photocurable cationic formulations for LED projector 3D printing is particularly outlined. The development of photoredox catalysts such as G1 is the new means of creating photoinitiating systems with an unprecedented reactivity.




Scheme 1. Photoredox catalytic cycle for the three-component G1/Iod/NVK system.

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# Alkoxyamine as probe to quantify the efficiency of the photochemical or thermal homolysis of C-O bond in nanostructured silicas

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Development of new materials with unusual functional groups, such as radicals, is of topical interest to enable new advances in spin sciences. Properties related to the presence of unpaired electrons, such as conductivity or magnetism, have been studied in order to develop smart devices.

Recently, our group focused his attention on the effect of nanostructuration on the behavior of transient radical. Therefore it has been shown that confinment of organic radicals in porous material allows a great increase of radical lifetime. [1-6]

In this study, we report the design of a nanostructured silica functionalized with an alkoxyamine which can led to a stable nitroxide radical upon either light irradiation or thermal heating. The formation of the nitroxide radical can be quantify and enables to evaluate the efficiency of the C-O bond homolysis in a mesoporous material.

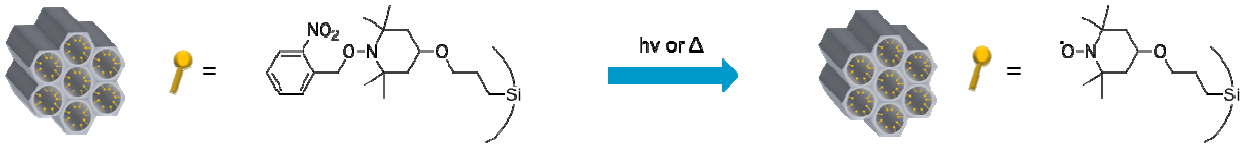


*Figure 1: Formation of nitroxide radical on mesoporous silica*

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# Red light-mediated Barton-McCombie reaction

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Barton-McCombie reaction is a radical-mediated deoxygenation reaction, which frequently plays a key role in total synthesis [1]. However, the typical conditions involve highly toxic organotin hydride and heating in the presence of explosive radical initiator such as azoisobutyronitrile, and therefore unsuitable for industrial application (Fig. 1). Even though photoredox conditions have also been reported, it required relatively high-energy light irradiation [2,3].

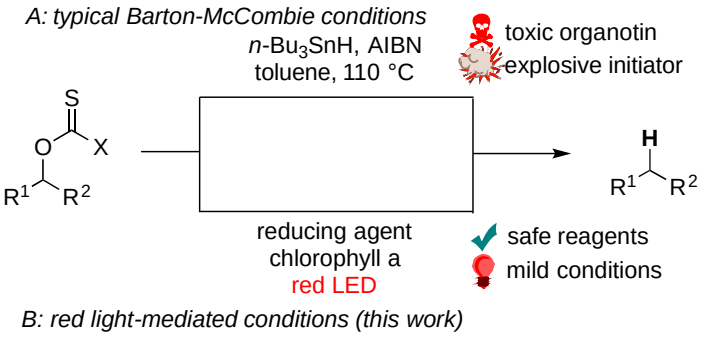
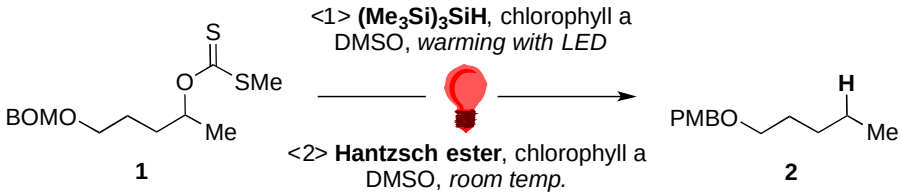



**Figure 1.** Barton-McCombie reaction.

Recently, Xu and Boyer reported a radical polymerization conditions using thiocarbonyl compound as a reversible radical initiator, chlorophyll as a photoredox catalyst and low-energy red light as an energy source [4]. Considering the similarity of reaction mechanism between the Xu-Boyer conditions and the Barton-McCombie reaction, we decided to develop a mild and environment-friendly radical deoxygenation reaction.

The xanthate **1** was irradiated with red LED in the presence of various reducing agents and readily available chlorophyll. We found two optimum conditions: <1> tris(trimethylsilyl)silane as the reducing agent and mild warming with LED-derived heat, which gave excellent yield, and <2> Hantzsch ester as the reducing agent with continuous cooling to room temperature (Scheme 1). Purification procedure is also simple, thus rendering Barton-McCombie reaction even more practical. The details of the reaction optimization, the substrate scope as well as reaction mechanism will be discussed.




