

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/07

SYNSTORIES ■ ■ ■ ■

■ Extracellular Palladium-Catalyzed Dealkylation of 5-Fluoro-1-propargyl-uracil as a Bioorthogonally Activated Prodrug Approach



■ Nickel-Catalyzed Reductive and Borylative Cleavage of Aromatic Carbon–Nitrogen Bonds in *N*-Aryl Amides and Carbamates

■ Remote Activation of the Nucleophilicity of Isatin

■ Young Career Focus:
Dr. Arturo Orellana
(York University, Canada)

CONTACT +++++

Your opinion about SYNFORM is welcome, please correspond if you like:
marketing@thieme-chemistry.com



Dear Readers,

A few days ago I was updating my CV and I scrolled up the list of publications, back to my first papers in the 90s. Reading titles and authors of those early articles I realized how much my scientific interests have

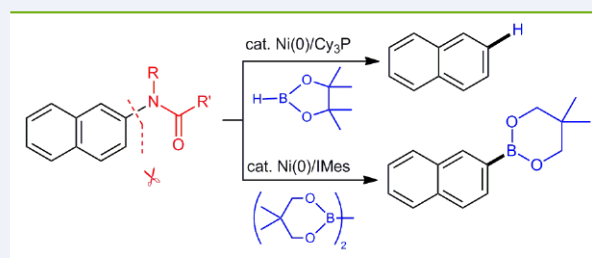
changed throughout more than 20 years of career. I started as a synthetic organic chemist, which I still am of course, with a keen interest in synthetic methodology. I remember the excitement of finding an unexpected reaction outcome or a stereoselective process, the time spent wondering how my substrates would react under different reaction conditions, how avidly I used to check TLCs scrutinizing the formation of new spots, looking forward to quenching the reaction and rushing through a flash chromatography for isolating the new product and finally run down to the NMR! Developing new synthetic methodology and synthesizing new molecules was all I was interested in: I spent all of my time reading organic chemistry journals, lost in chemical structures and amazing new reactions or new uses of old ones. But lots of things have changed and my interests have evolved in line with my career. First and foremost I don't have time for working in the lab anymore, which I am afraid is a necessary evil. Besides that, I am now much more interested in biomedical applications of organic synthesis rather than in the methodology itself. I have the fortune to work in a biomedical research institute, where only very few chemists are present and our role is to use organic chemistry for finding solutions to biomedical scientific problems, spanning from basic biology to applied medicine, from molecular imaging to drug discovery. That's what gives me excitement today, after more than 20 years of career! I am still very proud to be a chemist and I still believe that chemistry is the central science, but today the magic of chemistry for me is when my molecules are successfully used by my colleagues and I spend all of my time designing applications rather than synthetic methodology. We still have to synthesize our compounds, of course, and for that we try to go as straight and efficiently as possible to the target without bothering too much about the methodology aspect. Is this evolution? My answer is a yes, although I believe that there is absolutely nothing wrong with sticking to the same scientific interest and research orientation throughout an entire career, and I know many colleagues who did just that. Perhaps that's just a bit bizarre, taking into account how many stimuli a scientist receives from colleagues, environment and society, not to mention the funding bodies... So how is it possible not to be lured by curiosity to different research topics or areas? That's what happened to me, and also to many of you, I guess. On a slightly different note, I have absolutely no doubts that you will be lured by this new issue of **SYNFORM**, because it's once again packed full of great and exciting chemistry! We start with a new bioorthogonal process (very exciting!!!) developed by A. Unciti-Broceta (Scotland, UK),

IN THIS ISSUE

SYNSTORIES ■ ■ ■ ■

Extracellular Palladium-Catalyzed Dealkylation of 5-Fluoro-1-propargyl-uracil as a Bioorthogonally Activated Prodrug Approach.....A90

Nickel-Catalyzed Reductive and Borylative Cleavage of Aromatic Carbon–Nitrogen Bonds in *N*-Aryl Amides and CarbamatesA93



Remote Activation of the Nucleophilicity of IsatinA96

Young Career Focus: Dr. Arturo Orellana (York University, Canada).....A98

COMING SOONA100

and we continue with a novel method for achieving the cleavage of aromatic C–N bonds reported by N. Chatani (Japan). The third **SYNSTORY** covers a new method for using isatine as N-nucleophile in aza-Michael reactions developed by T. Kanger (Estonia). Finally, the Young Career Focus on A. Orellana (Canada), an up-and-coming young organic chemist interested in total synthesis and new synthetic methodology.

