Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry

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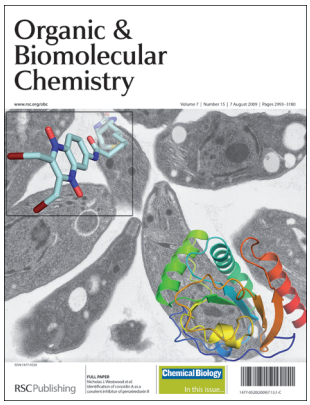
IN THIS ISSUE

ISSN 1477-0520 CODEN OBCRAK 7(15) 2993–3180 (2009)

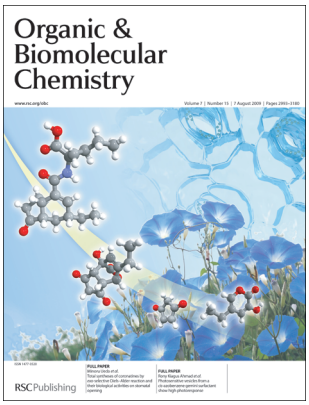


Cover

See Nicholas J. Westwood *et al.*, pp. 3040–3048.

Electron micrograph provided by Dr W. Barkhuff (Vermont) of two *T. gondii* parasites. The thimble-shaped conoid is extended in one (left) and retracted in the other. Conoidin A (inset) inhibits conoid extension and was found to bind covalently to the protein shown (peroxiredoxin II).

Image reproduced by permission of Nicholas J. Westwood from *Org. Biomol. Chem.*, 2009, **7**, 3040.



Inside cover

See Minoru Ueda *et al.*, pp. 3065–3073.

We established a unique synthetic route to coronatine employing an *exo*-selective Diels–Alder reaction as a key step. A remarkable difference in stomatal opening activity between the enantiomers of coronatine was observed.

Image reproduced by permission of Minoru Ueda from *Org. Biomol. Chem.*, 2009, **7**, 3065.

HIGHLIGHTS IN CHEMICAL BIOLOGY

B57

Highlights in Chemical Biology provides a 'snapshot' of the latest developments in chemical biology from all RSC publications, showcasing newsworthy articles and significant scientific advances.

Highlights in Chemical Biology

August 2009/Volume 4/Issue 8

www.rsc.org/chembiology

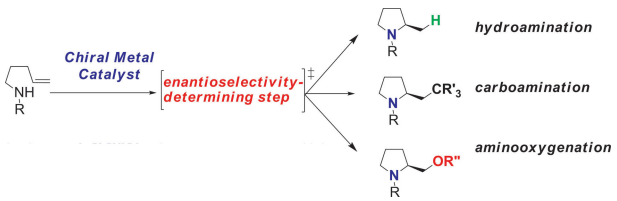
PERSPECTIVE

3009

The enantioselective intramolecular aminative functionalization of unactivated alkenes, dienes, allenes and alkynes for the synthesis of chiral nitrogen heterocycles

Sherry R. Chemler*

The enantioselective intramolecular aminative functionalization of unactivated alkenes and related π-systems is a straight-forward strategy for the synthesis of chiral nitrogen heterocycles. This perspective reviews the current work in the field and explores mechanistic trends that are common among the different catalysts and reaction types.



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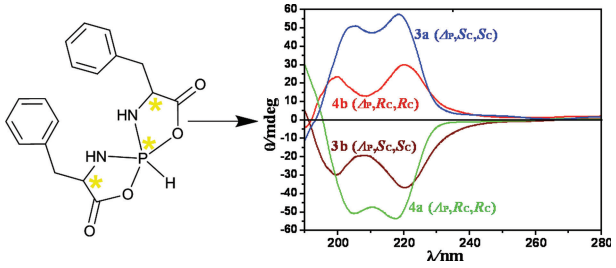
3020

Chirality at phosphorus in pentacoordinate spirophosphoranes: stereochemistry by X-ray structure and spectroscopic analysis

Jian-Bo Hou, Hui Zhang, Jian-Nan Guo, Yan Liu, Peng-Xiang Xu, Yu-Fen Zhao* and G. Michael Blackburn*

The absolute configurations of the 4 stereoisomers of spirophosphoranes constructed from two molecules of D- or L-phenylalanine are determined using X-ray diffraction and solid-state CD spectra.

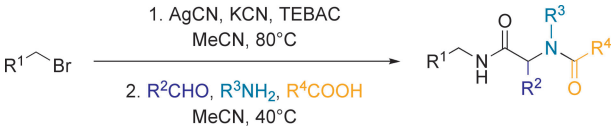


3024

"Isocyanide-free" Ugi reactions

Laurent El Kaïm,* Laurence Grimaud* and Aurélie Schiltz

High-yielding Ugi reactions have been carried out with *in situ*-prepared isocyanides, derived from the reaction of bromide derivatives with silver and potassium cyanide, thus alleviating the burden of the preparation, purification and subsequent use of isocyanides in multicomponent reactions.

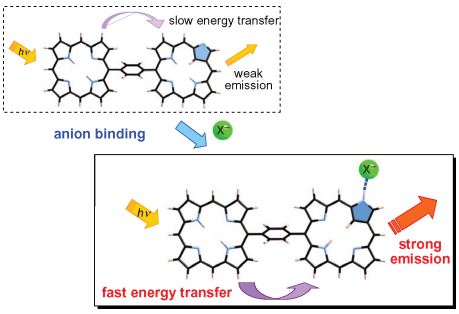


3027

Anion responsive dyad system of porphyrin and N-confused porphyrin

Motoki Toganoh, Hironao Miyachi, Hisanori Akimaru, Fuyuki Ito, Toshihiko Nagamura and Hiroyuki Furuta*

A dyad of porphyrin and N-confused porphyrin is synthesized for the first time, in which an efficient excitation energy transfer as well as enhancement of emission quantum yield induced by anion binding is observed.

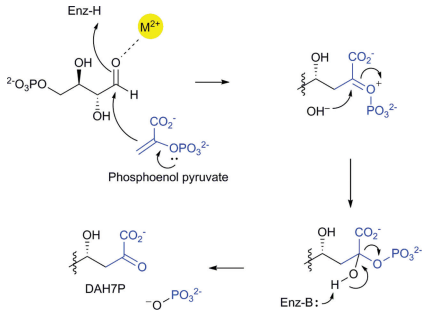


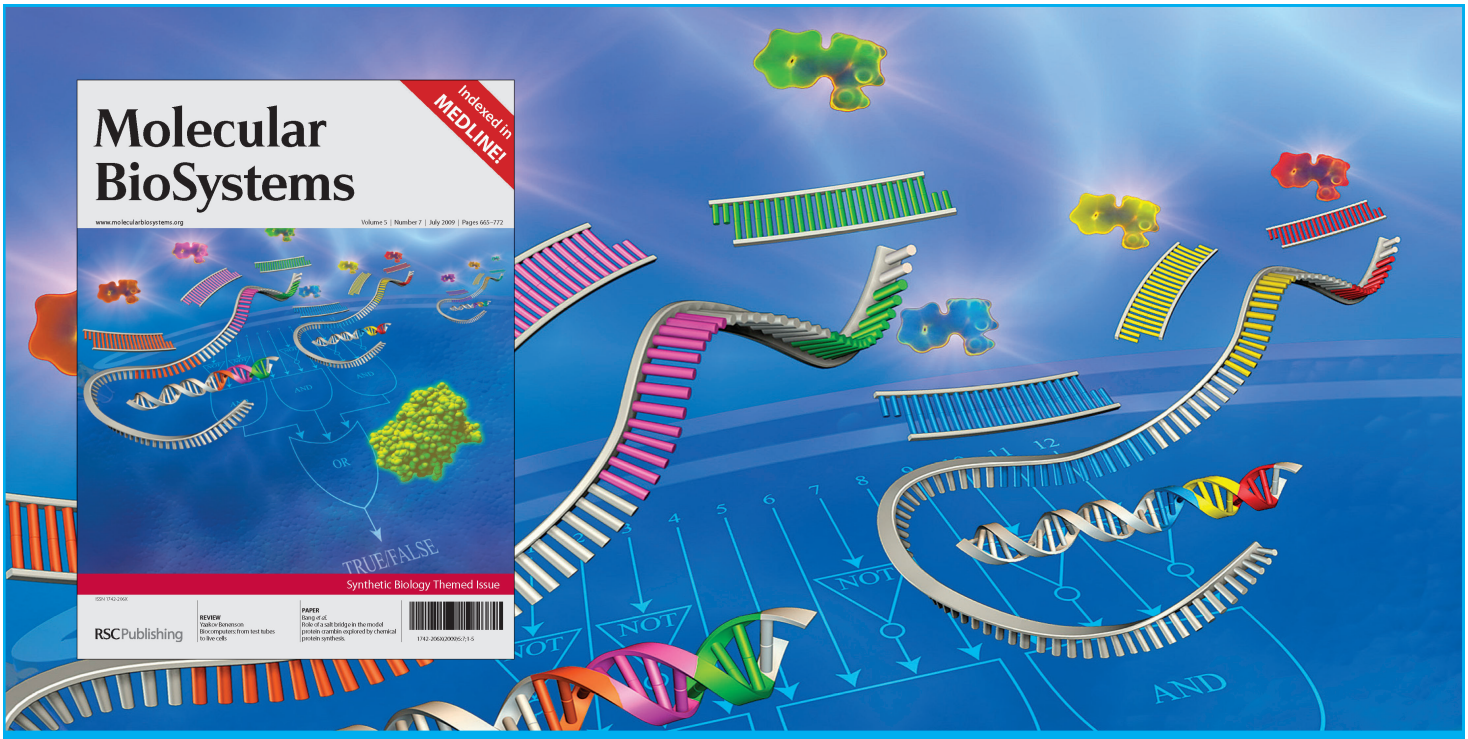
3031

Substrate and reaction intermediate mimics as inhibitors of 3-deoxy-D-*arabino*-heptulosonate 7-phosphate synthase