**Scheme 1.** Red light-mediated Barton-McCombie reaction.

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# Binding and Reactivity in Water Soluble Cavitands

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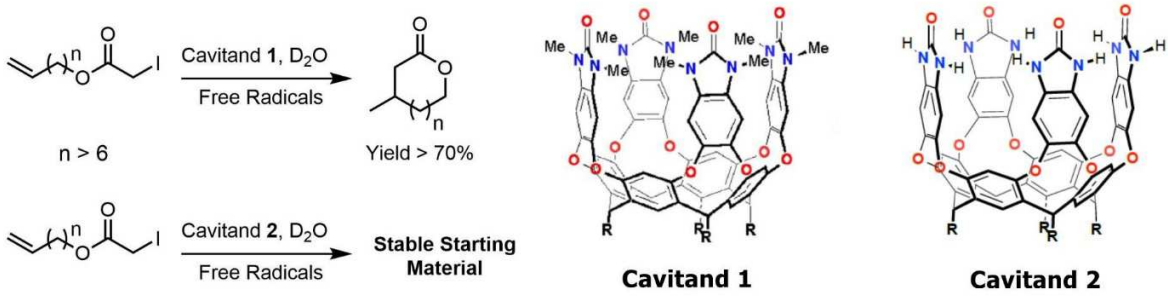
Radical processes in organic chemistry allow the production of new synthetic building blocks, but control of radicals is difficult due to their high reactivity. Moreover, the use of green solvents (i.e., water) is still far from extensive in this field [1]. The water-soluble cavitand host **1** is able to act as a template for macrocyclisations of several guests [2], and the binding of $\alpha$-iodo carbonyl compounds having a terminal alkene was studied. The reactivity of the host–guest complex was explored in aqueous medium, using free radical initiators. The macrolactones ($n_C$ > 10) were obtained in good yield (> 70%) under thermodynamic conditions (t > 40°C). The products were detected and confirmed by $^1$H-NMR and LCMS analyses. The new synthetic procedure for macrolactones may also be applicable to macroketones and macroalkanes to provide access to product selectivities differing from those of conventional reaction systems. The same process was studied using cavitand **2**, that captures guests to form stable capsules in aqueous medium [3]. The encapsulation guarantees stability towards free radicals in solution and promises the use of cavitands as protecting groups for chemical processes.




General scheme of the reactivity in water-soluble cavitands

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# ALKOXY RADICAL FRAGMENTATION (ARF) AS KEY STEP FOR THE SYNTHESIS OF 1-PHOSPHA-SUGARS

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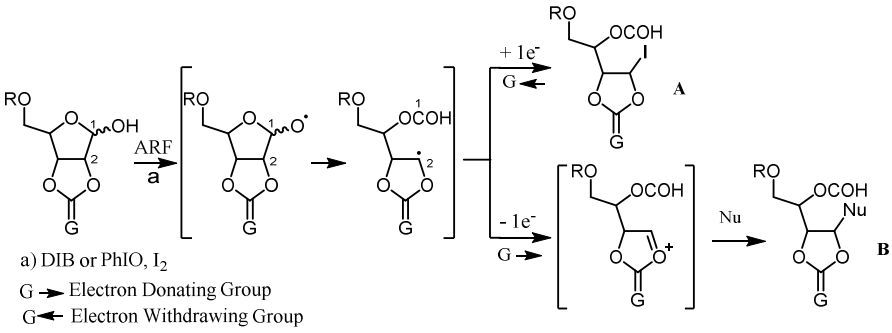
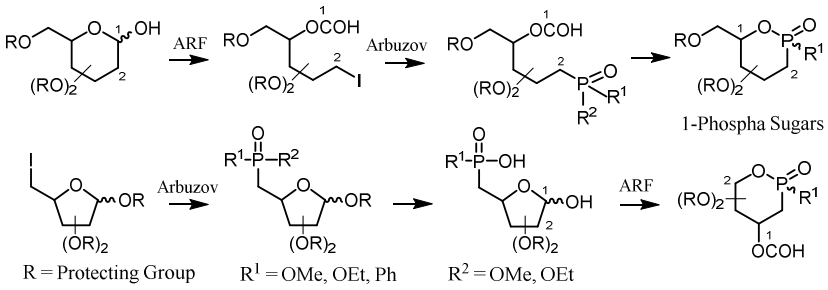
When we apply ARF[1] to carbohydrates, an alkoxy radical in anomeric position is formed, β-fragmentation takes place and generates a formate group at the anomeric carbon and a C2-radical. Substituent located in the C2-radical play a decisive role. When G is an electron withdrawing group, decrease the electron-density, the oxidation is more difficult and the radical can be trapped by iodine atom (A). When G is an electron donating group, C2 radical is always oxidized by an excess of the reagent to give an oxocarbenium ion through a radical polar crossover mechanism. This ion may be trapped inter or intramolecularly by nucleophiles (B).




1-Phospha-sugars have a phosphorus atom in place of the anomeric carbon. They have attracted some synthetic interest due to their potential activity as glycosidase inhibitors and anticancer agents. We design a new approach to obtain P-sugars (also called phostones[2] and phostines) in few steps and good yields starting from carbohydrates using ARF (A or B) as key step and Arbuzov[3] reaction to introduce phosphorus.

