

# SYNFORM

*People, Trends and Views in Synthetic Organic Chemistry*

2010/09

## SYNSTORIES

■ In Vivo Chemistry for Pretargeted Tumor Imaging in Live Mice



■ Quaternary Ammonium (Hypo)-iodite Catalysis for Enantioselective Oxidative Cycloetherification

■ Focus on the European School of Medicinal Chemistry (ESMEC), July 4<sup>th</sup>–9<sup>th</sup>, 2010, Urbino (Italy)

## CONTACT +++++

Your opinion about SYNFORM is welcome, please correspond if you like:  
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**Dear readers,**

The importance of organic synthesis is dramatically growing in biomedical research, as scientists are making great progress in understanding biomedical processes at molecular level and are learning how to rationally exploit

these molecular processes for diagnostic and therapeutic purposes. There is little doubt that one particular area of research where chemistry is playing a pivotal role, right at the center of the innovation process, is in the field of imaging, where the emphasis is currently all placed on the discovery of novel tracers and molecular systems for clinical applications.

Organic and synthetic chemists are increasingly working in multidisciplinary teams of researchers, side by side with biologists, physicists, engineers and medical doctors. This exciting trend is well exemplified by the first **SYNSTORY** of this issue, which reports on a truly brilliant chemistry-driven piece of research developed by a highly interdisciplinary team at Philips Research (The Netherlands) that led to the identification of an *in vivo* reaction allowing for an efficient tumor imaging in live mice. In my humble opinion, this is one of the most exciting recent achievements in the area of molecular imaging, which opens up whole new perspectives in molecular biomedicine. The second **SYNSTORY** reports on another exciting work dealing with a very timely area of research where organic chemistry obviously occupies a central role: catalysis and environmental sciences. Pressure is mounting on chemists to identify more environmentally compatible, sustainable and green chemical processes, and the work recently published by Professor K. Ishihara (Japan) goes in the right direction as, besides being a fantastic scientific contribution, it might help identifying more efficient organic catalysts for oxidation reactions, as an alternative for the more toxic metal catalysts. The issue is completed by a brief report on a very well organized and truly international School of Medicinal Chemistry for postgraduate researchers, the ESMEC, which is held annually in Urbino (Italy).

Enjoy your reading!

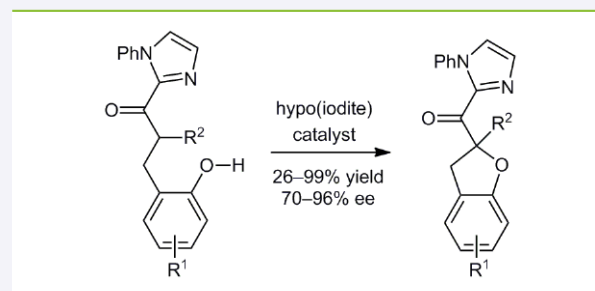
**Matteo Zanda**

*Editor of SYNFORM*

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**CONTACT +++++**  
 If you have any questions or wish to send feedback, please write to Matteo Zanda at:  
[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

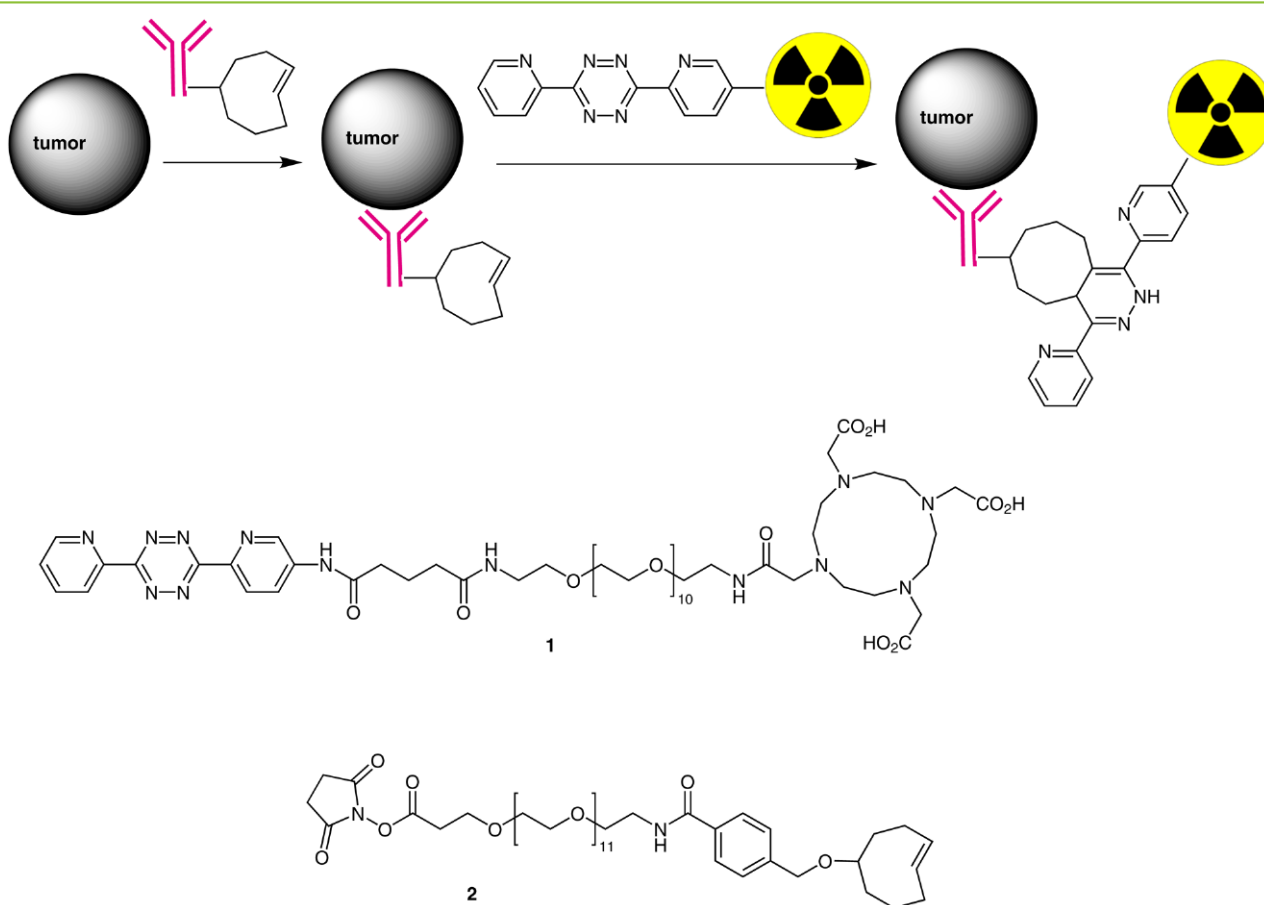
## NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## In Vivo Chemistry for Pretargeted Tumor Imaging in Live Mice

