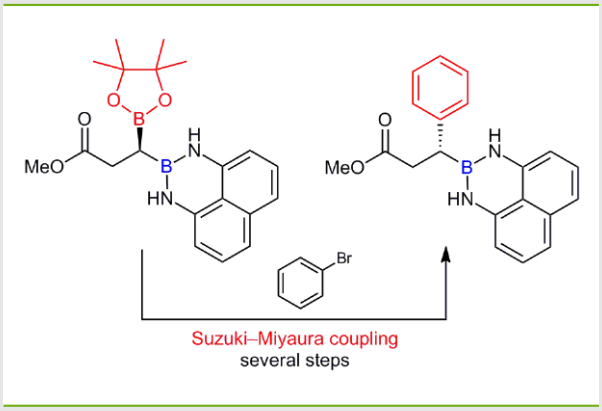
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2012/03

SYNSTORIES

- **Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds**



- **Gold-Catalyzed Oxidative Acyloxylation of Arenes**

- **SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Ulrich Koert (Philipps-Universität Marburg, Germany)**

CONTACT

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Thieme

Dear readers,

Last week I was preparing a conference call with an AstraZeneca research center in the UK, when I suddenly got a "cancellation" message, followed by an email stating that "Following on from today's announcements within AstraZeneca, we have decided to postpone the meeting today to allow everyone here to fully understand the implications". Surprised, I checked the News online and I immediately found the headline: "AstraZeneca to cut 7,300 jobs". Clearly I was witnessing live another major blow in the Big Pharma arena. This sad event follows previous payroll-cuttings from Pfizer, Novartis, Sanofi, Teva, Takeda Pharmaceuticals, and the list could continue. There are many reasons for this gloomy situation, generic competition is probably the most important one. But fortunately there was some good news too according to related online articles, because other smaller drug-maker companies seem to be doing well and the Wall Street Journal recently reported that industry experts are foreseeing a turnaround in 2013.On the other hand, Research & Development is undergoing a deep restructuring and reshaping virtually in every big pharmaceutical company, and this may lead to major opportunities for those who will be able to understand and adapt themselves to this change of scenario. Hopefully organic chemistry will re-emerge stronger than ever.

This issue of ***SYNFORM*** is opened by a ***SYNSTORY*** article on a boron-mediated carbon–carbon bond forming process discovered by Professor D. G. Hall (Canada), which is followed by a report on a gold-catalyzed introduction of an acyloxy group on aromatic residues developed by Dr. V. Michelet (France), and concluded by an Advisory Board Focus on Professor U. Koert (Germany). Clearly the global economic crisis is not affecting the quality of the science featured in ***SYNFORM***!

Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

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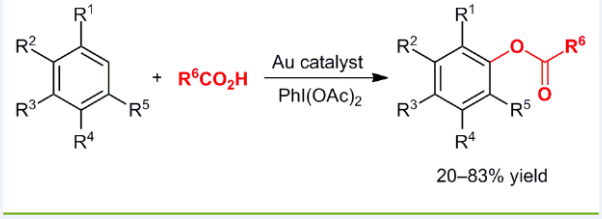

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CONTACT ++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

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NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds

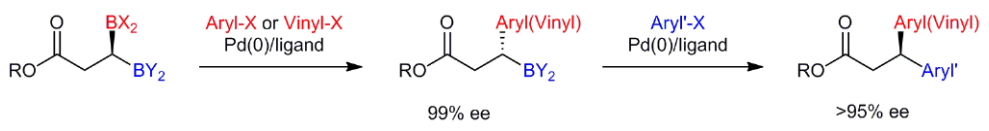
Nat. Chem. **2011**, *3*, 894–899

Novel methods to form carbon–carbon bonds in a stereocontrolled manner remain a landmark achievement in synthetic organic chemistry. Palladium-catalyzed cross-coupling reactions are extremely powerful tools to achieve this goal; however, cross-coupling processes involving sp^3 carbons are generally much more challenging than those involving sp^2 carbons (i.e., aryl and vinyl substrates). Boron compounds are very important in palladium-catalyzed cross-coupling chemistry, as demonstrated in the many outstanding applications of the Nobel Prize winning Suzuki–Miyaura coupling. However, some facets of this powerful methodology are still in need of development, such as stereoselective cross-couplings. Recently, the group of Professor Dennis G. Hall from the University of Alberta (Edmonton, Canada) reported very important progress in the field, describing the first preparation of optically pure 1,1-alkyldiboronyl compounds (*gem*-diboronic esters) along with their utilization in chemoselective and stereoselective cross-coupling chemistry. The underlying synthetic concept of this work is summarized in Scheme 1.