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# Organic Super Electron Donors Made Catalytic - A New Concept in Catalysis

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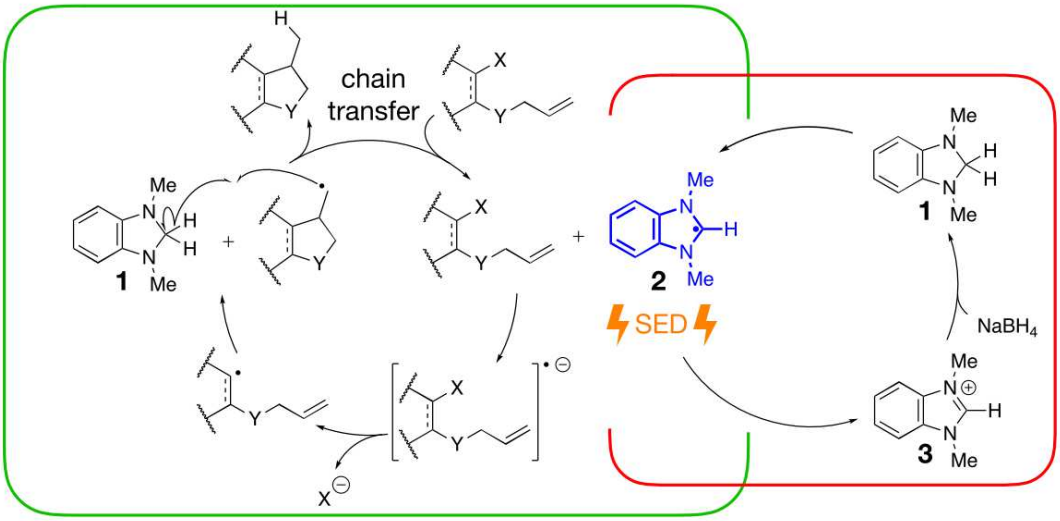
Organic electron donors are interesting from a sustainability and cost point of view and because they complement the reactivity of metal-based reducing agents. Accordingly, their study received much attention.[1] Strong organic or metallic reducing agents are usually used in stoichiometric amounts and they require elaborate techniques for manipulation due to their air-sensitivity. We found inspiration in the work of Giri,[2] Chikashita[3] and Tanner[4] to address these points.

*In a first step* we present how the reactivity of an organic super electron donor (SED) can be exploited in radical chain reactions starting from an easy-to-handle precursor **1**. Hydrogen abstraction from aminal **1** in the chain transfer step gives the single electron donor species **2**. The reactivity of the aminal **1** has been put to test with several model substrates.

*In a second step* aminal **1** was generated *in situ* from a catalytic amount of the salt **3** and a stoichiometric amount of a hydridic reducing agent. Similar reactivity was observed with the catalytic conditions for several model substrates. Overall, the catalytic protocol represents the conversion of an economical and mild hydridic reducing agent into a potent single electron donor species.

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# Photoredox catalysis with excited state anions: 9-Anthrolate catalyzed C-H functionalizations using visible light

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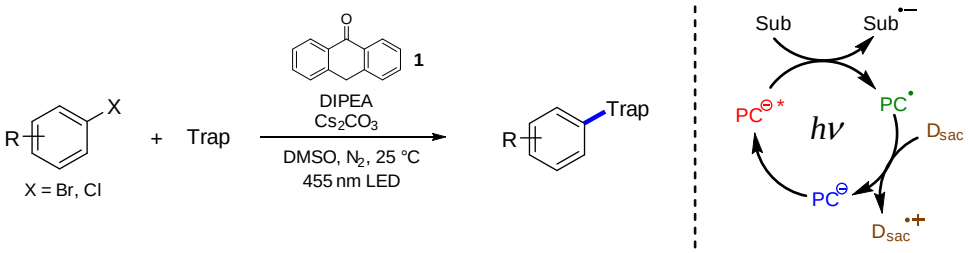
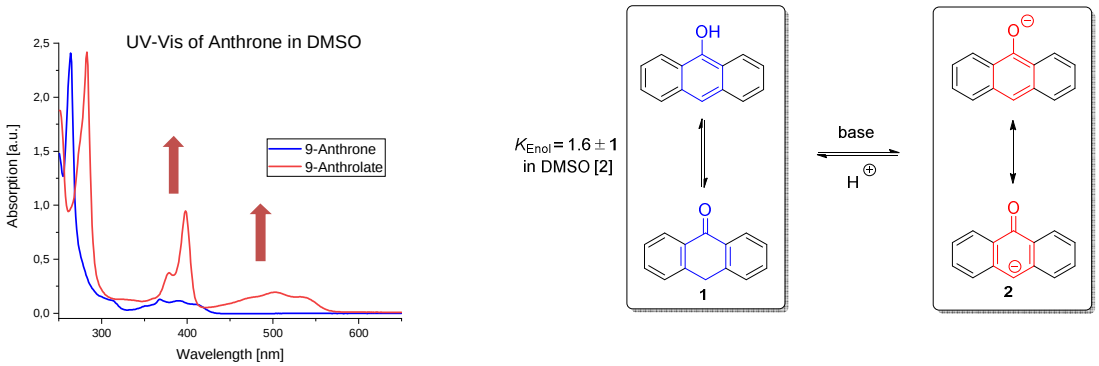
Forming C-C bonds has always been a ubiquitous challenge in synthetic organic chemistry to build up complex molecules from cheap and available starting materials. Photoredox catalysis emerged to an attractive tool and permits bond forming reactions under remarkably mild conditions. Widely used photocatalysts are, among others, the positively charged acridinium or triarylpyrylium-based dyes, which are known to act as powerful oxidants from their excited states.[1] However, contrary to those cationic representatives only little is known about anionic organic dyes in photoredox catalysis.