Scott R. Walker, Hemi Cumming and Emily J. Parker*

A series of compounds designed to mimic the properties of substrate phosphoenolpyruvate and the predicted reaction intermediate were synthesised and shown to be effective inhibitors of 3-deoxy-D-*arabino*-heptulosonate phosphate (DAH7P) synthase, the first enzyme of the shikimate pathway.





Synthetic Biology Themed Issue

Molecular BioSystems issue 7, 2009, is a themed issue on **Synthetic Biology** coordinated by Editorial Board members Hagan Bayley (Professor of Chemical Biology, Oxford University, UK) and Sachdev Sidhu (Assistant Professor, Banting and Best Department of Medical Research, University of Toronto, Canada).

Articles include:

Darwinian chemistry: Towards the synthesis of a simple cell
Phil Holliger and David Loakes

Synthetic Chemistry Used to Make, Study the Folding, and Determine the X-ray Structure of a Unique Protein Analogue, [V15A]Crambin-α carboxamide
Stephen Kent, Duhee Bang, Anthony A Kossiakoff, Valentina Tereshko

Biocomputers: from test tubes to live cells
Yaakov Benenson (also provided the cover image)

A Synthetic Metabolite-Based Mammalian Inter-cell Signaling System
Martin Fussenegger, Nicholas Denervaud, Marco Schütz, Wilfried Weber

Engineering and Exploiting Protein Assemblies in Synthetic Biology
Stefan Howorka and David Papapostolou

Synthetic Biology: Exploring Biological Modularity
Pam Silver and Christina Agapakis.


Hagan Bayley


Sachdev Sidhu

"Synthetic biology is one of the most exciting and rapidly evolving fields in life sciences, and with this special issue, we have aimed to provide a broad overview of the theories and technologies that are shaping the field"

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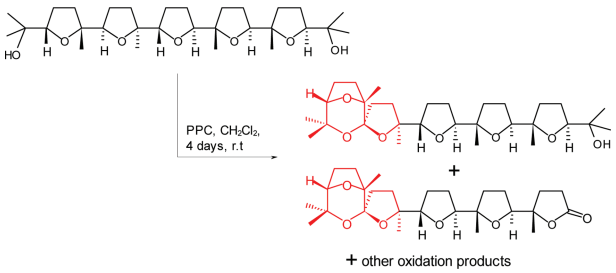
COMMUNICATIONS

3036

Discovery of a new PCC-mediated stereoselective oxidative spiroketalization process. An access to a new type of poly-THF spiroketal compound displaying anticancer activity

Vincenzo Piccialli,* Giorgia Oliviero, Nicola Borbone, Angela Tuzi, Roberto Centore, Akseli Hemminki, Matteo Ugolini and Vincenzo Cerullo

A new type of cytotoxic poly-THF compound, embodying a novel tricyclic spiroketal moiety, has been obtained through an unprecedented PCC-mediated stereoselective oxidative spiroketalization process.



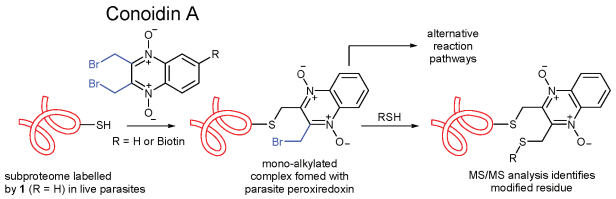
PAPERS

3040

Identification of conoidin A as a covalent inhibitor of peroxiredoxin II

Jeralyn D. Haraldsen, Gu Liu, Catherine H. Botting, Jeffrey G. A. Walton, Janet Storm, Timothy J. Phalen, Lai Yu Kwok, Dominique Soldati-Favre, Nicholas H. Heintz, Sylke Müller, Nicholas J. Westwood* and Gary E. Ward*

Conoidin A blocks an essential stage in the life cycle of the parasite *Toxoplasma gondii.* Using target identification and validation methods we show that Conoidin A inhibits the function of a parasite peroxiredoxin.

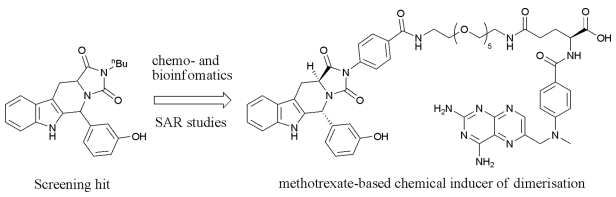


3049

Synthesis and biological evaluation of functionalised tetrahydro-β-carboline analogues as inhibitors of *Toxoplasma gondii* invasion

Jeffrey G. A. Walton, Stephen Patterson, Gu Liu, Jeralyn D. Haraldsen, Jonathan J. Hollick, Alexandra M. Z. Slawin, Gary E. Ward and Nicholas J. Westwood*

The synthesis of two CIDs for use in the yeast-3-hybrid approach to protein target identification is described. Both CIDs are based on the screening hit shown.

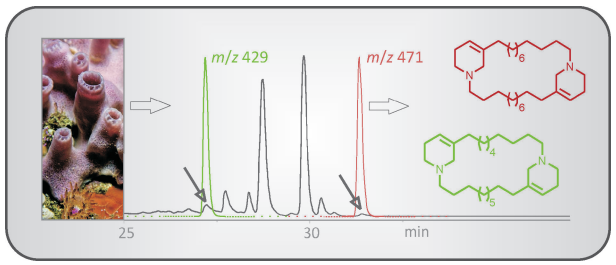


3061

New haliclamines E and F from the Arctic sponge *Haliclona viscosa*

Gesine Schmidt, Christoph Timm and Matthias Köck*

Two new marine alkaloids haliclamines E and F were identified from a very small amount of the crude extract by HR-LCMS. The proof of structure was provided by total synthesis of both compounds.



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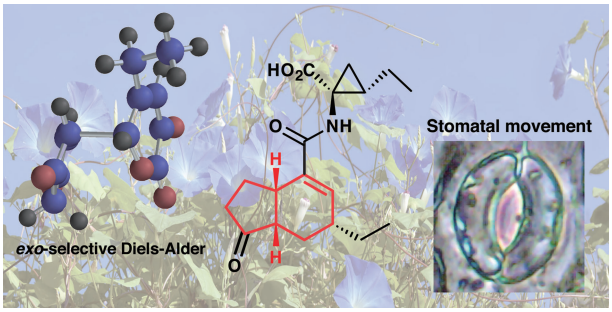
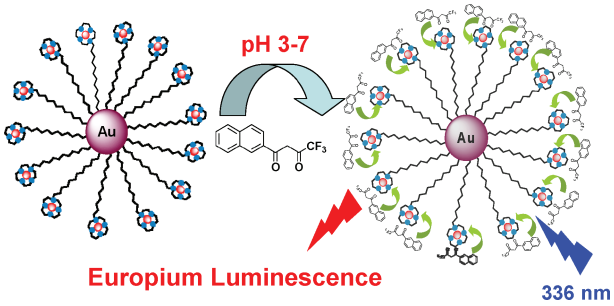


Total syntheses of coronatines by *exo*-selective Diels–Alder reaction and their biological activities on stomatal opening

Masahiro Okada, Satoko Ito, Akira Matsubara, Izumi Iwakura, Syusuke Egoshi and Minoru Ueda*

We synthesized four stereoisomers of coronatine employing the *exo*-selective Diels–Alder reaction as a key step and examined the effect of stereochemistry on stomatal opening activity.