"The project was inspired by a remarkable study, reported in 2010 by Endo and Shibata (*J. Am. Chem. Soc.* **2010**, *132*, 11033), who showed that achiral 1,1-diboronic esters can be subjected to a single, chemoselective Suzuki–Miyaura cross-coupling," acknowledged Professor Hall. "We wondered if the cross-coupling could be achieved in a stereoselective manner, so we set out to prepare the requisite, albeit unprecedented, optically enriched 1,1-diboronyl compounds." Professor Hall said that all of the experimental work was performed in the skilled hands of 4th year graduate student Jack Chang Hung Lee. "Over the past few years, Jack has developed a real knack for handling and purifying organoboron compounds and all those skills and experience served him well in this project," he added.

"Prior to our work," said Professor Hall, "there was only one single example (a single entry in a recent paper from Professor Molander and co-workers) of a stereoselective Suzuki–Miyaura cross-coupling of a secondary alkylboronate that is not benzylic (*J. Am. Chem. Soc.* **2010**, *132*, 17108). According to the elegant work of my Canadian colleague Professor Cathy Crudden (*J. Am. Chem. Soc.* **2009**, *131*, 5024)," he continued, "it is known that aryl groups facilitate the cross-couplings of chiral benzylic boronates with minimal loss of stereochemical integrity. The coupling of non-benzylic secondary alkylboronates with preservation of stereochemistry is a challenging problem, and our paper presents a valuable advance."

Professor Hall explained that his group's 'trademark approach' to the synthesis of chiral organoboronates is one where the boronate group is pre-installed in the substrate, as opposed to being introduced at a later stage with boronyl reagents. "Because B–C bonds are quite reactive, the challenge of this approach is to control several potential chemoselectivity issues. This fear has, for a long time, sustained a sort of 'borophobia' in the community and most research groups prefer to develop reactions by introducing boron as late as possible in order to avoid chemoselectivity issues," he said. According to Professor Hall, in the 1970s and 1980s, pioneering work by Professor Donald Matteson showed that chiral boronate units can be treated to series of homologation reactions using anionic rearrangements that preserve the integrity



Scheme 1

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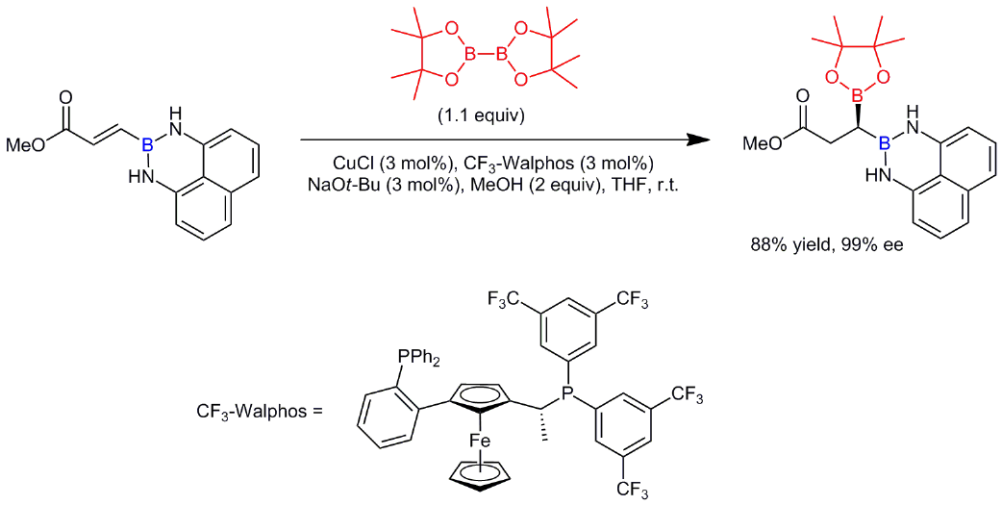
of the boronyl group (*Tetrahedron* **1998**, *54*, 10555 and references therein). "Our current and previous studies focusing on metal-catalyzed reactions show that it is possible and often very beneficial to introduce boron early in a synthesis involving those types of modern transformations," said Professor Hall. In the case of the *Nature Chemistry* paper, the authors had already shown that β-boronyl acrylates can act as Michael acceptors for carbon nucleophiles; therefore, they were not overly surprised that the conjugate borylation worked. "Key to success is to protect the β-boronyl group as a 1,8-diaminonaphthalene adduct, a versatile class of masking group for boronic acids developed in the laboratory of Professor Michinori Suginome at Kyoto University," acknowledged Professor Hall. "We were surprised, however, but very pleased that it afforded such a high enantioselectivity with the trifluoromethylated Walphos-type ligand. Jack Lee, the graduate student working alone on this project, was quite persistent because early results with other chiral diphosphines led to depressingly low ee values."