We found 9-anthrolate **2**, which can easily be generated in presence of a weak base like carbonate, to act as a strong reductant ($E_{red} \sim -2.1$ V vs. SCE) from its photoexcited state. Moreover, unlike the neutral 9-anthrone **1**, 9-anthrolate shows distinct absorption bands in the visible range and can therefore be excited with visible light. The excited state lifetime ($\tau_F = 19$ ns) determined for the anionic dye in DMSO was found to be remarkably long. The catalytic ability of 9-anthrolate **2** was examined in several C-C and C-Het bond-forming reactions which provide access to the corresponding coupling products in moderate to good yields. A reaction mechanism is proposed based on spectroscopic investigations.

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# Free Radical Polymerization Study on Vegetal Oils

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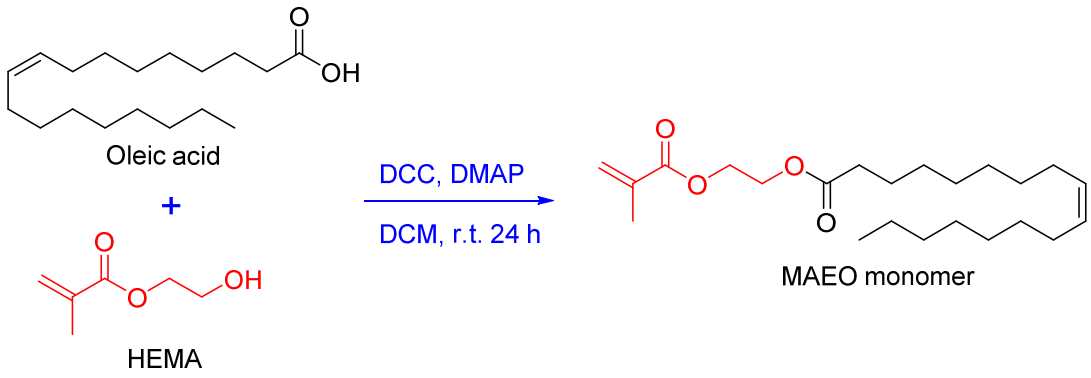
The interest in the production of biodegradable polymeric materials is continuously increasing in the last decade, with the scope to reduce the environmental impact caused by the large use of petroleum-based plastics. At the same time, a possible approach to a circular economy foresees the employment of derivatives from renewable sources. With this aim we are studying the possibility to produce polymers starting from fatty acids deriving from plant oils, eventually arising from waste materials. For this reason, we started considering oleic acid as a representative starting material which, in order to allow the production of the corresponding polymers, has been functionalized with metacrilic units as shown in the Scheme:




In such a study, different approaches have been evaluated, and the Free Radical Polymerization initiated by the AIBN thermal decomposition in the absence of any control agent has been taken as a reference. In the other approaches the reaction mixtures have been added with proper amounts of DPAIO nitroxide, [1] BlocBuilder® [2] and NMMA, [3] and the corresponding results have been compared considering the conversion yields, as well as the molecular weight of the obtained polymers. In addition, the retention level of the -C=C- double bond from the oleic acid moiety has been taken into account, in order to allow possible post polymerization modifications. Our preliminary results indicated that the use of NMMA as control agent produced the best results in terms of conversion yields as well as polymerization degree, although with a slight increase in polydispersity with respect to those recorded using BlocBuilder®. However, in all cases up to the 93% of -C=C- of oleic acid double bond retention has been found.

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# Mechanism of the Copper/TEMPO Catalyzed Aerobic Oxidation of Alcohols

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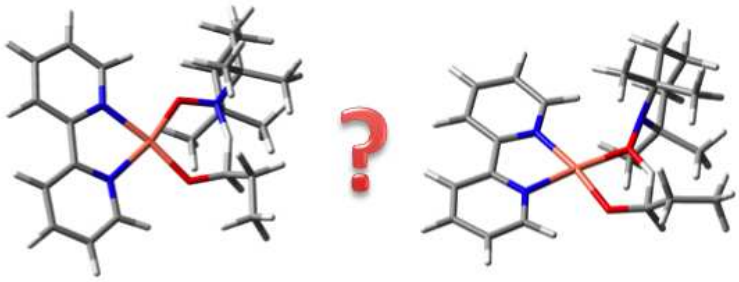
Text Identifying the mechanism of a catalytic reaction is paramount for designing new and improved catalysts. Several alternative catalytic cycles for the copper-TEMPO catalyzed aerobic oxidation of alcohols to the corresponding aldehydes or ketones were examined in their entirety using density functional theory at the SMD(CH3CN)-RIJCOSX-DSD-PBEB95/def2-TZVP//DF-PBED3BJ/def2-SVP level of theory.[1] A novel catalytic cycle in which TEMPO remains coordinated to copper throughout, was identified as the most likely mechanism. The overall 2 electron oxidation involves single electron changes in oxidation state for both copper and TEMPO. There are three components to the catalytic cycle: (1) hydrogen transfer from the alkoxy ligand to coordinated TEMPO (2) oxygen activation with formation of a peroxo complex, and (3) alcohol activation with transfer of the O–H proton to the peroxo ligand. The oxidation takes place via a six-membered intramolecular hydrogen transfer transition state. Importantly, this is not the rate determining step. Instead, the rate determining step involves oxygen activation and/or the initial alcohol activation.