3074

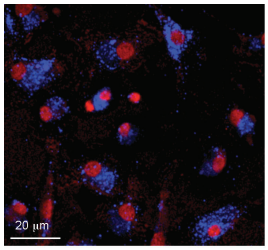


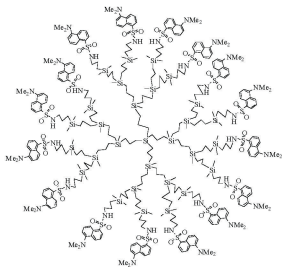
Lanthanide luminescent gold nanoparticles: pH-driven self-assembly formation between Eu(III)-cyclen conjugated AuNPs and sensitising β-diketonate antenna in water

Célia S. Bonnet, Julien Massue, Susan J. Quinn and Thorfinnur Gunnlaugsson*

The formation of Eu(III) luminescent gold nanoparticles is described using the cyclen based **AuNP-1**.**Eu** and **2**, and an aromatic antenna. The process is shown to be highly pH dependent where at acidic and neutral pH the self-assembly is highly luminescent.

3079



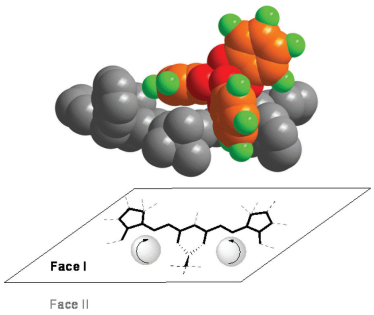


Carbosilane dendrimers peripherally functionalized with dansyl fluorescence tags and their cellular internalization studies

Paula Ortega, Mª Jesús Serramía, Rafael Samaniego, F. Javier de la Mata,* Rafael Gomez* and Mª Angeles Muñoz-Fernandez*

Carbosilane dendrimers containing dansyl groups at their periphery as fluorescence tags are internalised in primary cell cultures and can be considered as a new matrix for biomedical applications.

3086



Diastereoselective supramolecular ion-pairing between the TRISPHAT anion and *pro*-chiral heptamethine cyanine dyes

Pierre-Antoine Bouit, Christophe Aronica, Laure Guy, Alexandre Martinez, Chantal Andraud and Olivier Maury*

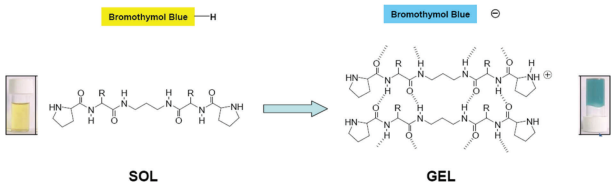
The association between the TRISPHAT anion and a *pro*-chiral heptamethine cyanine dye leads to the formation of a diastereoselective ion-pairing effect evidenced by NMR spectroscopy and crystallography.

3091

Remarkable increase in basicity associated with supramolecular gelation

Francisco Rodríguez-Llansola, Beatriu Escuder* and Juan F. Miravet*

Supramolecular gels formed by L-proline derivatives show an amazing basicity increase in the aggregated (gel) state. As a result they behave as enantioselective catalysts for the aldol reaction in solution but produce a base-catalyzed aldol racemisation in the gel state.

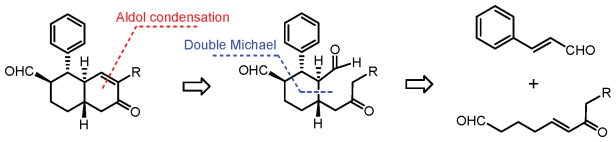


3095

Enantioselective synthesis of highly functionalized octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehydes *via* organocatalytic domino reactions

Bor-Cherng Hong,* Roshan Y. Nimje and Ju-Hsiou Liao

Organocatalytic double Michael reaction and the subsequent aldol condensation of (*E*)-7-oxooct-5-enal and 3-arylpropenal (*e.g.*, cinnamaldehyde) provided octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehyde in high diastereoselectivity and high enantioselectivity.

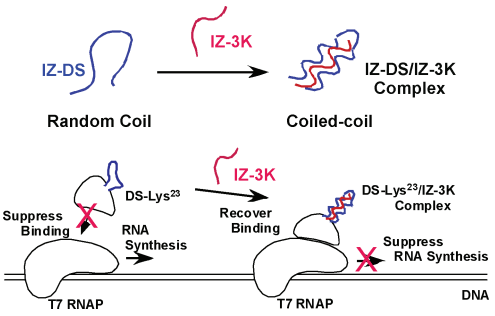


3102

Manipulation of protein-complex function by using an engineered heterotrimeric coiled-coil switch

Toshihisa Mizuno,* Kumiko Suzuki, Tatsuya Imai, Yuya Kitade, Yuji Furutani, Motonori Kudou, Masayuki Oda, Hideki Kandori, Kouhei Tsumoto and Toshiki Tanaka*

By designing the metamorphosis peptide **IZ-DS** sequence and the counterpart peptide **IZ-3K** based on the **IZ** sequence, and optimizing the introduction site for the **IZ-DS** sequence for T7 lysozyme, we succeeded in tuning the interaction between T7 RNAP and T7 lysozyme, resulting in regulation of the RNA synthesis of T7 RNAP.

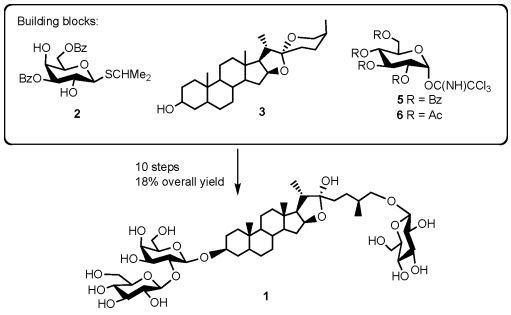


3112

Total synthesis of a furostan saponin, timosaponin BII

Shuihong Cheng, Yuguo Du,* Baiping Ma and Dawei Tan

An effective and general route for the regioselective synthesis of furostan timosaponin BII has been developed using a partially protected glycosyl donor strategy. The cytotoxic activity was evaluated against HL-60 human promyelocytic leukaemia cells.



RNAi Asia

14 - 16 October 2009 Kunshan, China

The Chinese government has recently announced the establishment of the country's biggest siRNA R&D complex in Kunshan (near Shanghai) which will house both basic research and commercial startup companies.

In partnership with local organizers, Select Biosciences has been asked to host this inaugural international conference (circa. 500 expected). Attendance represents a major opportunity to forge brand new links and collaborations as this area will be the centre of RNAi activities in China going forwards.

Confirmed Speakers include:

Dinshaw J. Patel, Memorial Sloan-Kettering Cancer Center
Alan Sachs, Vice President, RNA Therapeutics, Merck Research Laboratories
Runsheng Chen, Professor, Institute of Biophysics, Chinese Academy of Sciences
Stephen Cohen, Senior Principal Investigator, Temasek Life Sciences Laboratory, Singapore
Hakim Djaballah, Director, Memorial Sloan Kettering Cancer Centre
Narry Kim, Assistant Professor, Seoul National University, S.Korea
Jørgen Kjems, Professor, University of Aarhus, Denmark
Troels Koch VP, Research Division, Santaris Pharma
Jens Kurreck Professor, University of Stuttgart, Germany
Zicai Liang, Professor, Institute of Molecular Medicine, Peking University
Bing Lim, Senior Group Leader, Genome Institute of Singapore
Patrick Lu, President and CEO, Sirnaomics
Andy Miller, Professor, Imperial College London
Yijun Qi, Assistant Investigator, National Institute of Biological Sciences, Beijing
Haruhiko Siomi, Professor, Keio University School of Medicine, Japan

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- Transfection
- siRNA Therapeutics
- in vivo RNAi
- siRNA Library Screens
- microRNAs in
  - Disease Biology
  - Stem Cell Biology
  - Diagnostics
  - Virology
  - Biogenesis
  - Development

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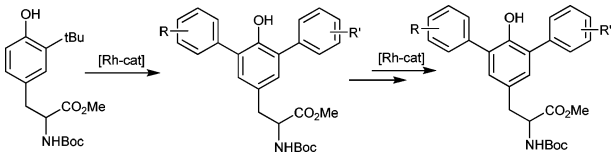
3119

The catalytic *ortho*-arylation of tyrosine

Robin B. Bedford,* Mairi F. Haddow, Ruth L. Webster and Charlotte J. Mitchell

Rhodium-catalysed direct *ortho*-arylation of protected racemic 2-*tert*-butyl tyrosine has been developed. Subsequent removal of the *tert*-butyl group allows for the construction of tyrosine-based terphenyls.