*Angew. Chem. Int. Ed.* **2010**, *49*, 3375–3378

■ The field of bioconjugates, and more specifically that of bioorthogonal chemistry, has rapidly expanded over the last few years, and the sequential discovery of more effective reactions has unearthed a wealth of exciting new possibilities for probing and perturbing biological systems. The exquisite selectivity of these reactions has been successfully exploited for biomolecule modifications in complex environments such as live cells. “However,” pointed out Dr. Marc S. Robillard, from the Biomolecular Engineering group of Philips Research in Eindhoven (The Netherlands), “these reactions have only in a few cases been successfully used in living organisms.” For

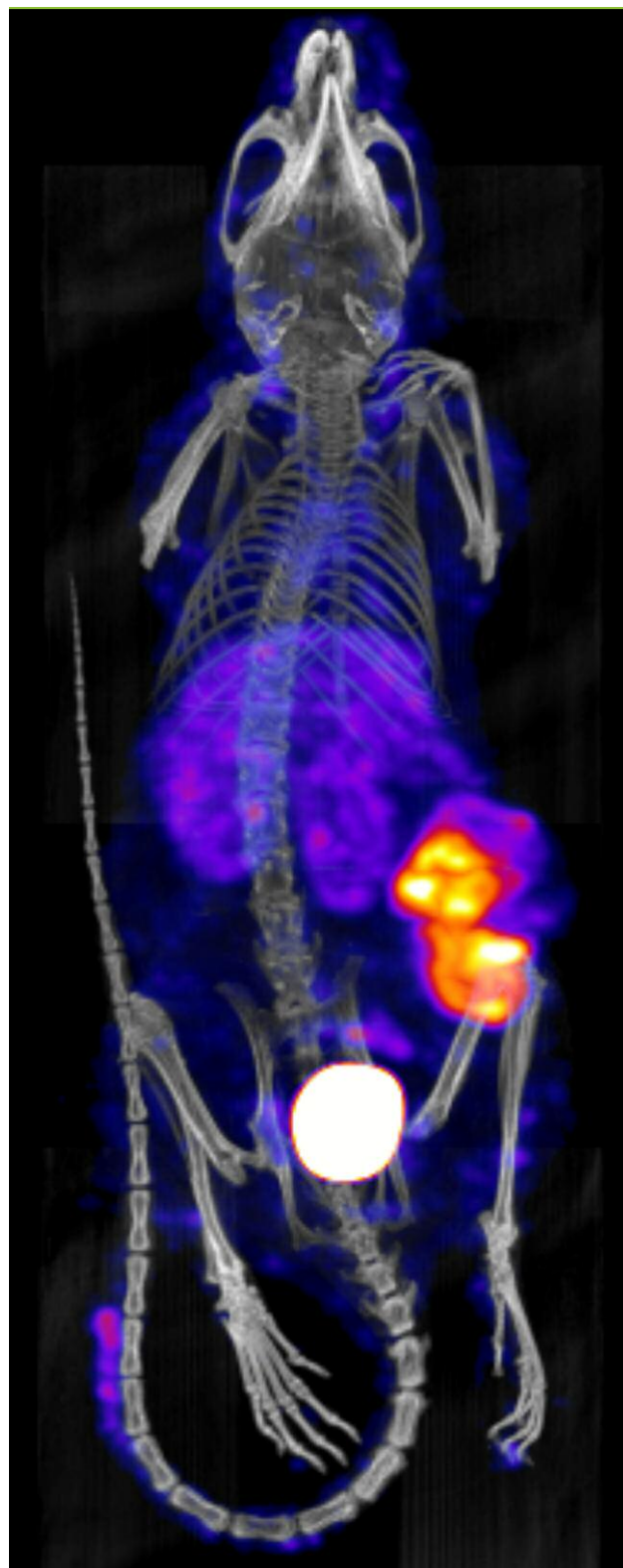
example, previous work by the group of C. Bertozzi from the University of California, Berkeley (USA) centered on the metabolic labeling of biomolecules followed by reaction with a detectable probe in mice and zebrafish embryos (*Science* **2008**, *320*, 664 and references therein). Dr. Robillard also acknowledged that previous work by J. M. Fox (*J. Am. Chem. Soc.* **2008**, *130*, 13518) and R. Weissleder (*Angew. Chem. Int. Ed.* **2009**, *48*, 7013) showed the reactivity and selectivity of the inverse-electron-demand Diels–Alder reaction in serum and on cells in vitro.



Recently, the group at Philips Research described the first use of a selective chemical reaction, the inverse-electron-demand Diels–Alder cycloaddition, between two exogenous moieties in a mammalian disease model for the non-invasive imaging of low-abundance targets at clinically relevant conditions. “We demonstrated non-invasive pretargeted imaging in a murine tumor model, with its challenging pharmacokinetic constraints, involving intravenous administration of a small, semi-equimolar amount of probe (nmol) to effectively delineate a tumor-bound antibody in 52% chemical yield. This selectivity and reactivity at low and semi-equimolar concentrations has never been demonstrated before in a living animal,” explained Dr. Robillard.