Professor Hall revealed that, when he first measured the enantiomeric excess of the 1,1-diboronyl compound **1** synthesized from the trifluoromethylated Walphos ligand, Jack Lee thought that perhaps he had used the wrong sample for chiral HPLC, since only one peak was observed. "After checking carefully with his NMR data and racemic samples he gladly confirmed that it was the right sample and that the synthesized diboronyl product was highly enantiomerically enriched (99% ee)!" he said.

The stereochemistry and other structural features of the enantiomerically pure 1,1-diboronyl compound **1** were assessed by X-ray crystallography, revealing a small distance between the carbonyl oxygen of the methyl ester and the boron atom of the pinacolate unit. This, in turn, suggested that the boron pinacolate moiety could be involved in the subsequent Suzuki–Miyaura reaction, favoring the observed complete inversion of stereochemistry at the boron-substituted reacting carbon.

"During the determination of the absolute configuration of the 1,1-diboronyl compound synthesized, Jack was so desperate that several times he brought our crystallographer samples of amorphous solids that actually looked like crystals," recalled Professor Hall. "Unfortunately, they did not diffract and no X-ray data could be collected from these solids. Our crystallographer and co-author, Dr. Robert McDonald was very patient!"

This new methodology is not only innovative and elegant, it's also very useful and versatile as demonstrated in the synthesis of optically enriched β,β-diaryl carboxy esters, which could be obtained by sequential chemoselective Pd(II)-catalyzed cross-coupling reactions. Unfortunately, the initially