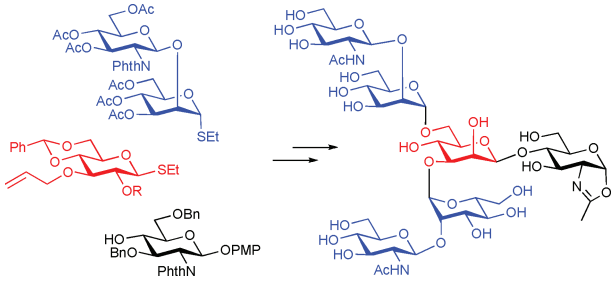


3128

Synthesis of a truncated bi-antennary complex-type *N*-glycan oxazoline; glycosylation catalysed by the endohexosaminidases Endo A and Endo M

Thomas B. Parsons, James W. B. Moir and Antony J. Fairbanks*

The total synthesis of a truncated bi-antennary complex-type *N*-glycan oxazoline furnishes an activated substrate for glycosylation of GlcNAc containing glycoconjugates as catalysed by the endohexosaminidases Endo A and Endo M.

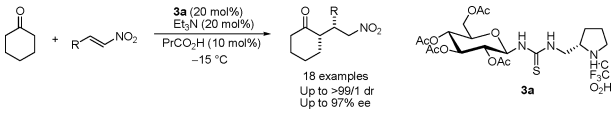


3141

Highly enantio- and diastereoselective Michael addition of cyclohexanone to nitroolefins catalyzed by a chiral glucose-based bifunctional secondary amine-thiourea catalyst

Aidang Lu, Peng Gao, Yang Wu, Youming Wang, Zhenghong Zhou* and Chuchi Tang

A novel secondary amine-thiourea organocatalyst bearing a saccharide-scaffold was synthesized, which worked well as an efficient bifunctional organocatalyst to promote the highly efficient asymmetric Michael reaction of cyclohexanone to both aryl and alkyl nitroolefins.

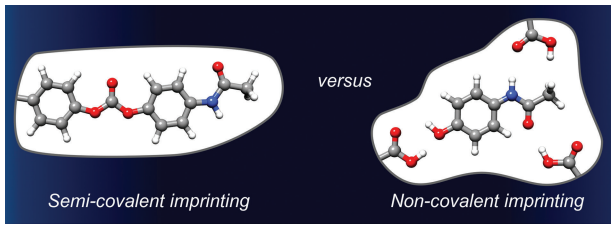


3148

Synthesis and ligand recognition of paracetamol selective polymers: semi-covalent *versus* non-covalent molecular imprinting

Jenny P. Rosengren-Holmberg, Jesper G. Karlsson, Johan Svenson, Håkan S. Andersson and Ian A. Nicholls*

Molecular imprinting of small poorly functionalised targets is a challenge. Combining the respective advantages of *semi-covalent* and *non-covalent* imprinting strategies for paracetamol provided synthetic receptors with improved recognition characteristics.



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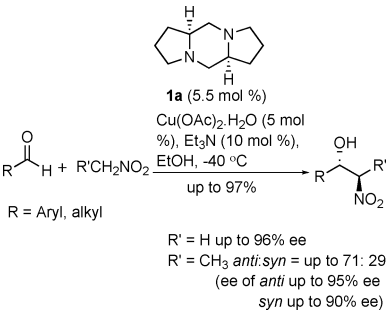
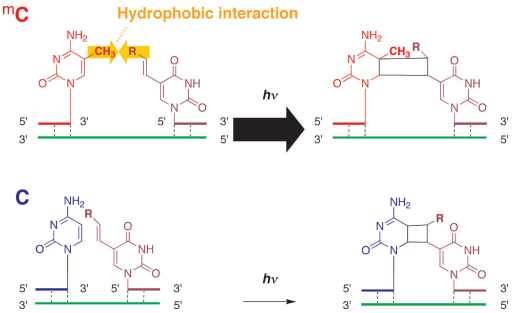


Enantioselective Henry reaction catalyzed by C_2-symmetric chiral diamine–copper(II) complex

Sermadurai Selvakumar, Dhanasekaran Sivasankaran and Vinod K. Singh*

A C_2-symmetric chiral diamine–$Cu(OAc)_2{\cdot}H_2O$ complex efficiently catalyzes an enantioselective Henry reaction with high chemical yields (up to 97%) and enantiomeric excesses (up to 96%).

3163



Detection of methylcytosine by DNA photoligation *via* hydrophobic interaction of the alkyl group

Masayuki Ogino, Yuuta Taya and Kenzo Fujimoto*

We report a nonenzymatic 5-methylcytosine detecting system by hydrophobic interaction *via* DNA photoligation. Significantly, the photoligation yield of the 5-methylcytosine case was approximately 5.6-fold higher than that in the case of cytosine.

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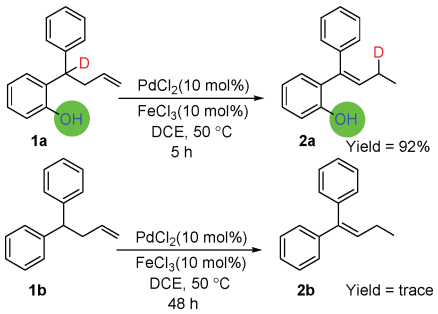
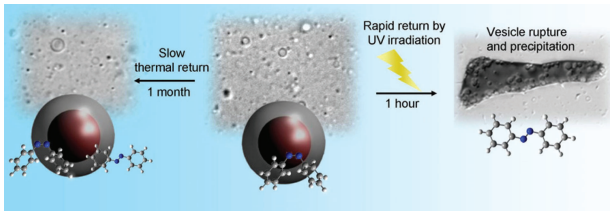


Palladium catalyzed isomerization of alkenes: a pronounced influence of an *o*-phenol hydroxyl group

Jinmin Fan, Changfeng Wan, Qiang Wang, Linfeng Gao, Xiaoqi Zheng and Zhiyong Wang*

A novel palladium catalyzed isomerization of alkenes has been found, where an *ortho*-phenol hydroxyl group has a pronounced influence on the isomerization.

3173



Photosensitive vesicles from a *cis*-azobenzene gemini surfactant show high photoresponse

Rony Kiagus Ahmad, Delphine Faure, Pascale Goddard, Reiko Oda* and Dario M. Bassani*

Light the way! An azobenzene surfactant forms light-sensitive vesicles from the photochemically-generated *cis* isomer.

AUTHOR INDEX

Ahmad, Rony Kiagus, 3173
Akimaru, Hisanori, 3027
Andersson, Håkan S., 3148
Andraud, Chantal, 3086
Aronica, Christophe, 3086
Bassani, Dario M., 3173
Bedford, Robin B., 3119
Blackburn, G. Michael, 3020
Bonnet, Célia S., 3074
Borbone, Nicola, 3036
Botting, Catherine H., 3040
Bouit, Pierre-Antoine, 3086
Centore, Roberto, 3036
Cerullo, Vincenzo, 3036
Chemler, Sherry R., 3009
Cheng, Shuihong, 3112
Cumming, Hemi, 3031
de la Mata, F. Javier, 3079
Du, Yuguo, 3112
Egoshi, Syusuke, 3065
El Kaïm, Laurent, 3024
Escuder, Beatriu, 3091
Fairbanks, Antony J., 3128
Fan, Jinmin, 3168
Faure, Delphine, 3173
Fujimoto, Kenzo, 3163
Furuta, Hiroyuki, 3027
Furutani, Yuji, 3102
Gao, Linfeng, 3168
Gao, Peng, 3141
Goddard, Pascale, 3173
Gomez, Rafael, 3079
Grimaud, Laurence, 3024
Gunnlaugsson, Thorfinnur, 3074
Guo, Jian-Nan, 3020
Guy, Laure, 3086
Haddow, Mairi F., 3119
Haraldsen, Jeralyn D., 3040, 3049
Heintz, Nicholas H., 3040
Hemminki, Akseli, 3036
Hollick, Jonathan J., 3049
Hong, Bor-Cherng, 3095
Hou, Jian-Bo, 3020
Imai, Tatsuya, 3102
Ito, Fuyuki, 3027
Ito, Satoko, 3065
Iwakura, Izumi, 3065
Kandori, Hideki, 3102
Karlsson, Jesper G., 3148
Kitade, Yuya, 3102
Köck, Matthias, 3061
Kudou, Motonori, 3102
Kwok, Lai Yu, 3040
Liao, Ju-Hsiou, 3095
Liu, Gu, 3040, 3049
Liu, Yan, 3020
Lu, Aidang, 3141
Ma, Baiping, 3112
Martinez, Alexandre, 3086
Massue, Julien, 3074
Matsubara, Akira, 3065
Maury, Olivier, 3086
Miravet, Juan F., 3091
Mitchell, Charlotte J., 3119
Miyachi, Hironao, 3027
Mizuno, Toshihisa, 3102
Moir, James W. B., 3128
Müller, Sylke, 3040
Muñoz-Fernandez, Mª Angeles, 3079
Nagamura, Toshihiko, 3027
Nicholls, Ian A., 3148
Nimje, Roshan Y., 3095
Oda, Masayuki, 3102
Oda, Reiko, 3173
Ogino, Masayuki, 3163
Okada, Masahiro, 3065
Oliviero, Giorgia, 3036
Ortega, Paula, 3079
Parker, Emily J., 3031
Parsons, Thomas B., 3128
Patterson, Stephen, 3049
Phalen, Timothy J., 3040
Piccialli, Vincenzo, 3036
Quinn, Susan J., 3074
Rodríguez-Llansola, Francisco, 3091
Rosengren-Holmberg, Jenny P., 3148
Samaniego, Rafael, 3079
Schiltz, Aurélie, 3024
Schmidt, Gesine, 3061
Selvakumar, Sermadurai, 3156
Serramía, Mª Jesús, 3079
Singh, Vinod K., 3156
Sivasankaran, Dhanasekaran, 3156
Slawin, Alexandra M. Z., 3049
Soldati-Favre, Dominique, 3040
Storm, Janet, 3040
Suzuki, Kumiko, 3102
Svenson, Johan, 3148
Tan, Dawei, 3112
Tanaka, Toshiki, 3102
Tang, Chuchi, 3141
Taya, Yuuta, 3163
Timm, Christoph, 3061
Toganoh, Motoki, 3027
Tsumoto, Kouhei, 3102
Tuzi, Angela, 3036
Ueda, Minoru, 3065
Ugolini, Matteo, 3036
Walker, Scott R., 3031
Walton, Jeffrey G. A., 3040, 3049
Wan, Changfeng, 3168
Wang, Qiang, 3168
Wang, Youming, 3141
Wang, Zhiyong, 3168
Ward, Gary E., 3040, 3049
Webster, Ruth L., 3119
Westwood, Nicholas J., 3040, 3049
Wu, Yang, 3141
Xu, Peng-Xiang, 3020
Zhang, Hui, 3020
Zhao, Yu-Fen, 3020
Zheng, Xiaoqi, 3168
Zhou, Zhenghong, 3141