The technology represents a potential improvement over existing direct-targeted nuclear imaging and therapy using radiolabeled antibodies. Indeed, according to Dr. Robillard, the absorbed dose in the tumor vs. normal tissue is an important predictor for therapeutic success and occurrence of side effects in radioimmunotherapy (RIT). “In contrast to lymphohematopoietic cancers (for which two approved radioactive antibodies are on the market), solid tumors such as colorectal cancer have been much less responsive to RIT,” he explained. “Solid tumors show a very low uptake (0.001–0.01% injected dose per gram tumor) of the targeting antibody, resulting in a low and ineffective cumulative tumor dose. When the tumor uptake is limited, the dose needed to achieve a therapeutic response cannot be administered because of other normal organ dose limitations. The slow plasma clearance properties of radiolabeled antibodies result in prolonged exposure of the highly radiosensitive bone marrow to ionizing radiation.” Dr. Robillard pointed out that despite the high clinical need and large potential markets, solid tumors have remained out of RIT’s reach. “Therefore, the major challenge of radioimmunotherapy (and -imaging) of cancer is to enhance the nuclear radiation dose delivered to the tumor while minimizing the dose in healthy tissues. This can be achieved by using pretargeting, which involves the usual slow tumor delivery and accumulation of the targeting antibody in the first step, and subsequently a very fast binding of a small radiolabeled probe to the tumor-localized antibody in the second step. “Now that we have established that the Diels–Alder reaction can be effectively used *in vivo*, we are developing the system towards application in solid tumor therapy,” said Dr. Robillard.

According to the Philips researchers, current pretargeting is based on non-covalent recognition between biological constructs and the drawbacks of these techniques are linked to their biological nature. “The two most prominent technologies are based on streptavidin-biotin and bispecific antibodies,” explained Dr. Robillard. “*Streptavidin* is highly immuno-



SPECT/CT imaging of a live mouse bearing a colon carcinoma xenograft: anterior projection of a mouse pre-injected with a tumor-targeting antibody labeled with trans-cyclooctene derivative **2** followed one day later by  $^{111}\text{In}$ -tetrazine compound **1**

genic, hampering repeat treatments. Moreover, it is bulky and results in a pronounced alteration of the tumor-targeting construct, when used as antibody tag. Biotin is an endogenous molecule and can compete with the pretargeting procedure. *Bispecific antibodies* require reengineering of the parent antibody,” said Dr. Robillard. “The use of chemical components will possibly give less or no immunogenicity issues. Since the presented components are bioorthogonal and abiotic (components react selectively and are normally not present in the body) there is little competition of endogenous elements. Lastly, the components are small and will result in reduced/minimal perturbation of the parent antibody, antibody fragment, or other types of biomolecules. Our published technology is based on straightforward NHS coupling to lysine residues and can in principle be applied to tag and track in vivo a wide range of medium- to large-sized proteins without severe alteration of their in vivo properties.”

This research presents exciting perspectives, developments, and potential applications. “The inverse-electron-demand Diels–Alder reaction has the potential to improve the state-of-the-art of pretargeting, because it circumvents the use of immunogenic streptavidin systems and the protein engineering techniques used for bispecific antibodies,” said Dr. Robillard, who pointed out that “this technology potentially allows tackling solid tumors (large unmet clinical need) instead of only blood-borne tumors.”

In general, the Philips researchers believe that the inverse-electron-demand Diels–Alder reaction has the potential to expand the realm of in vivo chemistry from chemical biology to molecular imaging and therapy with biomolecules that are not compatible with direct labeling, for example due to size and/or slow or undesired pharmacokinetics. “For example,” said Dr. Robillard, “this approach may reintroduce full-length antibodies to nuclear imaging, and may serve as a point of entry for a wider range of chemical applications in living systems.”

To extend the proof of principle published in the paper to effective pretargeted radioimmunotherapy Dr. Robillard’s work is now centered on increasing the tumor/non-tumor ratio. “As soon as we have completed the parameter optimization we will start with pre-targeted radioimmunotherapy in LS174T xenografted mice,” he said. “Furthermore, in parallel to the ongoing validation of this technology, we have started exploring the possibilities for a joint clinical development together with external investors and pharmaceutical or biotech partners.”

Dr. Robillard shared some interesting “behind-the-scenes” of this project with **SYNFORM**. “Last year our team managed to achieve what we’d been working on for years: conduct the

first selective and effective chemical reaction ever inside a living being for a novel cancer radiotherapy approach,” he said. “After synthesizing the first series of Diels–Alder components we started the in vitro evaluation (probe stability, antibody conjugation, probe-antibody reactivity),” continued Dr. Robillard. “We were happy to see that our first tetrazine probe design was stable enough for the intended application. Next, we were flabbergasted when the first reactivity results came in. When we later wanted to determine the kinetics of the reaction between the tetrazine and the *trans*-cyclooctene, we had the luxury problem of finding an experimental setup and reaction conditions in which the reaction would proceed slow enough to be followed. Our first test in vivo was to determine if the modified antibody and the probe would react in circulation in mice,” he said. “Five minutes after injection of the antibody we injected the probe and three hours later we determined the remaining radioactivity in blood.” The researchers had previously determined that the tetrazine probe cleared rapidly from circulation. Therefore, any remaining radioactivity in blood after three hours had to be due to tetrazine that had reacted with the much slower clearing antibody. “When the results came in showing that the radioactivity in blood was several orders of magnitude higher compared to the probe alone, we broke out the champagne,” said Dr. Robillard. “One month later we had our first tumor pretargeting biodistribution results. After some more optimization we soon thereafter got our first tumor pretargeted image.” Dr. Robillard acknowledged that this rapid progress is due to several factors. “In part it is due to the experience we had with working on other reactions for pretargeting in the years before,” he said. “Also, the robustness of the inverse-electron-demand reaction and its components facilitated this rapid progress. Our laboratory, the Life Science Facilities, has all relevant disciplines (organic chemistry, material analysis, cell and molecular biology, radiochemistry, imaging, preclinical experimentation) under one roof, which really accelerated our work. And last but certainly not least, the drive, flexibility and “gung-ho” nature of our team. The fact that they all came through whenever it mattered meant that we finally achieved the result we had hoped for,” he concluded. ■

Matteo Zanda



### About the authors



The Philips team, standing from left: S. van den Bosch, Dr. M. Robillard, R. Vuldere, Dr. J. Lub, Dr. I. Verel, P. Renart Verkerk, sitting: Dr. R. Rossin

**Raffaella Rossin**, first author of the paper and senior radiochemist in the Biomolecular Engineering (BME) group of Philips Research, involved in the design and execution of almost all aspects of the paper. Raffaella Rossin (born in 1972) obtained her MSc in organic chemistry at the University of Padova (Italy) in 1998 after which she started her PhD research on the production of new Tc-99m radiopharmaceuticals in collaboration with the Faculty of Pharmacy of the same university. After her graduation in 2003, Dr. Rossin joined the School of Medicine of Washington University in St. Louis, MO (USA), where she worked as a Postdoctoral Research Associate first and as a Research Instructor later. During this time, she focused on new nanomaterials and developed methods to radiolabel them with positron-emitting radionuclides. In early 2008, Dr. Rossin joined the BME group at Philips Research in Eindhoven as a senior scientist to work on molecular imaging and drug delivery.