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# Dual modes of Catalysis of Novel α-Hydrogen Nitroxide Radicals

Hila Toledo,[a,b] Michal Amar,[a,b] Sukanta Bar,[b] Mark A. Iron,[c] and Alex M. Szpilman[a] *

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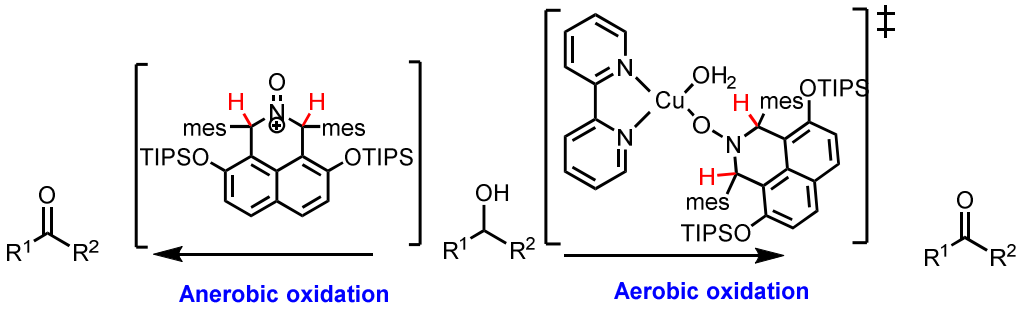
Nitroxide radicals have been used as radical trapping reagents as well as catalysts for oxidation of alcohols into carbonyl compounds and allylic transposition reactions.[1] One of the most efficient and widely used nitroxides is TEMPO. However, it has limited reactivity do to its highly hindered structure. A logical way to diminish the steric congestion is to replace an α-alkyl substituent with a hydrogen. Recently, we developed a new concept for designing stable α-hydrogen nitroxyl radicals.[2,3] We now report a study of their activity as catalysts in anaerobic[4] and aerobic[5] oxidations of alcohols. In each case the catalytic cycle and the reactive species are different. For instance, in aerobic oxidation the use of a copper-bipyridine co-catalyst is essential. In contrast, in anaerobic (two electron) oxidation the nitroxide alone functions as the catalyst.

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# Imidazolium *versus* aminopyridinium carboxylate adducts as precursors of Organic Electron Donors

**Guillaume Tintori**, [a] Pierre Nabokoff, [a] Ruqaya Buhaibeh, [a] David Bergé-Lefranc, [b] Sébastien Redon, [a] Broggi*[a] and Patrice Vanelle*[a]

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Organic electron donors (OEDs) with exceptionally negative redox potentials have been shown to be potent and chemoselective in the reduction of challenging substrates. [1] They promote the formation of radical or anionic intermediates by single- or double-electron transfers. These strong reducing agents are now attracting more and more the interest for original applications in diverse domains (coupling partners, polymerization initiators, redox switches, greenhouse gas reduction). [2] Nonetheless, their stability issues in atmospheric oxygen or over time complicate their manipulation and storage.

To overcome these constraints and enhance OED's practicality, new air- and moisture-stable azolium carboxylate and carbonate precursors were synthesized and thermally activated to *in situ* generate the potent electron donor. [3] Carboxylate adducts proved to be excellent OED-latent systems allowing easy and efficient reduction of challenging substrates.

We will present our comparative study between imidazolium and *hitherto* unknown aminopyridinium carboxy precursors. Their reducing properties are correlated to their structural characteristics by thermogravimetric and mechanistic analysis.

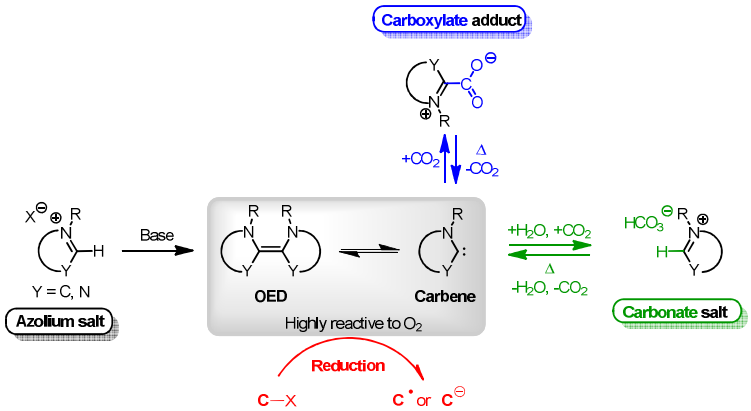


*Figure 1: In situ generation of OEDs*

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# Acessing intramolecular 1,5-HAT reactions of iminyl radicals by radical coupling to α-azidostyrene utilizing organic photoredox catalysts