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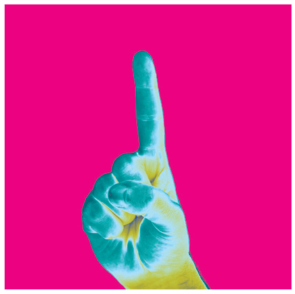

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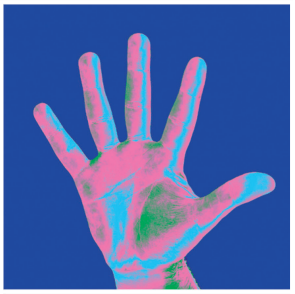

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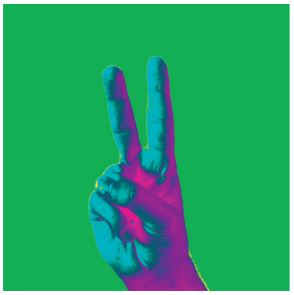

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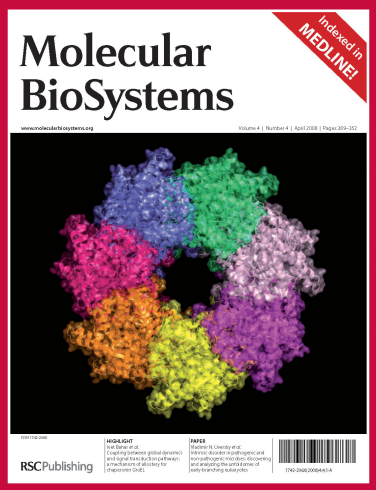

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Highlights in Chemical Biology

Inkjet printer delivers bilayer-coated particles with size and frequency control

Printing artificial cells

In a step towards cell mimics, an inkjet printer is being used to make lipid-coated balls containing proteins.

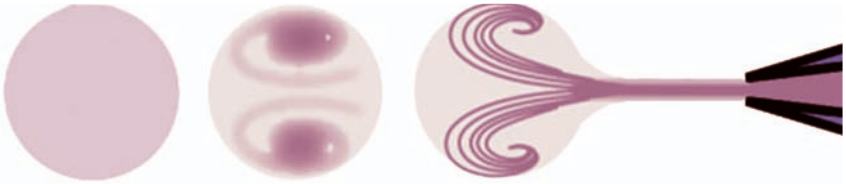
Daniel Fletcher from the University of California in Berkeley and coworkers from the US and France, developed the method to make single-lipid vesicles – fluid spheres encased in a lipid bilayer.

Fletcher explains that the work's significance is in allowing them to load complex biomolecular mixtures into cell-like particles. 'Despite the recent achievements of genetic engineering,' he comments, 'it remains a significant challenge to harness and amplify useful cellular functions, while attenuating peripheral functions and keeping the cell alive.' An alternative approach is to create more sophisticated cell mimics. 'This method will enable the construction of cell-like synthetic structures of unprecedented complexity and potential,' says Fletcher.

Each vesicle is formed when a set of pulses is applied to the inkjet, creating a jet of fluid. The inkjet is directed so that the fluid, which contains a protein, crosses a planar lipid bilayer, which then deforms to form protein-containing vesicles.

Increasing the number of pulses in a set increases the vesicle diameter, allowing the researchers to tune the vesicle size, offering an advantage over the researchers' previous microfluidic method for preparing vesicles. Thomas Pfohl, at the University of Basel, Switzerland, whose research area is in the dynamics of biological matter and microfluidics, explains that this allows the researchers to form and load uniform vesicles with 'a huge variety of diameters – from cell-sized to giant.'

The approach also allows faster vesicle production, as pauses between the pulse sets can be tuned to adjust the vesicle formation frequency.



Protein-containing fluid from the inkjet crosses a planar lipid bilayer which deforms to form vesicles

Pfohl suggests that 'the method opens a wide range of new and exciting fundamental research and applications.' Something Fletcher's team intends to pursue. 'The initial application of our work will likely be the bottom-up reconstitution of biological processes in order to gain fundamental scientific insights,' says Fletcher. 'For example, to find the role of specific biochemical components in a process or the necessary and sufficient components to recreate a specific cellular function. Further applications of our technique could include designing smart therapeutics that encapsulate drugs and guide them to specific sites within the body.' *Mary Badcock*

Reference
J C Stachowiak *et al*, *Lab Chip*, 2009, **9**, 2003 (DOI: 10.1039/b904984c)

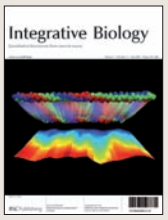
In this issue

Brewing a drug delivery platform
Tea compound used to make pH-responsive drug-releasing film

An alternative to quantum dots
Yttrium-based bioimaging agents override background fluorescence in tissue

Interview: Talking stem cells
Blagoy Blagoev on how proteomics could be the key to understanding the unique biological properties of stem cells

Instant insight: True blue flowers
What makes a purple pigment blue? Kumi Yoshida outlines how understanding this could lead to the elusive blue rose



Research highlights

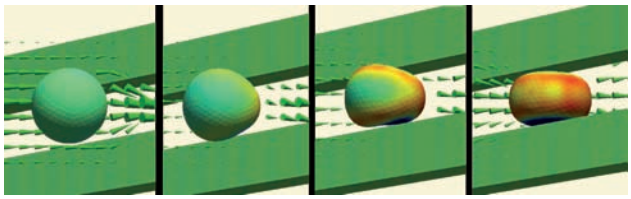
Calculations suggest ridged channels will separate hard and soft cells

Stiff resolution for cells

Scientists in the US have proposed a design for small channels that could sort cells according to their stiffness, with the potential to rapidly detect disease.

Cell stiffness is emerging as an important property. In medicine, for example, researchers have shown that cancerous cells are less rigid than their healthy counterparts. Measuring a cell's mechanical properties, however, requires expensive, time-intensive techniques such as atomic force microscopy, which physically probe individual cells. A cheap and efficient means of evaluating stiffness could therefore be an invaluable diagnostic tool.

'Cancer cells are softer,' says Alexander Alexeev, who works in the field of fluid mechanics at the Georgia Institute of Technology, Atlanta. 'But there could be just a few cells present in a sample, so you need a high-throughput device to be able to select those cells.' To this end, Alexeev and colleague John Arata have used computer modelling to simulate cell-like particles flowing through a microfluidic channel. They found that when their models included diagonal ridges across the channel, the calculations suggest the cells will migrate to opposite sides according to their stiffness, thus segregating them. 'Our results need to be experimentally verified,' points out Alexeev, 'but this should be a very low-cost, express method for analysis.'