**Pascal Renart Verkerk**, organic chemistry technician responsible for the synthesis of the tetrazine probe and the *trans*-cyclooctene tag in this paper. Pascal Renart Verkerk (born in

1979) started his career at General Electric but after one year he joined Mercachem, a CRO company, doing organic synthesis for pharmaceutical companies. In 2008 he joined the BME group at Philips Research for synthesis and labeling of molecular imaging probes. Currently, he holds a position as synthetic chemist at Synthon in Nijmegen.

**Sandra van den Bosch**, cell and molecular biology research engineer responsible for the antibody modifications and corresponding in vitro and ex vivo reactivity studies in the paper. Sandra van den Bosch (born in 1981) obtained her BSc in microbiology at the Fontys Hogescholen in Eindhoven (The Netherlands) in 2003, after which she joined the Department of Pathology at the University of Maastricht (The Netherlands), where she worked mainly on the discovery of early biomarkers for colorectal cancer. In 2008 she joined the BME group of Philips Research Eindhoven to work on nuclear agents for imaging and therapy.

&gt;&gt;

**Roland Vulderson**, cell and molecular biology research engineer responsible for the cell culture and antibody production and characterization in this paper. Roland Vulderson (born in 1977) obtained his degree in microbiology at the Fontys University of Applied Sciences in Venlo (The Netherlands) in 2000 and started his career as a technician at Semaia Pharmaceuticals, a biotech startup located in Utrecht (The Netherlands). There he was responsible for the development of screening assays for novel lead candidates aimed at interfering in signal transduction pathways associated with cancer and diabetes. He also participated in a genome-wide synthetic lethal RNAi screen in *C. elegans*. In 2005 Roland joined Philips Research where he started to work in the field of molecular imaging.

**Iris Verel**, coordinator of preclinical studies in the Life Science Facilities and as such contributed to the animal experiments described in this paper. Iris Verel (born in 1975) obtained her MSc in biology at the University of Utrecht in 1998. She performed her PhD research at the VU University, Amsterdam (The Netherlands), developing a zirconium-89 radiolabeled antibody against head and neck squamous cell carcinoma, for diagnostic purposes with positron-emission tomography (1998–2003). After obtaining her PhD, she worked as a postdoctoral researcher for one year at the Center for Molecular Imaging Research, Massachusetts General Hospital, Boston (USA). At the end of 2004, she started working at Philips Research as a radiochemist in the BME group. In 2006, she changed groups within Philips and joined the Life Sciences Facilities.

**Johan Lub**, principal scientist at Philips Research in the field of organic chemistry and involved in all synthetic topics in the paper. Johan Lub (born in 1955) obtained his PhD in organic chemistry at the University of Amsterdam in 1985 after which he joined the Philips Research laboratories in Eindhoven. Until 1988 he worked in the field of polymer chemistry and polymer surface analysis. Since 1988 he has been engaged in the organic synthesis of materials for various projects at Philips Research, including liquid crystal chemistry and technology, materials for optical recording, batteries and light applications, chemistry of contrast agents and biodegradable polymers for drug delivery.

**Marc Robillard**, principal investigator of the paper and project leader of the corresponding Philips Research project on pretargeted radioimmunoimaging and -therapy using bioorthogonal reactions. Marc Robillard (born in 1972) obtained his MSc in bioinorganic and bioorganic chemistry at the University of Groningen (The Netherlands) in 1996, after which he briefly joined the contract research company Syncom in Groningen as a synthetic chemist. He started his PhD research at the end of 1997 at the Leiden Institute of Chemistry (The Netherlands) on the acceleration of the platinum-based anticancer drug discovery process by developing the solid-phase (parallel) synthesis of peptide platinum complexes and their rapid in vitro screening, and obtained his PhD in early 2003. He subsequently joined Kreatech Diagnostics in Amsterdam for a short-term project on the development of probes for drug-targeting applications, as well as for labeling and microarray-based detection of DNA, RNA and proteins. At the end of 2003, Marc joined the BME group of Philips Research in Eindhoven to work on molecular imaging.

# Quaternary Ammonium (Hypo)iodite Catalysis for Enantioselective Oxidative Cycloetherification

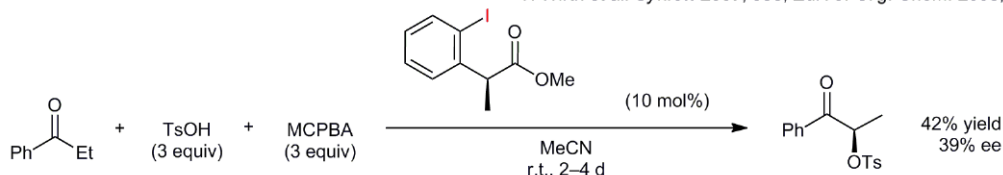
*Science* **2010**, *328*, 1376–1379

■ Organocatalysis is a very hot area of research and a number of acid and base organocatalysts have been developed recently. In contrast, there are only a few known organic redox catalysts. “I am convinced that hypervalent halogen com-

pounds will soon become competitive with transition-metal redox catalysts,” said Professor Kazuaki Ishihara from Nagoya University (Japan). “Transition-metal elements such as platinum group metals (Ru, Rh, Pd, Os, Ir, Pt) are known to

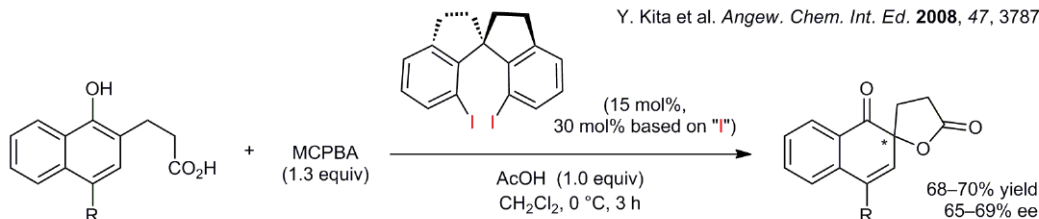
## Enantioselective oxidative $\alpha$ -oxysulfonylation of propiophenone