Scheme 2

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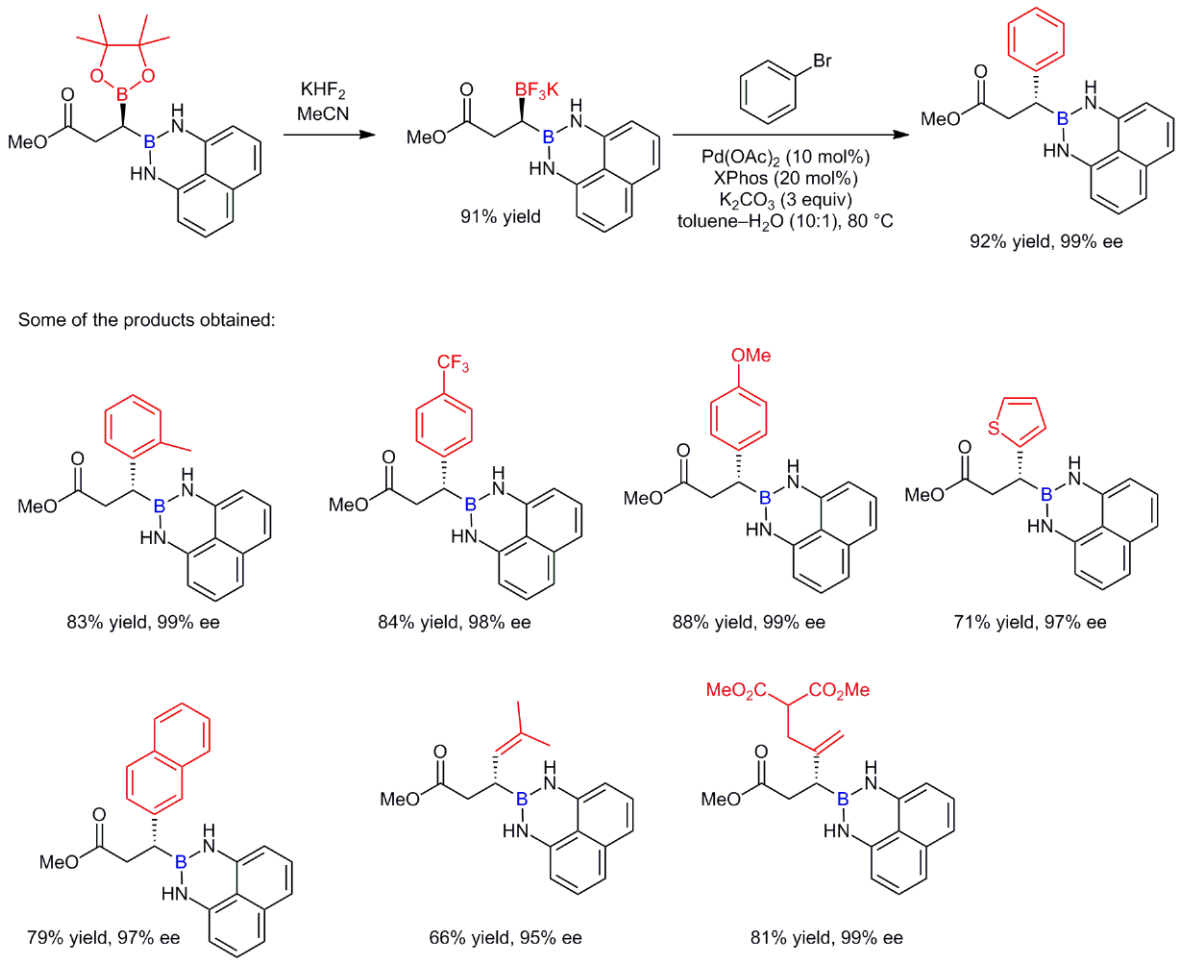
formed boron pinacolate and diaminonaphthalene boron moieties were poorly reactive and had to be transformed (with retention of configuration) into more reactive trifluoroborate salts, which are the actual intermediates in the cross-coupling reactions. The first Suzuki–Miyaura coupling on the 1,1-diboryl substrate has rather broad scope, as portrayed in Scheme 3.

Subsequently, the second cross-coupling process gave access to diarylmethane derivatives in high ee (Scheme 4). However, besides the usual conversion of the boron moiety into trifluoroborate salt, the methyl ester had to be transformed into an amide prior to achieving the desired transformation.

"Our findings that a boronyl substituent permits a stereospecific cross-coupling reaction on the adjacent boryl group not only allows a stereoselective access to important diarylmethane-containing drugs and intermediates, it may also open doors towards a new area of cross-coupling reactions with 1,1-diboryl and (if we can be allowed to dream...), 1,1,1-triboryl and- 1,1,1,1-tetraboryl compounds," said Professor Hall. "Such simple boron-rich templates could serve as progenitors to a vast number of optically pure organic molecules with tertiary and quaternary centers. Numerous examples of natural products and pharmaceutical agents contain these units," he added.

Regarding the motivations to undertake this research, Professor Hall said: "We felt that it would be an exciting fundamental advance to be able to make an optically enriched 1,1-diboryl compound that is chiral by virtue of having two