Particles show strain (brown) as they pass through diagonal ridges allowing them to be separated by stiffness

Reference
J P Arata and A Alexeev, *Soft Matter*, 2009, DOI: 10.1039/b908213a

For Andreas Fery, an expert in colloid and interface science at the University of Bayreuth, Germany, the study is also an important demonstration that mechanical properties can be exploited, and not simply measured. 'In nature, mechanical stability is used to create smart systems,' he says. 'This work is a step in that direction: using mechanical stability to make decisions. We need these visionary, concept papers to open minds,' Fery adds. 'This is something we will see much more in the future.'

Alexeev now intends to refine his model to enable the physical realisation of his idea. 'There are many design parameters which can be changed to improve the device,' he explains. 'We need to understand these before we build a working system.'

Philip Robinson

Bone cell precursors show size-specific reaction to nanopatterns

Size matters to stem cells

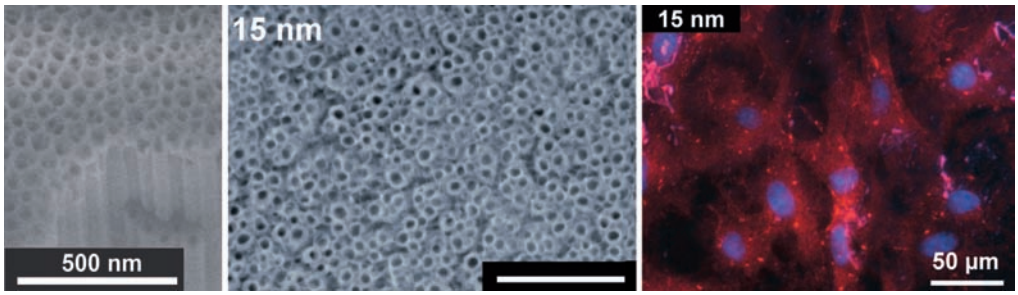
Scientists in Germany have found that surface topography can be more important than chemistry for stem cells.

Patrik Schmuki of the Friedrich-Alexander University of Erlangen-Nuremberg, and colleagues looked at how stem cells behave on nanotube-coated surfaces and found that they show a size-specific reaction to the nanopatterns. The researchers propose that nanopatterned surfaces could have potential applications in tissue engineering and in medical implants, such as replacement hips. Schmuki suggests that decorating implant surfaces with patterns on a similar scale to cells (around 10μm) may improve the implants' integration into the body.

Surface patterns on the microscale are already known to influence cell growth and activity, but little is known about the sub-100nm range, explains Schmuki. He and his team created patterns of titanium and zirconium oxide nanotubes (oxides widely used for implant surfaces) of differing heights. They then modified clinically relevant cells – mesenchymal stem cells, which can differentiate into bone-forming cells called osteoblasts – to express a green fluorescent protein. The researchers could then watch the cells interact with the nanopatterns using fluorescence microscopy. They found that the cell density on the surface depended on the nanotubes' diameter but not their length or chemistry.

Matthew Dalby from the University of Glasgow, UK, an expert on stem cell responses to nanoscale surfaces, sees the importance of the results. 'This is a question of topography versus chemistry,' he says, 'and [this work] shows that topography is winning!' Dalby adds that he would now like to see how the surfaces affect activity such as cell differentiation.

Schmuki agrees that differentiation studies are an important next step. He is also planning to extend the work to hematopoietic stem cells – cells that give rise to blood cells – and would like to investigate nanotube surfaces as potential drug and biomolecule delivery systems. *Hilary Burch*



Stem cells (right) proliferate on 15nm diameter zirconium oxide nanotubes (left and centre)

Reference
S Bauer *et al*, *Integr. Biol.*, 2009, DOI: 10.1039/b908196h

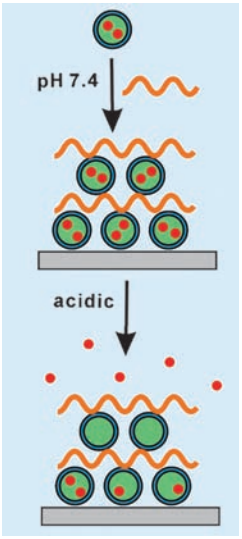
Tea compound used to prepare pH responsive drug-loaded film

Brewing a drug delivery platform

A pH responsive film that releases drugs to kill cancer cells could find applications from implant coatings to drug delivery systems, say scientists in the US and Korea.

Paula Hammond from Massachusetts Institute of Technology, Cambridge, and colleagues created the film by trapping polymeric spheres in a multilayered surface. To make the spheres they attached a hydrophobic chemotherapeutic agent – doxorubicin – to a biocompatible polymer using a labile, pH-responsive linker. On adding a buffer, the drug-loaded polymer forms a suspension of spherical hydrophobic micelles in the aqueous liquid. The researchers then integrated the micelles into thin films using a layer-by-layer (LbL) deposition technique.

Usually it is difficult to incorporate hydrophobic species into layers under physiological conditions (pH 7.4) due to their limited functionality. Hammond overcame this problem by creating a hydrogen-bonded system, using tannic acid, a compound found in tea. The acid forms hydrogen bonds with the polymeric micelles, ensuring that the multilayer remains stable and intact under biological conditions.



Drug-loaded micelles are trapped between layers of tannic acid (orange) to build the multilayer films

The pH-responsive linkers in the micelles can then be used to control doxorubicin's release from the film when it is required, by changing the pH conditions of the solution surrounding the film. Hammond's team was able to demonstrate this in tests with cancer cells and showed that the doxorubicin remained bioactive even after encapsulation in the film.

Frank Caruso, an expert in the field of LbL assembly for biomedical applications, based at the University of Melbourne, Australia, says that the strategy is an innovative approach to drug delivery. 'Such films are likely to serve as a platform technology to develop engineered thin films with potential in the delivery of therapeutics in biomedical applications,' he suggests.

Hammond says that future work could look at combining drug-loaded micelles that respond to different chemical or physical triggers, such as redox reactions or light. Hammond adds that their drug release system could be used as an ultrathin surface coating that she hopes 'will be of great interest for localised delivery of cancer therapeutics and vaccines.' To achieve this, she explains, a particular challenge will involve making all individual components of the LbL constructs fully biocompatible and non-toxic.

Emma Shiells

Reference
B-S Kim *et al, Chem. Commun.*, 2009, DOI: 10.1039/b908688a

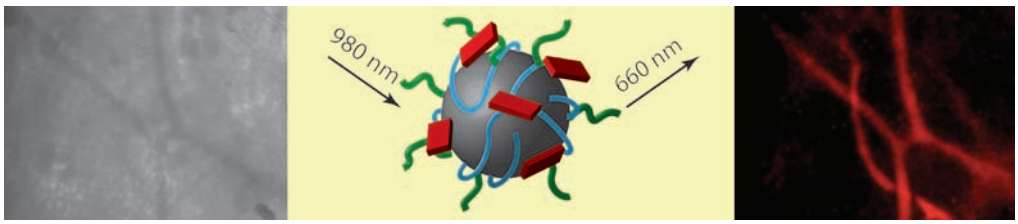
Yttrium-based bioimaging agents override background fluorescence in tissue

An alternative to quantum dots

US scientists have developed an in vivo imaging method that offers a potentially safer and more stable alternative to current methods.

Scott Hilderbrand and co-workers from the Harvard Medical School, Charlestown, have investigated the luminescent properties of yttrium-based nanomaterials and have used the materials to obtain images of blood vessels in mice.

The method relies on a process called upconversion, in which particles absorb light of one wavelength and emit light of a shorter wavelength. As Hilderbrand explains, this recent approach to imaging has many advantages over existing methods, such as the use of quantum dots. 'Although very strong emission signals can be obtained, [quantum dots] suffer from potential interference from tissue autofluorescence which can result in poor target to background ratios,' he says. 'Upconversion materials have the potential to eliminate complications from autofluorescence as few, if any, biological components show upconversion luminescence.'



Yttrium oxide particles (centre) give clear images (right) of blood vessels compared to blue light images (left)

Hilderbrand's team used yttrium oxide nanoparticles for the in vivo imaging. The oxide is known to have good stability to light, unlike some imaging materials such as organic dyes. By attaching a polymer coating the team was able to make the particles water-soluble – a requirement for in vivo imaging. The researchers then incorporated a fluorophore on the coating to make the particles luminescent. They found that the particles overcame the problem of autofluorescence and could be used to generate clear images.

Manuel Perez, an expert in the field of nanoparticle technologies and molecular imaging, from the University of Central Florida, Orlando, US, says that the work is promising. 'The novelty of the approach is that the nanoparticles are composed of less toxic materials, in contrast to quantum dots,' he explains, suggesting an added benefit over current imaging methods.

The researchers suggest that the nanoparticles could find a future use in angiography, intraoperative imaging or other bioimaging applications.