T. Wirth et al. *Synlett* **2007**, 538; *Eur. J. Org. Chem.* **2008**, 5315



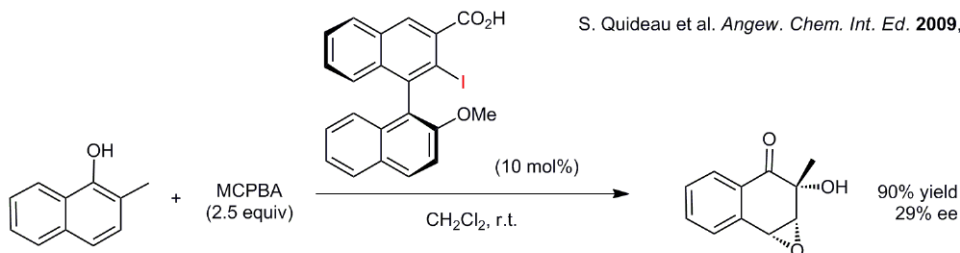
## Enantioselective oxidative dearomatization of 1-naphthol derivatives (Kita oxidative spirolactonization)

Y. Kita et al. *Angew. Chem. Int. Ed.* **2008**, *47*, 3787



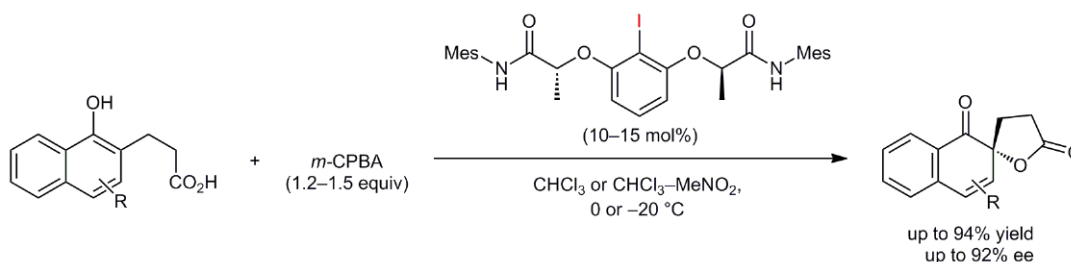
## Enantioselective oxidative dearomatization of 2-methyl-1-naphthol

S. Quideau et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 4605



## Enantioselective Kita oxidative spirolactonization

K. Ishihara et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 2175; *Tetrahedron* **2010**, *66*, 5841

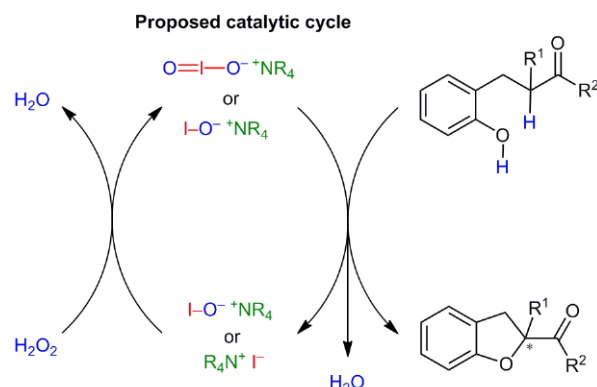




be rare and expensive metals; moreover, generally speaking, organocatalysts are greener than metal catalysts, which are more toxic. Halogens can mimic transition metals as redox catalysts for oxidative coupling reactions, and may well represent an advantageous choice in enantioselective catalysis.”

“To date only four examples of enantioselective oxidative reactions catalyzed by chiral hypervalent iodine compounds have been reported, to the best of our knowledge,” continued Professor Ishihara. “All these chiral hypervalent iodine(III) compounds are prepared in situ from iodoarenes and MCPBA. In sharp contrast, our new iodine catalyst is prepared in situ from a quaternary ammonium iodide and hydrogen peroxide or *tert*-butyl hydroperoxide (TBHP). This finding is a real breakthrough to overcome the limiting factors using chiral iodine reagents,” he said.

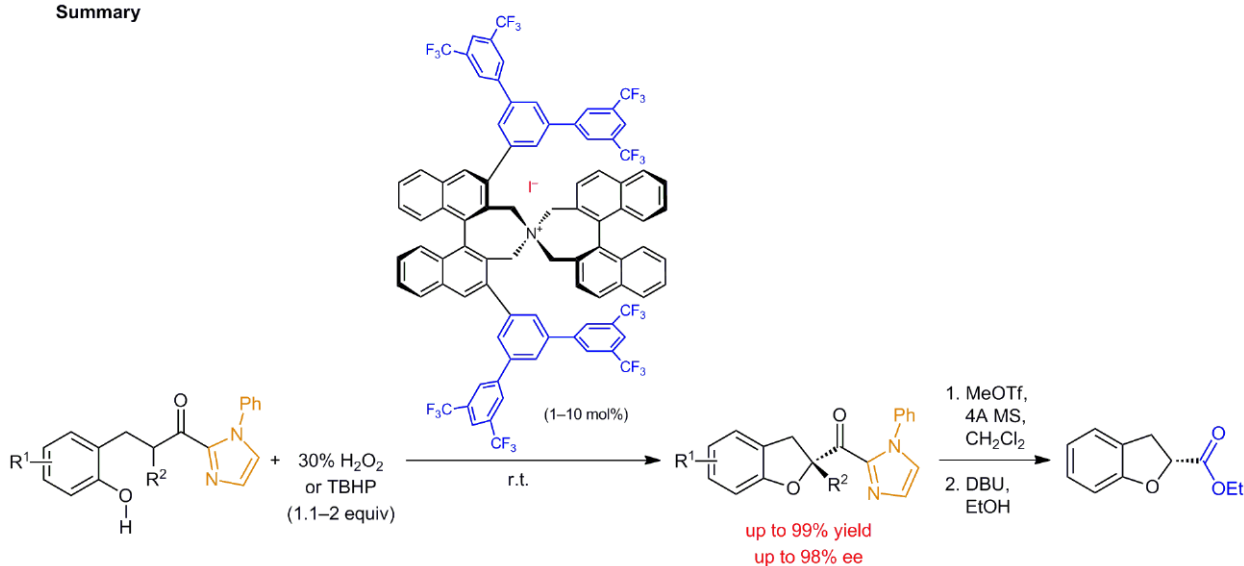
According to Professor Ishihara, an iodide anion is easily oxidized to hypoiodite and/or iodite anions with hydrogen peroxide and TBHP. “Inorganic hypoiodite ( $\text{IO}^-$ ) or iodite ( $\text{IO}_2^-$ ) anions should be real catalytic species. However, iodoarenes cannot be oxidized to iodosyl arenes with hydrogen peroxide or TBHP,” explained Professor Ishihara. “We reasoned that if an appropriate chiral organoammonium cation could be designed as a counter cation of the inorganic (hypo)iodite anion, greener catalytic asymmetric oxidative coupling reactions could be developed. Furthermore,” he continued, “the design of chiral salt catalysts is superior to that of chiral single-molecule catalysts in terms of diversity, because screening of both a cation and an anion moiety is possible.”