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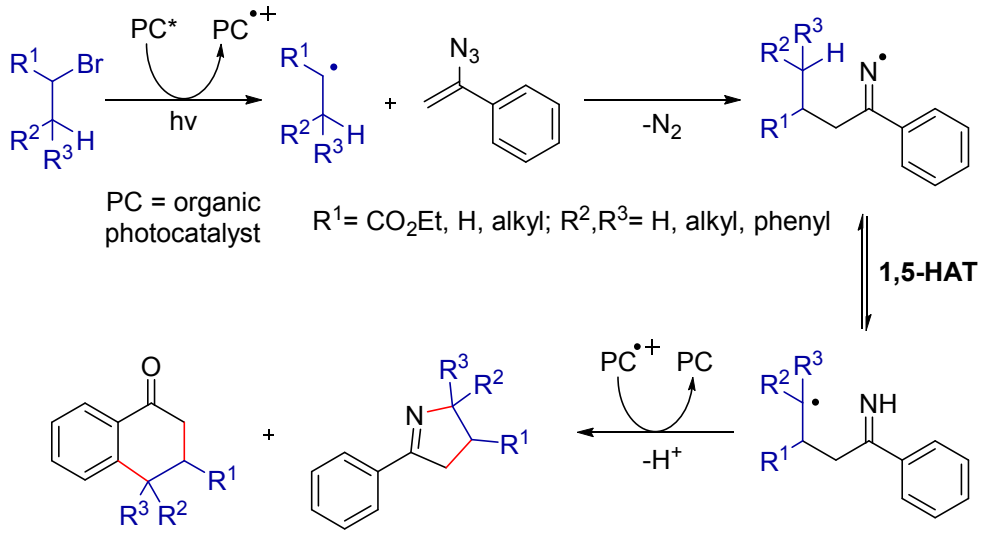
The ability to utilize C$sp^3$-H bonds as latent functional group under mild conditions is of great interest in chemistry.[1] While nature accomplishes this by highly evolved enzymes, various approaches using 1,5-hydrogen atom transfer (HAT) processes employing oxygen and nitrogen radicals have been established.[2] Similar to the Hofmann-Loeffler-Freytag reaction, many reactions rely on demanding radical precursors such as N-X bonds (X=Halide, O) and harsh reaction conditions to achieve the necessary reactivity.[3] In contrast to this, photoredox catalysis was recently used to generate iminyl radicals from oximes under mild conditions.[4,5]
Using α-azidostyrene as a starting material avoids the laborious synthesis of *N*-oxime or similar difficult precursors. A radical, generated by visible light photocatalysis utilizing strongly reducing organic photocatalysts,[6] can couple with the unsaturated moiety of α-azidostyrene, subsequently releasing nitrogen gas.[7] The resulting iminyl radical takes part in a 1,5-HAT process with a secondary or tertiary C$sp^3$-H in α-position to the initially generated radical. This radical can be oxidized, regenerating the catalyst and forming 3,4-dihydro-2*H*-pyrroles. Alternatively, the radical can cyclize with a phenyl ring, forming 3,4-dihydronaphtalenones (**Scheme 1**). The formation of products depends on the substitution pattern of the starting materials and applied reaction conditions. 3,4-Dihydronaphtalenones are significant as scaffolds in various biologically active compounds.




***Scheme 1.*** *Proposed mechanism for the formation of 3,4-dihydro-2H-pyrroles and 3,4-dihydronaphtalenones from α-azidostyrene and a photochemically generated radical.*

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# Synthesis of Polyvalent Organic Electron Donors: Application in Organic Synthesis

Yuxi Zhao, Guillaume Tintori, Sébastien Redon, Patrice Vanelle and Julie Broggi*

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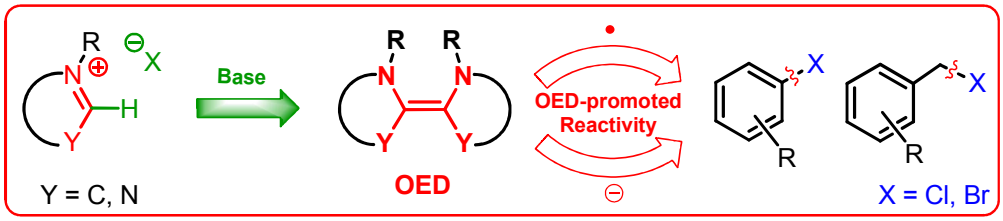
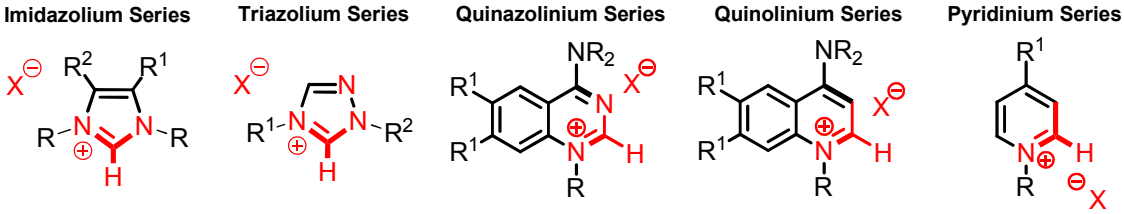
Organic electron donors (OEDs) containing an electron rich olefin have attracted considerable attention in organic synthesis because of their abilities to form radical or anionic intermediates by the stepwise transfer of one or two electrons to organic substrates.[1,2] Recently, we demonstrated that these organic reducers are also remarkable polymerization initiators.[3] Nonetheless, the structural diversity of OEDs has been scarcely studied and the knowledge concerning their reactivity is much less advanced compared to metallic reducers. Hence, the development of new series of polyvalent organic electron donors and the understanding of their electron transfer mechanisms constitute a very significant challenge.

In this study, various azolium salts were synthesized and then deprotonated to *in-situ* generate the OED. We show that their redox properties are highly dependent of the nature of the heterocycle and their *C*- or *N*-substituents. The reactivity of the new azafulvalene derivatives is challenged in the reduction of aryl and benzyl halides substrates under thermal- or photo-activation. The diversification of the structures allows us to rationalize the factors governing single- or double-electron transfers and to correlate them to the reducing powers.