Ben Merison

Reference
S A Hilderbrand *et al, Chem. Commun.*, 2009, DOI: 10.1039/b905927j

NMR used to follow Alzheimer's-linked tau protein as it tangles

Probing protein aggregation

In 2006 an estimated 26.6 million people worldwide had Alzheimer's disease and those numbers are expected to have quadrupled by the year 2050. Now scientists in the US have developed a probe to better understand protein aggregation processes linked to the disease.

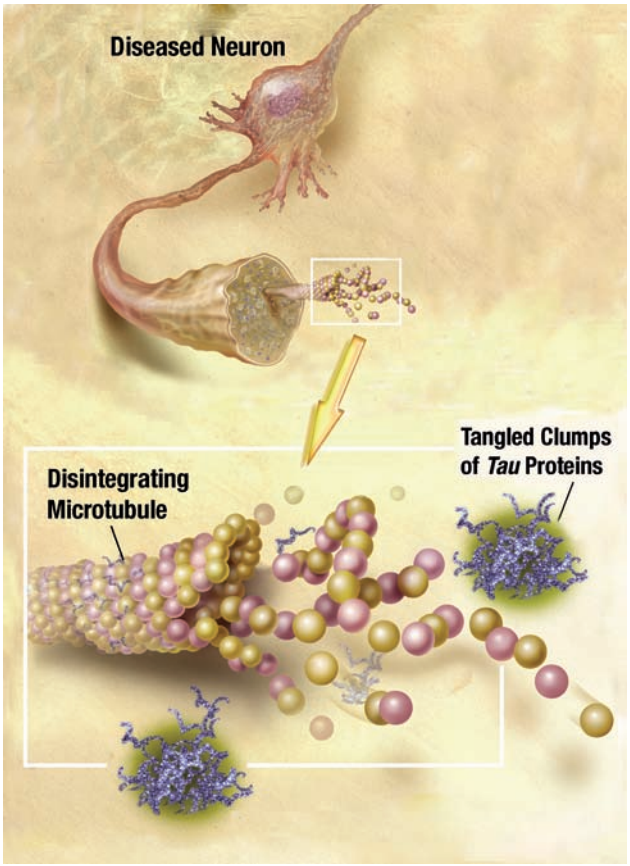
Songi Han at the University of California, Santa Barbara, and coworkers made the nitroxide-based molecule, which can be attached to specific amino acid sites in a protein.

Tangles of tau proteins, proteins which are abundant in neurons, are thought by many to give rise to Alzheimer's disease. Han and her colleagues attached their probe to a tau protein at position 322, which sees only moving water molecules within 5Å. The probe can be used to measure the water's local diffusion coefficient on the surface of the protein as the interaction between the unpaired electron of the probe's nitroxide group and a proton in water increases the probe's nuclear magnetic resonance signal. This allows the researchers to measure water surface dynamics at low concentration, making it a very sensitive tool.

Han's team used the probe to follow tau protein aggregation on the molecular level. As Han explains, 'being able to measure interfacial and surface hydration dynamics provides us with a unique tool to map out interactions between species or the transport of protons and water across membranes.' Introducing the probe into amyloid fibre proteins, such as those formed by tangled tau proteins, could give a clearer picture of how the fibres form and lead to further insight into the proteins' structural characteristics.

Mark Wilson, an expert in protein aggregation, University of Wollongong, Australia, agrees that 'the approach could offer structural insights into those parts of a protein directly involved in inter-protein binding events underpinning aggregation.' Han adds that understanding protein function in this way is 'key to understanding the building blocks and machinery of life, or the mechanism of failure.'

Paul Cooper



NATIONAL INSTITUTES OF HEALTH (NIH)

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Lalla Aicha Ba *et al*, *Metallomics*, 2009, **1**, 292 (DOI: 10.1039/b904533c)

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Interview

Talking stem cells

Blagoy Blagoev on how proteomics could be the key to understanding the unique biological properties of stem cells. Leanne Marle finds out more

Blagoy Blagoev

Blagoy Blagoev is an associate professor in the department of biochemistry and molecular biology at the University of Southern Denmark in Odense. He is also a member of the *Molecular Biosystems* editorial board. His research focuses on studying cell signalling and how cells communicate using quantitative proteomics.

Why did you become a scientist?

Looking back I was always very interested in chemistry, especially mixing things together to see what would happen. I can remember how exciting it was dipping iron into copper sulfate solution and watching the colour change from blue to green. At the same time, I was also (and still am) very interested in animals and biology in general. So I guess it combined the two to go on to study biochemistry and molecular biology.

I find it very exciting to work in an area where you seek the answers. You don't do something where you know what is going to happen or know the answers in advance. You just do the experiments, which you believe are good, and see what they show you.

What projects are you working on at the moment?

Like most scientists these days I am working on several projects. One project, which has been my focus for a long time now, is looking at cell signalling by growth factor receptors. For example, we are studying how the signalling networks organised by these receptors are controlling various processes. In particular we are looking at phosphorylation and other protein modifications that are basically responsible for the different growth factor effects on human cells.

Another exciting research area in the laboratory is related to human embryonic stem cells. They provide an ideal system to study the processes of cell development and differentiation. We are using quantitative mass spectrometry-based proteomics to look at the mechanisms of self-renewal and differentiation of these cells. We are hoping to understand better how a stem cell works. However, the more scientists figure out about cellular systems it becomes clearer that these systems are very complex.

Why is proteomics an important tool for studying stem cells?

First of all, it is a very powerful technology for looking directly at the protein. It is now widely appreciated that there are many more mechanisms involved in regulating protein activities. Post-translational modifications are one of these mechanisms. Proteomics allows you not to just look directly at the proteins and the protein expression levels, but to also see their modifications. This makes it a very powerful tool for functional studies. By using a labelling technique called SILAC (stable isotope labelling by amino acids in cell culture) for quantification, we hope to gain a much better understanding of the mechanisms of self-renewal and differentiation in human embryonic stem cells.

What are the major challenges in this area?

In general mass spectrometry technology has become much more user friendly and as a result more widespread, with an increasing number of universities and institutions having their own instrumentation. Whilst the instruments are much easier to operate, they are not a black box instrument in which you can just push a button and produce a list of answers. The major challenge will be to educate people to use the instrumentation appropriately and to deal with the large amounts of data that are generated. There is a lot of knowledge that has to be transferred to scientists to make sure they properly process the resulting data to get the correct information. Otherwise this could lead to false results being reported and a bad reputation for proteomics.

Has there been anyone in particular that has inspired you during your career?

If I had to pinpoint one particular person that has inspired me, I would have to say my former PhD supervisor, Professor Matthias Mann. He is a really great scientist, not just in proteomics but in general. He's a great person to have worked with. But, I've been lucky to have worked with many great scientists during the entire period of my studies and later on in my career. So every one of them has been inspiring to one degree or another. Even now I have a wonderful team of young people, a very clever and talented group, and their enthusiasm inspires me. Interacting with them keeps me excited about the science.

What advice would you give to a young scientist wanting to pursue a career in science?

I think I would say to the young starters in science that it is not easy. Science is a lot of fun but you have to be passionate about it.

Those who do decide to follow science should keep their minds open. What I often see with young researchers is that they just get caught in what they are doing and don't pay much attention to what is happening around them. You have to stay open to what is happening in other fields and other technologies to boost your research projects and interests. So to stay more open would be my top tip.

Instant insight

True blue flowers

What makes a purple pigment blue? The answer could lead to the elusive blue rose says Kumi Yoshida of Nagoya University, Japan

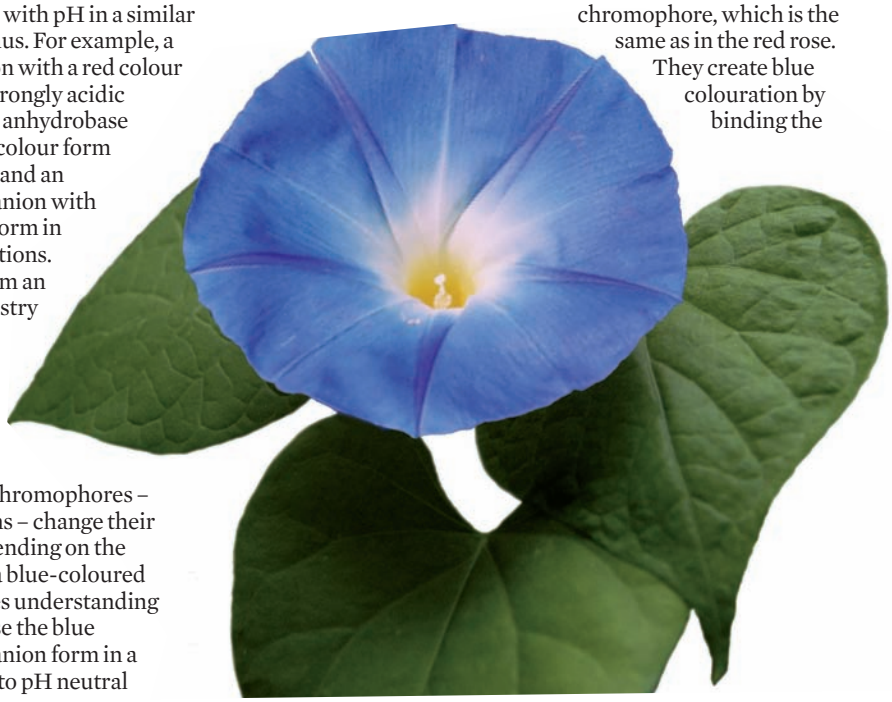
Anthocyanins are to be thanked for beautiful flower colours. These sugar-containing flavonoids differ from other plant pigments – such as green chlorophylls, yellow and orange carotenoids and purple betalains – by exhibiting a wider variety of colours. When anthocyanins are found in petals, dissolved in the petal cells' vacuoles (large sacs that make up over 90 per cent of the cells' volume), they are responsible for an assortment of reds, purples and blues.