Recently, the group of Professor Ishihara published a groundbreaking article describing the use of enantiomerically pure organoammonium iodide salts for enantioselective oxidation reactions, replacing more toxic metal catalysts.

“We found that a chiral spirobis(binaphthyl)-type ammonium cation was suitable for asymmetric catalysis of the present oxidative coupling reaction,” explained Professor Ishihara, who acknowledged that this spirobis(binaphthyl)-type ammonium cation had been developed as a counter cation of chiral phase-transfer catalysts by Professor K. Maruoka from Kyoto University (Japan). “The *N*-phenylimidazolyl group of the substrates was an important auxiliary for achieving high enantioselectivity. In addition, the *N*-phenylimidazolyl group of the products was easily transformed to the ethoxycarbonyl

#### Summary

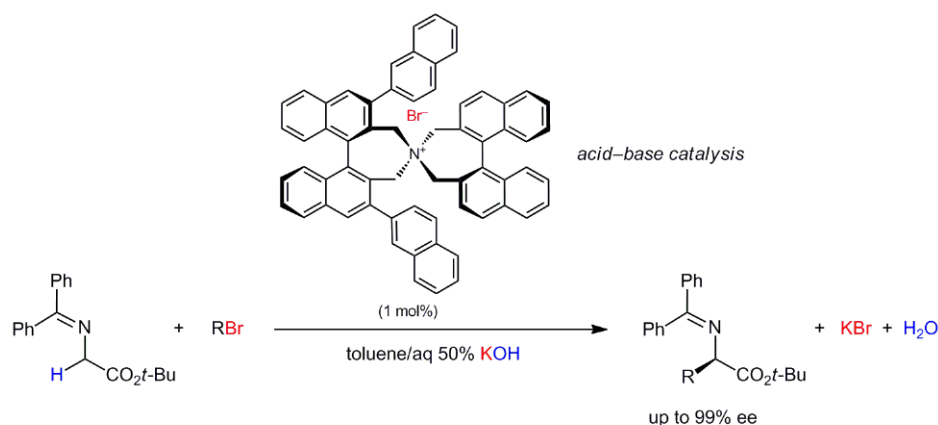


group without reducing the optical purity,” said Professor Ishihara. “These products become key intermediates for the synthesis of biologically and optically active compounds bearing 2,3-dihydrobenzofuran skeletons.”

“Professor Maruoka and co-workers have developed asymmetric phase-transfer catalysts. We applied this chiral ammo-

nium cation to a chiral counter cation of our oxidation catalyst. Our catalyst might also be a phase-transfer catalyst when 30% aqueous  $\text{H}_2\text{O}_2$  is used as co-oxidant. However, it worked as a homogeneous catalyst when TBHP was used as co-oxidant. Therefore, ‘phase transfer’ is not so important for our catalysis,” said Professor Ishihara.

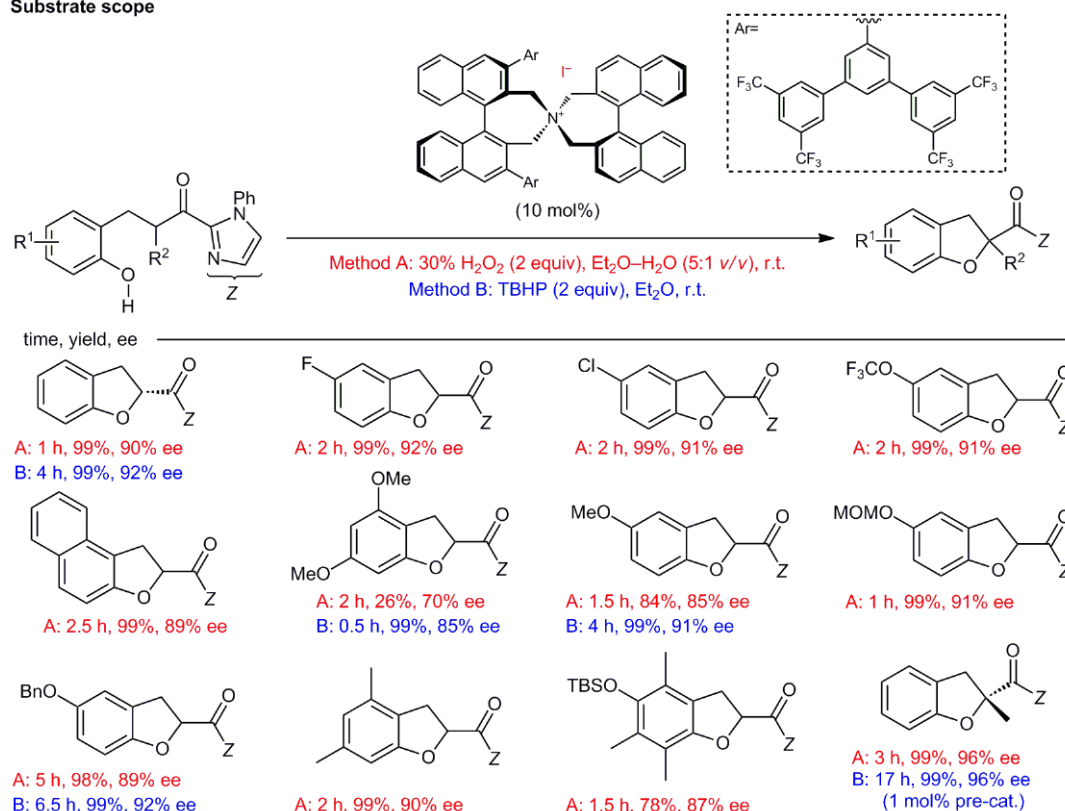
#### Maruoka's chiral phase-transfer catalysis