Scheme 3

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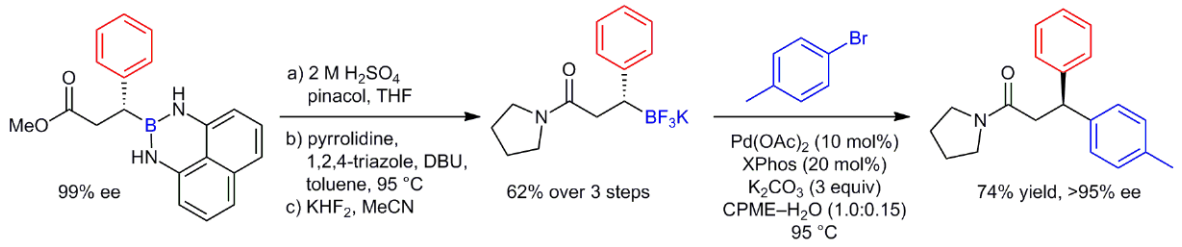
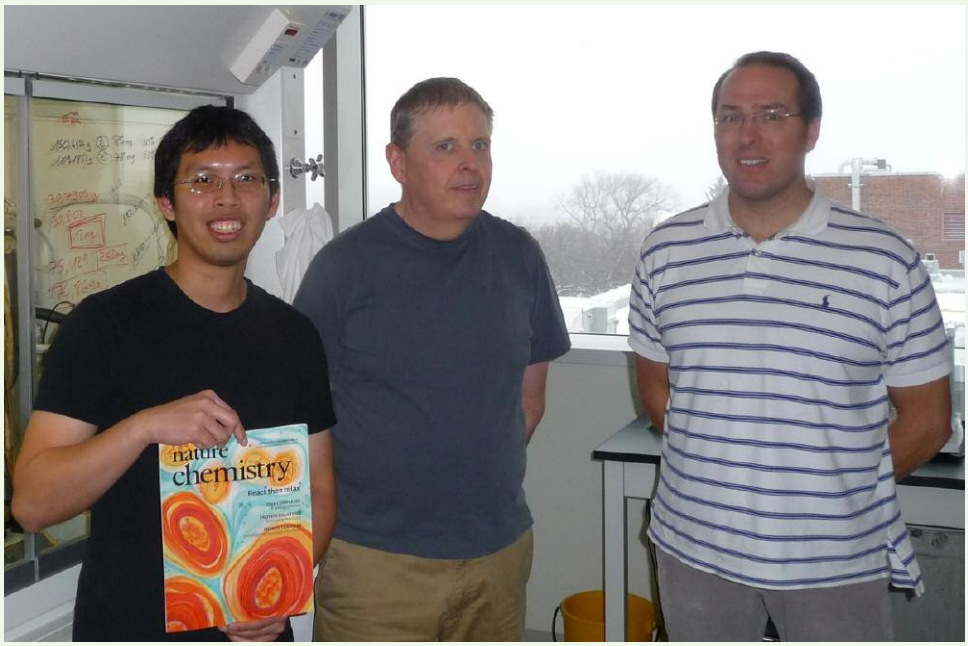


Scheme 4

different boronyl units." Although the results are already very exciting, Professor Hall admitted that the cross-coupling applications still leave room for improvements, mainly because the initially formed boron pinacolate and diaminonaphthalene boron unit need to be transformed into derivatives such as trifluoroborates that are more reactive. "We are currently working towards streamlining the cross-coupling applications of these chiral 1,1-diboryl intermediates," he concluded.

Matteo Zanda

About the authors



From left: J. C. H. Lee, Dr. R. McDonald, Prof. D. G. Hall

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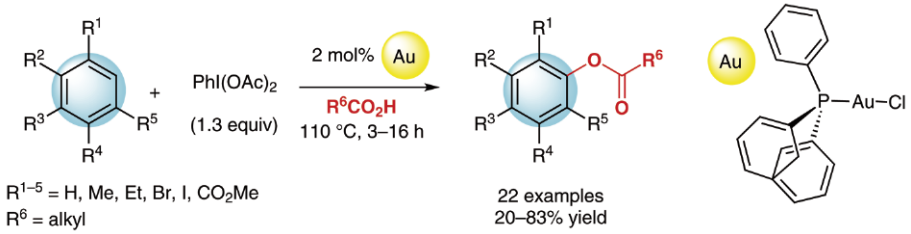
Gold-Catalyzed Oxidative Acyloxylation of Arenes

Org Lett. **2011**, *13*, 6086–6089

The design of new catalytic systems is one of the most challenging and competitive fields in modern organic chemistry. Although various reactions relied on the specific reactivity of different transition-metal complexes, the recent upsurge of interest associated with studies involving carbophilic Lewis acids such as gold has opened the way to the development of families of highly active and selective catalysts presenting a unique reactivity. "Long underrated due to their alleged lack of catalytic activity, gold complexes were recently subjected to a reinvestigation of their chemical features that resulted in one of the major changes of perspective in the homogeneous catalysis community during the last decade," said Dr. Véronique Michelet, from the Chimie ParisTech, Laboratoire Charles Friedel, UMR 7223 (Paris, France). "The groups of Bond, Haruta, Hutchings, Ito and Hayashi initiated key contributions regarding gold reactivity and opened new perspectives for the chemical community," she added. Recently, the group of Dr. Michelet reported a novel gold-catalyzed reaction to oxidatively introduce an acetoxy group onto a variety of aromatic molecules, including hindered and non-activated ones.