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# Photopolymerization under visible light: Squaraine compounds as new photoinitiators

Guillaume Noirbent;[a,*] Aude-Héloise Bonardi;[b] Jacques Lalevée;[b] Didier Gigmes[a] and Frédéric Dumur[a,*]

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In recent years, photopolymerization has witnessed intense research effort due to the constant growth of industrial applications associated with the synthesis of new photoinitiators PI and monomers. The use of photoinitiated polymerization is continuously growing in industry as reflected by the large number of applications in not only conventional areas such as coatings, inks, and adhesives but also high-tech domains, optoelectronics, laser imaging, stereolithography, and nanotechnology. Photopolymerization offers many stricking advantages over traditional thermo-polymerization such as temporal and spatial control of initiation, cost efficiency and solvent-free systems. In order to cut cost, use of soft irradiation conditions is required and the development of new photoinitiators strongly absorbing in the visible region and exhibiting high molar extinction coefficients are actively researched by the academic and industrial communities. For industrial applications, minimization of the risk for the operator has to be considered and use of light sources emitting beyond the UV region or as expected in the following years in the visible range is of crucial importance for the operator safety. Another requirement for industry is the possibility to use low-power consumption LEDs to cut cost and avoid the use of expensive photochemical equipments. Recently, a new approach based on the photoredox catalysis has been proposed for the development of new systems active upon soft visible light conditions.

Here, we present unprecedented works on squaraine derivatives used as photoinitiators of polymerization. These results pave the way towards the development of a new generation of highly efficient, low cost and non-toxic photoinitiators operating under visible light and soft irradiation conditions, what is currently not at disposal in industries.

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# Diazene-Functionalized Lamellar Materials as Nanobuilding Blocks: Application as Light Sensitive Fillers to Initiate Radical PhotoPolymerizations

Cyrielle Dol,[a] François Vibert,[a] Michèle P. Bertrand,[a] Jacques Lalevée,[b] Stéphane Gastaldi,*[a] Eric Besson [a]

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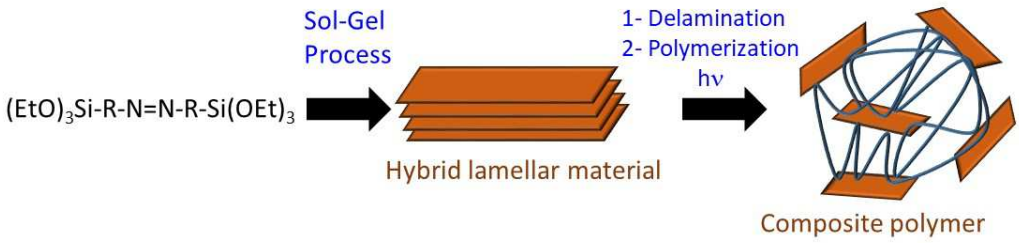
Recently, we investigated the effect of nanoconfinement on the behavior of transient radicals. When localized on the pore or in the framework of a SBA-15 type silicas, it was possible (i) to modulate half-lifetimes of these species [1],[2] and (ii) to study their reactivity by EPR at room temperature.[3],[4]

We wished to report the high potential of another nanostructure: radical functionalized lamellar materials. New polysilsesquioxane-based lamellar materials, functionalized with radical precursors, were synthesized.

They play a double role in the preparation of composite materials: first, as filler homogenously dispersed in the monomer after delamination, second as radical initiator in photopolymerization. These polysilsesquioxanes enable fast and efficient photopolymerization upon UV light for thick samples. High conversions in monomers as well as the formation of hybrid polymers covalently linked to the filler are observed.




This strategy, based on a double bottom-up approach, avoids the solubility/dispersion problem encountered in the classical preparation of composite polymers from pre-formed organic polymers. [5]

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# pH-sensible alkoxyamine : a new tool for conjugation and ligation in mild conditions

L. Autissier,[a] K. Mabrouk,[a] N. Gil, [a] C. Chendo,[b] Y. Guillaneuf,[a] M. Rollet,[a] L. Charles,[a] D. Gigmes[a]* and T. Trimaille[a,]*

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A catalyst/initiator-free radical addition reaction performed in mild conditions (water, 30°C) with high yields is reported for the first time[1]. This reaction implies simple pH-mediated alkoxyamine dissociation followed by addition onto olefinic substrate. Due to an off/on process, non-activated alkoxyamine can be easily stored and manipulated, in contrast, triggered alkoxyamine could be added on actived olefin at temperature nearly room temperature. Based on the work of Marque and *al.*[2] protonation of the pyridinyl moiety exhibited a strongly increased C-ON rate bond homolysis. In our case dissociation $E_a$ values of the alkoxyamine of 115.2 kJ.mol$^{-1}$ for the non-protonated and 105.4 kJ.mol$^{-1}$ for the protonated form.

The versatility and relevance of this selective reaction for macromolecular conjugation and engineering was particularly shown through synthesis of (i) block copolymers, through the NMP macro-initiation approach (Fig.1, top); (ii) hydrogels containing *in situ* loaded protein, namely the horseradish peroxidase (HRP) (Fig.1, bottom) or more recently peptide ligation. Interestingly, the mild conditions afforded by such addition allowed to retain biological activity of the protein, whereas standard thermal radical conditions led to complete protein inactivation, highlighting the potential of this new radical-based conjugation tool.