**The first report:** T. Ooi, K. Kameda, K. Maruoka *J. Am. Chem. Soc.* **1999**, 121, 6519

**Review:** T. Ooi, K. Maruoka *Angew. Chem. Int. Ed.* **2007**, 46, 4222

#### Substrate scope



Professor Ishihara pointed out that the most important features of this new organocatalytic system are:

(1) 1 mol% catalyst loading is the best known result in asymmetric iodine catalysis;

(2) 96% ee is the best known result in asymmetric iodine catalysis; and

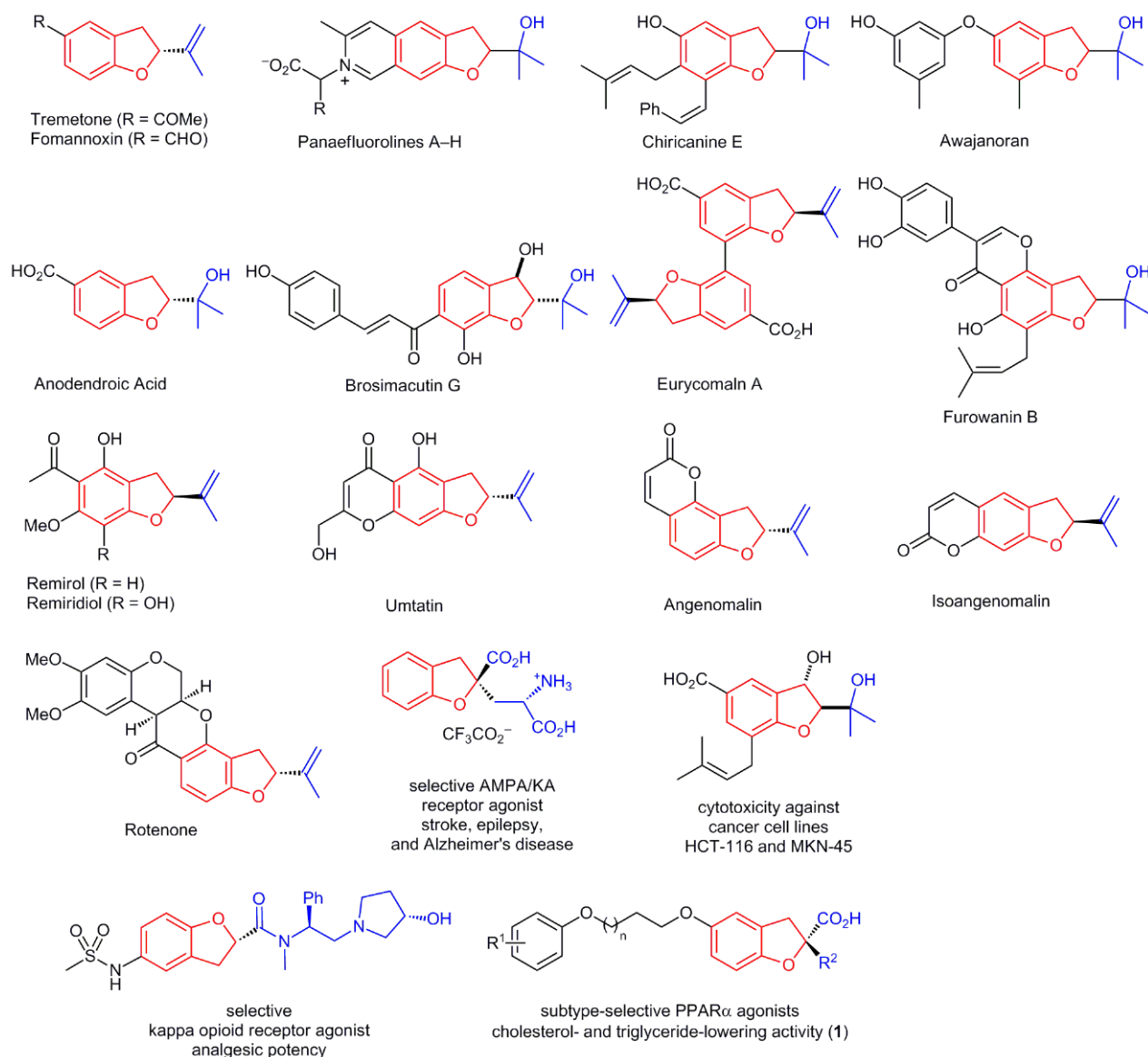
(3) the use of  $\text{H}_2\text{O}_2$  as co-oxidant is the first known example in asymmetric iodine catalysis.

“It is difficult to synthesize chroman compounds in high yields accompanied by high enantioselectivity,” said Professor Ishihara. “Furthermore, the intermolecular coupling reaction is much more difficult: these will be our future subjects.”

“We believe that a variety of oxidative coupling reactions will be controlled by chiral ammonium (hypo)iodites in place of transition-metal catalysts in the future,” he continued. “Moreover, in the near future we would like to develop asymmetric hypervalent iodine catalysts for *intermolecular* oxidative coupling reactions. This is one of the most challenging subjects.”

Professor Ishihara emphasized that there are a number of biologically active natural products and potentially active pharmaceutical products bearing 2,3-dihydrobenzofuran skeletons. “For example, *tremetone* has both antifungal and insecticidal properties and is derived from a plant extract,” he