"We entered the gold homogeneous catalysis field in 2004, while studying cycloisomerization of enynes and functionalized alkynes (*Chem. Commun.* **2004**, 850)," recalled Dr. Michelet. "In this paper, we describe the selective oxidation of non-activated, hindered aromatic rings, which represents a highly interesting and challenging organic transformation too. Considering the seminal contributions on gold-catalyzed C–H activation reactions, including the work of He on amination (*J. Am. Chem. Soc.* **2007**, *129*, 12058) and of Nevado, Tse and co-workers on C–C coupling reactions (*J. Am. Chem. Soc.* **2010**, *132*, 1512 and references therein), the main issue of our work was to drive the reaction towards acyloxylation versus C–C bond formation," she continued. Dr. Michelet explained that homocoupling reactions of aromatic derivatives were expected to occur in accordance with what is described in contributions from Tse's group (*Chem. Commun.* **2008**, 386; *J. Organomet. Chem.* **2009**, *694*, 524). "We privileged the use of $(PPh_3)AuCl$, as a stable, easy-to-handle gold precursor and optimized the reaction conditions employing di(acetoxy)-iodobenzene (DAIB) as an oxidant for the gold(I) catalyst," said Dr. Michelet. "We were able to demonstrate that this association allows the formation of hindered acetoxylated-functionalized aromatic rings in moderate to good isolated yields, the key parameter allowing the orientation of the selectivity towards acetoxylation *versus* arene homocoupling being the steric hindrance on the aromatic partner."

Dr. Michelet and co-workers further challenged this methodology by investigating the unprecedented acyloxylation reaction of arenes in the presence of the same catalytic system. "Considering that the formation of bis(acyloxy)iodoarenes could be achieved by ligand metathesis between DAIB and carboxylic acids, we anticipated that the replacement of acetic acid by other acids would result in the direct incorporation of the latter in the product," said Dr. Michelet. The acyloxylation reactions were therefore carried out in a carboxylic acid as solvent, and rewardingly proceeded efficiently for a variety of carboxylic acids. "This work nicely complements the Pd-catalyzed arene acyloxylation reaction (*J. Mol. Catal. A: Chem.* **1996**, *108*, 35; *Chem. Rev.* **2010**, *110*, 1147; *Chem. Eur. J.* **2011**, *17*, 2353 and references therein; *Org. Lett.* **2005**, *7*, 4149), which is not operating on hindered substrates and allows the gold-catalyzed unprecedented



R^{1-5} = H, Me, Et, Br, I, CO_2Me
R^6 = alkyl

22 examples
20–83% yield

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acyloxylation reaction of arenes implying various carboxylic acids," added Dr. Michelet. "This methodology will undoubtedly inspire further development, thus opening new perspectives in the selective oxidation of non-activated aromatic rings for the synthesis of aryl esters and phenols," she concluded.

Matteo Zanda

About the authors

A. Pradal

Alexandre Pradal was born in 1987 in Maisons-Laffitte (France). He received his undergraduate education at the Ecole Supérieure de Chimie Organique et Minérale (ESCOM) in Cergy Pontoise (France). He obtained a Master's degree from the Université de Picardie Jules Verne (UPJV, Amiens, France) in 2008. In 2009, he joined the group of Dr. V. Michelet for PhD studies. His current research concerns electrophilic carbocyclization and asymmetric cycloisomerization reactions of 1,*n*-enynes in the presence of platinum and gold catalysts.

Dr. P. Toullec

Patrick Toullec studied chemistry at the University of Rennes (France) and completed his PhD at the Ecole Polytechnique (Palaiseau, France) under the guidance of Prof. F. Mathey in 2002. After postdoctoral studies with Prof. A. Togni at the ETH Zürich (Switzerland) and Prof. B. Feringa at the University of Groningen (The Netherlands), he joined the group of Prof. J.-P. Genêt and Dr. V. Michelet in 2005 at the Ecole Nationale Supérieure de Chimie de Paris (ChimieParisTech, France) where he holds a position of Maître de Conférences. His research interests include the development of new transition-metal-catalyzed synthetic organic transformations with a specific focus on asymmetric variants.