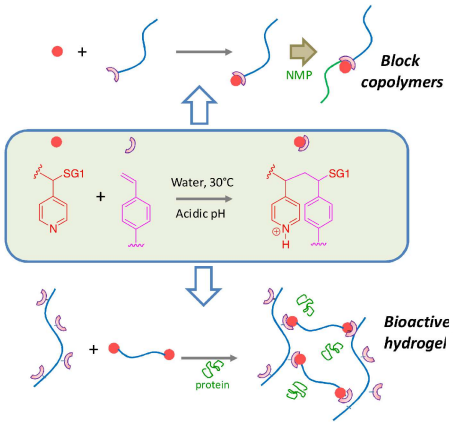


**Figure 1**. The pyridinyl-based alkoxyamine radical addition and its use as a macromolecular conjugation tool.

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# Nitroxide Mediated Polymerization and Addition for Synthesis of Novel PNIPAAm-based Biodegradable Copolymers

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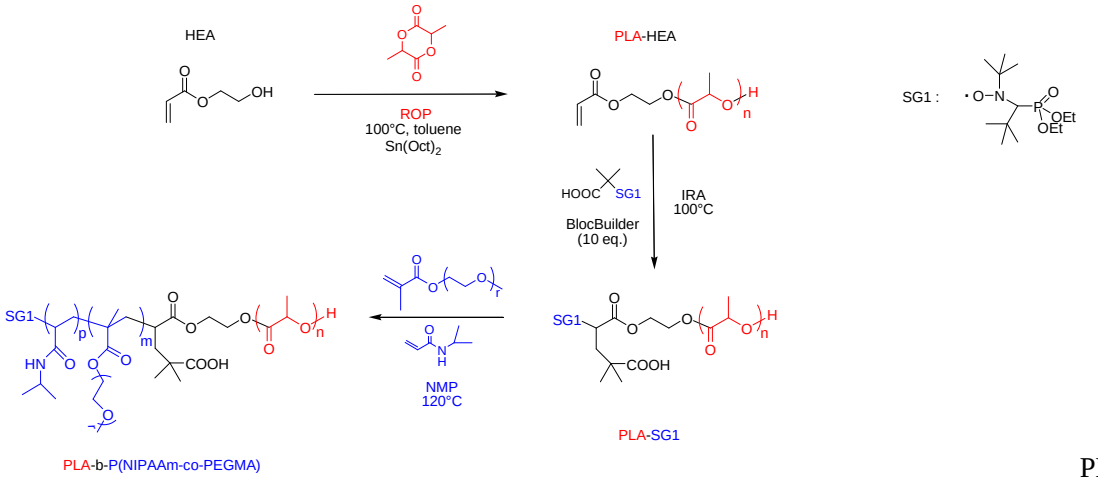
Poly(N-Isopropylacrylamide) (PNIPAAm) is one of the most used polymers for in-situ gel forming thermosensitive hydrogels [1]. However, its non-degradable character and its poor water retention property are limiting its biomedical applications. To address these issues, we synthesized a novel amphiphilic copolymer, polylactide-block-P(NIPAAm-co-poly(ethylene glycol) methacrylate) (PLA-b-P(NIPAAm-co-PEGMA)), expected to form gel through micelle packing/rearrangement upon heating. The synthesis was based on the strategies of ring opening polymerization (ROP), intermolecular radical addition (IRA) and nitroxide mediated polymerization (NMP). PLA-b-P(NIPAAm-co-PEGMA) was prepared in a three-step process starting with ROP. In the presence of stannous octoate catalyst, 2-hydroxyethyl acrylate (HEA) initiated the ring opening of lactide (LA) to form a PLA-HEA polymer. Next, BlocBuilder alkoxyamine was added onto PLA-HEA through IRA leading to a functionalized macroalkoxyamine initiator, PLA-SG1, with a nearly 100% functionalization yield. Applying a temperature of 100°C resulted in the decomposition of BlocBuilder, thereby breaking the C-O bond and releasing the alkyl moiety which was added to the double bond, followed by recombination of SG1. In the final step, NIPAAm and PEGMA monomers were polymerized from PLA-SG1 through NMP at 120°C, which led to the formation of PLA-b-P(NIPAAm-co-PEGMA).




PLA-b-P(NIPAAm-co-PEGMA) and PLA-b-PNIPAAm analogs were characterized by $^{1}$H NMR and SEC analyses. The NMP of PNIPAAm was shown to be partially controlled. Dynamic light scattering (DLS) was used to investigate the thermosensitive behavior of the copolymers in PBS. In conclusion, nitroxide-based techniques can be successfully applied in the synthesis of improved PNIPAAm-based materials.

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- Manage 8 platforms and facilities that provide academic and private communities with access to leading edge instrumentation and services.

- Contribute to the scientific animation of the site by organizing a weekly conference program and supporting local scientific events.

- Discuss employment and major instruments purchasing policies in its fields of action.

Prof. Stéphane VIEL
Director, Fédération Sciences Chimiques Marseille
(more information at: http://fr-chimie.univ-amu.fr)