#### Biologically active compounds bearing 2,3-dihydrobenzofuran skeletons

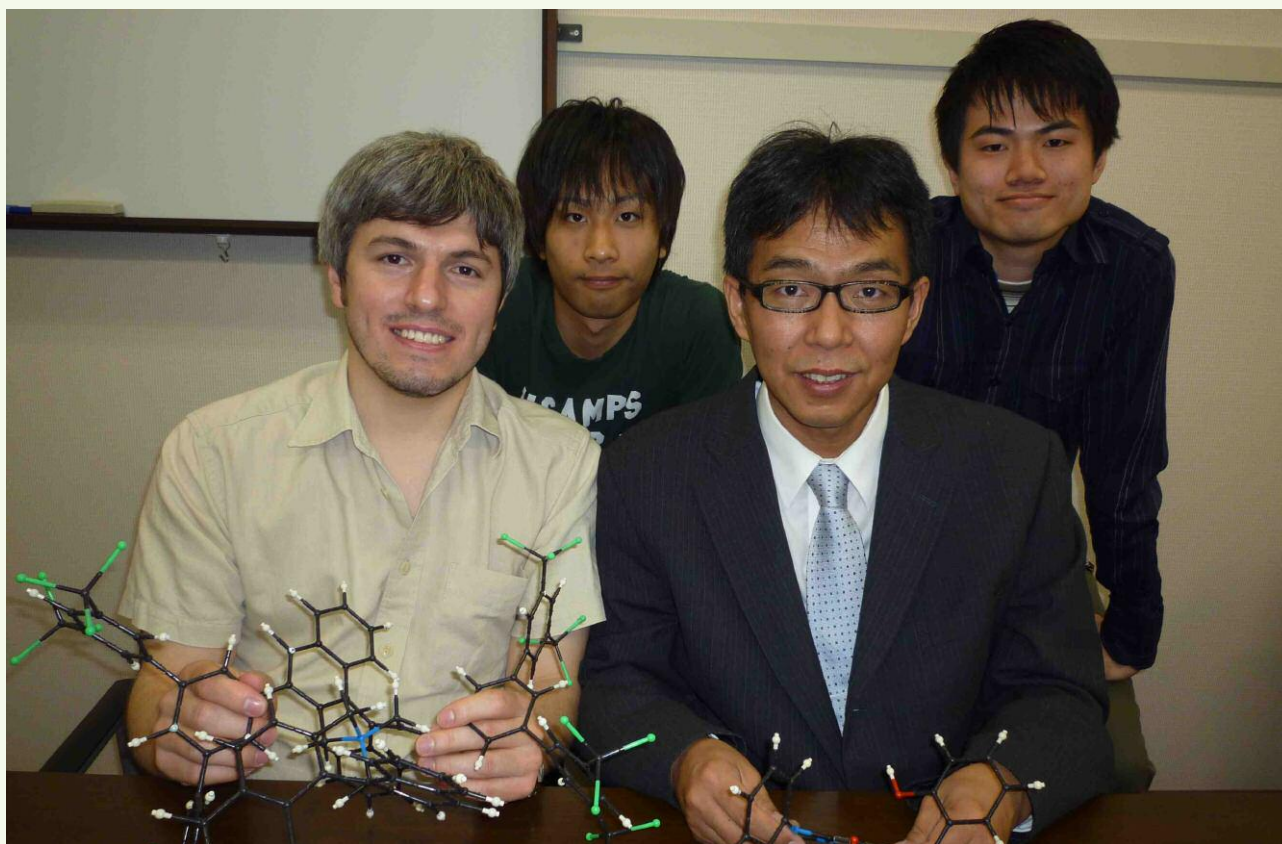


said. "A similar natural compound, *rotenone*, is a potent anti-leukemic drug candidate as well (*Phytochemistry* **1988**, *27*, 2795). In 2005, the Merck Company reported the synthesis of a drug candidate (**1**) with this same backbone that modulates the levels of serum triglycerides and high-density lipoprotein in the blood (*J. Med. Chem.* **2005**, *48*, 5589). A synthesis of

this target with this new method could be accomplished in fewer steps than in the 2005 method, producing less waste, and reducing costs," concluded Professor Ishihara. ■

Matteo Zanda

### About the authors



From left: Assistant Prof. M. Uyanik with a chiral ammonium cation model, T. Yasui, Prof. K. Ishihara with a substrate-(hypo)iodate anion model, H. Okamoto



## Focus on the European School of Medicinal Chemistry (ESMEC), July 4<sup>th</sup>–9<sup>th</sup>, 2010, Urbino (Italy)

■ From July 4<sup>th</sup> to 9<sup>th</sup>, 2010, Urbino (Italy) hosted the European School of Medicinal Chemistry (ESMEC, <http://www.esmec.eu/>). The venue was the Scientific Campus of the University of Urbino, located on a hill at about 3 km from the historical city center of Urbino, with its charming view of the surrounding countryside. The school was attended by 196 young scientists, 170 of them being PhD students, from 10 different European countries.

This year the scientific program included the following topics:

- (i) Infection Diseases: Focus on AIDS and Flu
- (ii) Drug Delivery to the Targets
- (iii) Challenges in the Synthesis of Bioactive Compounds
- (iv) Hot Topics (PET imaging, microfluidic devices, etc.)

Out of the 18 speakers, 13 came from abroad, including Professor Stephen Hanessian (University of Montreal, Canada), Dr. Ian Baxendale (University of Cambridge, UK), and Professor Klaus Mueller (F. Hoffmann-La Roche, Basel, Switzerland). The rich program was completed by training sessions and workshops.

Again this year, the school proved to be an excellent opportunity for postgraduate students and researchers from industry and academia to gather and take part in informal and relaxed yet extremely effective training sessions on some of the hottest topics in modern medicinal and biological chemistry. Last but not least, the School offered very good opportunities for social life and intelligent relaxation involving both students and speakers. The School was very well organized by the Scientific Committee directed by Professor Gloria Cristalli (University of Camerino, Italy) and the Organizing Committee headed by Lucia Bedini (University of Urbino, Italy). The next edition of the ESMEC is expected to be held in July 2011 at the same venue. ■

Matteo Zanda



Participants of the ESMEC 2010

COMING SOON ►► COMING SOON ►►

# SYNFORM 2010/09

## is available from

## September 22, 2010

In the next issues:

## SYNSTORIES ■ ■ ■ ■

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*(Focus on an article from the current literature)*

### ■ Cascade Cyclization To Produce a Series of Fused, Aromatic Molecules

*(Focus on an article from the current literature)*

## FURTHER HIGHLIGHTS +++++

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#### Review on: Transition-Metal-Catalyzed C–P Cross-Coupling Reactions

*(by M. Oestreich)*

## SYNLETT

#### Account on: Synthesis of Organosulfur Compounds Based on Cyclocondensation Reactions of 3-Arylthio-1-silyloxy-1,3-butadienes and 1,3-Bis(silyloxy)-1,3-butadienes

*(by P. Langer)*

## SYNFACTS

#### Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of R207910](#)

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