Dr. V. Michelet

Véronique Michelet completed her graduate studies at the Ecole Nationale Supérieure de Chimie de Paris (ChimieParisTech, France) in 1993 and received her PhD degree in 1996 from the University P. et M. Curie (France) in the group of Professor J.-P. Genêt. After two years of postdoctoral research in the groups of Professors J. D. Winkler (University of Pennsylvania, Philadelphia, USA) and A. G. M. Barrett (Imperial College, London, UK), she was appointed to the ENSCP (ChimieParisTech, France) as Associate Researcher in 1998. In 2003, she obtained her Habilitation and was promoted Director of Research in 2007. She is group leader of the team "Chimie de l'or, Catalyse et Architectures Complexantes". Her research interests combine basic and applied aspects of catalysis for the development of new synthetic methodologies for carbon–carbon and carbon–heteroatom formations. They involve asymmetric catalysis, the development of novel catalytic systems (carbophilic metals: platinum and gold) for atom- and step-economical reactions such as cycloisomerizations of 1,*n*-enynes and metallo-organocatalysis. The synthesis of fluorescent complexing agents is also developed in her group for the detection of polluting metal ions.

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SYNTHESIS/*SYNLETT* Advisory Board Focus: Professor Ulrich Koert (Philipps-Universität Marburg, Germany)

Background and Purpose. ***SYNFORM*** is from time to time portraying **SYNTHESIS/*SYNLETT*** Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this issue, we present Professor Ulrich Koert, Philipps-Universität Marburg (Germany).

BIOGRAPHICAL SKETCH

Prof. U. Koert

Ulrich Koert was born in Hanau (Germany) in 1961. He studied chemistry at the Goethe University in Frankfurt am Main (Germany) where he was awarded his doctoral degree in 1988 with Professor G. Quinkert. After a post-doc with Professor J.-M. Lehn in Strasbourg (France; 1988–1990) he moved to the Philipps-Universität in Marburg (Germany) where he finished his habilitation in 1994. In 1994/1995 he was visiting Associate Professor at the University of Wisconsin at Madison (USA). In 1996 he moved to the Ludwig-Maximilians-Universität in München (Germany) as a C3 Professor for organic chemistry. From October 1996 until September 2001 Professor Koert was C4 Professor for organic and bioorganic chemistry at the Humboldt University in Berlin (Germany). Since October 2001 he is C4 Professor for organic chemistry at the Philipps-Universität Marburg in Germany. His awards include the Dozenten - stipendium of the Fonds der Chemischen Industrie and the Otto-Bayer Award.

INTERVIEW

SYNFORM | *Professor Koert, what are your main current research interests?*

U. Koert | One topic is the stereoselective synthesis of natural products and the development of efficient synthetic methods. A second research area is the synthetic modification of membrane-bound ion channels.

SYNFORM | *What is your most important scientific achievement to date and why?*

U. Koert | In total synthesis the next step ahead is usually the most important. Our successful tuning of ion selectivity in the ion-channel area is worth mentioning.

SYNFORM | *Can you mention a recent discovery in the area of organic chemistry, which you consider to be particularly important?*

U. Koert | C–C and C–N/O cross coupling.

SYNFORM | *Do you have hobbies besides chemistry?*

U. Koert | Books, cooking, family, and cross-country skiing.

SYNFORM | *What is your main goal in your scientific career?*

U. Koert | Sapere aude!

Matteo Zanda

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SYNFORM 2012/04 is available from March 20, 2012

In the next issues:

SYNSTORIES

Intermolecular [3+2] Cycloaddition of Cyclopropylamines with Olefins

(Focus on an article from the current literature)

Nickel-Catalyzed C–H/C–O Coupling of Azoles with Phenol Derivatives

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: Recent Developments in the Palladium-Catalyzed Formation of Five- and Six-Membered Fused Heterocycles

(by K. C. Majumdar et al.)

SYNLETT

Account on: Bidentate Lewis Acids as Catalysts for the Activation of 1,2-Diazenes in Organic Synthesis

(by H. A. Wegner, S. N. Kessler)

SYNFACTS

Synfact of the Month in category "Organo- and Biocatalysis": Asymmetric Counteranion-Directed Phase-Transfer Catalysis

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