Many years of research have focused on the development of flower colour, particularly how blues are created. Numerous efforts have been undertaken to resolve two major mysteries: how so few anthocyanin chromophores can produce so many colours and what makes these colours, usually unstable above pH 4, survive inside living cells.

An anthocyanin solution can change colour with pH in a similar fashion to litmus. For example, a flavilium cation with a red colour may form in strongly acidic conditions, an anhydrobase with a purple colour form at neutral pH, and an anhydrobase anion with a blue colour form in alkaline conditions. Therefore, from an organic chemistry perspective, it is very simple to say that flower colour comes about because anthocyanin chromophores – anthocyanidins – change their structure depending on the pH. Creating a blue-coloured flower involves understanding how to stabilise the blue anhydrobase anion form in a weakly acidic to pH neutral plant vacuole.

Reference
K Yoshida, M Mori and T Kondo, *Nat. Prod. Rep.*, 2009, **26**, 884 (DOI: 10.1039/b800165k)

Heavenly blue anthocyanin gives the petals of blue Morning glory their colour



Plants use four main strategies to bloom blue flowers: generating a more oxidised chromophore; increasing the vacuolar pH; complexing the anthocyanins with metals; and stacking aromatic groups with the anthocyanidin chromophore, shifting where it absorbs in the visible spectrum and so changing its colour. Usually two or more of these phenomena occur concurrently, resulting in a beautiful blue petal.

The most important technique in producing blue flower colouration involves the metalloanthocyanins – complexes of anthocyanins, flavones and metal ions which are found in blue dayflowers, cornflowers and salvias. These pigments use the metal-complexation and aromatic stacking strategies to generate their colour. For example, cornflowers contain the cyanidin chromophore, which is the same as in the red rose. They create blue colouration by binding the chromophore to paramagnetic Fe^{3+}. The blue dayflower, on the other hand, also resorts to the oxidised chromophore strategy. It uses a delphinidin chromophore, which has one more hydroxyl group than the cornflower's cyanidin. When its components are mixed with Mg^{2+} ions, they rapidly produce a blue supramolecule.

Blue hydrangea sepals and blue poppy petals are also coloured due to metal complexation – with Al^{3+} and Fe^{3+}, respectively. But in addition they use non-stoichiometric amounts of flavonols as co-pigments, which work by molecular stacking. Blue morning glory also exploits the stacking strategy but in combination with increasing the vacuolar pH. The petal anthocyanin contains three *p*-coumaroyl groups, and the aromatic parts of these groups stack intramolecularly and stabilise the blue colour. The pH of the blue cells increases to 7.7 at the opened flower-stage, which is an unusually high pH value for a plant. The same mechanisms are found in blue gentians, delphiniums, butterfly pea flowers and others. Almost all these petals use the oxidation strategy but the pH effect is not yet determined.

So could the true blue rose be on the horizon? Its pursuit has persisted for decades. Molecular breeding techniques have led to advanced flower colour chemistry so that you can now see roses and carnations with bluer hues. But they are not yet truly blue in colour. For the true blue rose to be developed, a multilateral strategy is necessary. Clarification of petal-bluing mechanisms is a crucial step that should open the door to this long-sought flower.

Read more in Yoshida et al*'s review 'Blue flower color development by anthocyanins: from chemical structure to cell physiology' in issue 7, 2009 of* Natural Product Reports.

Essential elements

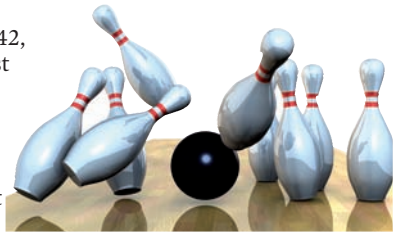
Record impact factors

RSC Publishing celebrates the 2008 impact factor results calculated by ISI® as the highest ever achieved for the majority of RSC journals. The average impact factor for the RSC portfolio now stands at 4.7, equal to the ACS collection. That's a rise of 8.2 per cent in the average impact factor for RSC since last year's results were released.

Nearly all the RSC journals increased in impact factor, immediacy index and article influence, with 3 journals noticeably standing out. *Chem Soc Rev* increased by 33 per cent to an incredible 17.42, confirming its position as a first class international chemistry journal.

Lab on a Chip celebrates a 28 per cent rise taking its impact factor to 6.48, placing it within the top ten journals in the multidisciplinary chemistry category. *PCCP* also faired well, with an impressive 20 per cent increase to its highest ever impact factor of 4.06. Its new immediacy index (0.81) also remains the highest value for any journal publishing general primary research in the fields of physical chemistry and chemical physics.

In addition, RSC journals feature in the top 10 rankings (by impact factor and immediacy index) in 6 of the 7 core chemistry categories* as listed on ISI, and, of the top 100 chemistry journals, ranked by impact factor, 15 are from RSC Publishing.



James Milne, editorial director for RSC Publishing comments: 'RSC journals have attracted a significant increase in submissions, with nearly 60 per cent more material published (over the past 5 years).' He continues: 'To provide more articles and also higher quality articles is a clear reflection of the dedicated support the journals receive from authors, editors and referees throughout the world; for this contribution, I would like to sincerely thank all the scientists involved.'

Visit www.rsc.org/publishing to read more about the journals' impact factor results.

* The 7 chemistry journal subject-categories as listed by ISI: Chemistry, Analytical; Chemistry, Applied; Chemistry, Inorganic & Nuclear; Chemistry, Medicinal; Chemistry, Multidisciplinary; Chemistry, Organic; Chemistry, Physical.

e-Platform

In 2010 RSC Publishing will launch a powerful new content delivery platform that supports multiple content types. The new website will deliver world-class RSC-hosted journal, book and database content in a single platform. The new platform will span more than 165 years of premium content, including 20 000 book chapters; 300 000 journal articles; and 450 000 database records.

RSC has worked with experts in software engineering to develop the platform functionality and has consulted a leading web design agency on building the user interface. Designed around our readers' preferences (identified from a detailed user-interview process), our user-friendly platform will offer faster browsing, intelligent searching, consistent user experience irrespective of content type sought, and simpler more intuitive navigation.

Graham McCann, publisher, is spearheading the project and his enthusiasm for the platform makes it clear something exciting is happening. 'The next stage is beta-testing; we can't wait to show some of our users the innovative platform we're working on,' he says. 'Our aim is to combine rich functionality and powerful searching with some additional features that will deliver an exceptional online experience. True to RSC reputation as an innovator in chemical science publishing, we're going to deliver something unique and different.'

For the rest of 2009, the platform will undergo extensive user testing. To be among the first to hear the latest news about the new Platform follow ChemPub on Twitter (www.twitter.com/ChemPub).

Metallomics

Since its launch in January this year, new journal *Metallomics: Integrated Biometal Science* has attracted articles from some of the leading names in the field. This timely new journal is expected to be the core publication for the emerging metallomics community as they strive to fully understand the role of metals in biological, environmental and clinical systems.

Metallomics celebrated its 2009 launch at the Second International Symposium on Metallomics (ISM'09), held in Cincinnati, Ohio, US, from 7–10 June. The journal was proud to sponsor this high profile meeting, which attracted many leading researchers, and saw sessions covering human metallomics, microbial metallomics, metallomics technology, phytometallomics and environmental metallomics. *Metallomics* is the recommended avenue of publication for ISM'09: watch out for a themed issue early in 2010 featuring work presented at the conference.

The current issue of *Metallomics* is free to all readers online throughout 2009 and 2010, and free institutional online access to all 2009 and 2010 content is available following a simple registration process.

Find out more at www.rsc.org/metallomics

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