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

CONTACT + + + +
If you have any questions or wish to send feedback, please write to Matteo Zanda at:
synform@outlook.com

Extracellular Palladium-Catalyzed Dealkylation of 5-Fluoro-1-propargyl-uracil as a Bioorthogonally Activated Prodrug Approach

Nat. Commun. **2014**, *5*, 3277

■ Chemotherapy is most effective at killing cells that divide rapidly, which is one of the principal features of cancer cells. However, non-cancerous cells are also heavily affected by the chemotherapeutic treatment. As a result, antineoplastic drugs are limited by lack of selectivity. To mitigate unwanted side effects, many efforts have been made on the design of cancer-specific strategies such as prodrugs, which are inactive precursors of cytotoxic agents that are *biochemically* converted into their active forms in a specific biological setting. As an unprecedented prodrug approach, the Edinburgh Cancer Discovery Unit (University of Edinburgh, Scotland, UK) is investigating the application of solid metals as implantable activating devices to modulate the cytotoxic activity of anti-neoplastic drugs in a spatially controlled manner.

The novel approach, so-called bioorthogonally activated chemotherapy, is based on the use of palladium, a benign metal able to catalyze various chemical reactions in biocompatible environments (*Nat. Chem.* **2011**, *3*, 239; *Synform* **2011**, *06*, A48; *Nat. Protocols* **2012**, *7*, 1207; *Chem. Soc. Rev.* **2013**, *42*, 7943). “While soluble palladium species such as Pd²⁺ complexes exhibit inherent cytotoxic properties, metallic palladium (Pd⁰) is biocompatible (e.g., it is employed in dental restoration) and we have now shown that it is catalytically active both in vitro (cell culture) and in vivo (zebrafish),” said Dr. Unciti-Broceta, who led the research program that resulted in this *Nat. Commun.* article.

As opposed to classical prodrugs, whose activation process relies on metabolic pathways, an efficient palladium-activated prodrug therapy ought to be entirely dependent on the presence of this metal and the prodrug should remain intact in distant tissues and organs. “The principal challenges to overcome were to make the prodrug metabolically stable (= bio-orthogonal) while at the same time sensitive to palladium catalysis,” confirmed Dr. Unciti-Broceta. 5-Fluorouracil (5FU), a potent antimetabolite drug, whose clinical use has been limited by a narrow therapeutic index, was used to develop such a prodrug. According to the authors, 5FU was

modified at its N1 position (i) because of its relatively low pK_a value due to the heterocycle’s lactam/lactim tautomerism, which was expected to promote its properties as a leaving group, and (ii) due to its relevance in the drug’s mode of action (see Figure, A). “We hypothesized that the alkylation of the N1 position of 5FU would both suppress the drug’s cytotoxic properties and make the resulting prodrug become resistant to enzymatic cleavage,” said Dr. Unciti-Broceta.

“We have found that inactive prodrugs can be generated by masking the N1 position of 5FU with allyl, propargyl and benzyl groups. Our results show, however, that only the propargyl derivative displays high sensitivity to palladium in biocompatible conditions and enables the bioorthogonal generation of 5FU by heterogeneous palladium catalysis in cancer cell culture (see Figure, B),” said Jason Weiss, currently a final-year PhD student in the Unciti-Broceta group. The authors noted that the oxidative cleavage of the propargyl group generates 1-hydroxyacetone, a harmless natural compound, as reaction byproduct, making the reaction optimal to activate any kind of prodrug in vivo (not only cytotoxic ones).

“This is the first example showing that the pharmacological activity of a clinically approved antineoplastic drug can be locally activated by means of an internal self-renewable control element rather than an external radiation source (such as in photodynamic therapy),” said Dr. Neil Carragher, a group leader of the Edinburgh Cancer Research UK Centre and expert in phenotypic screening. According to Dr. Carragher, this novel approach would allow for a reduction in adverse side effects of current chemotherapeutic regimes. The proposed strategy would be optimal to treat advanced cancers that cannot be resected by surgery, since it would allow local treatment with increased dosing. Once the tumor has shrunk to a resectable size, the surgeon could remove the tumor along with the palladium implants. Dr. Unciti-Broceta concluded: “The next steps of the project are to validate this approach in a mouse cancer model and to expand the chemistry to other pharmaceuticals.” ■

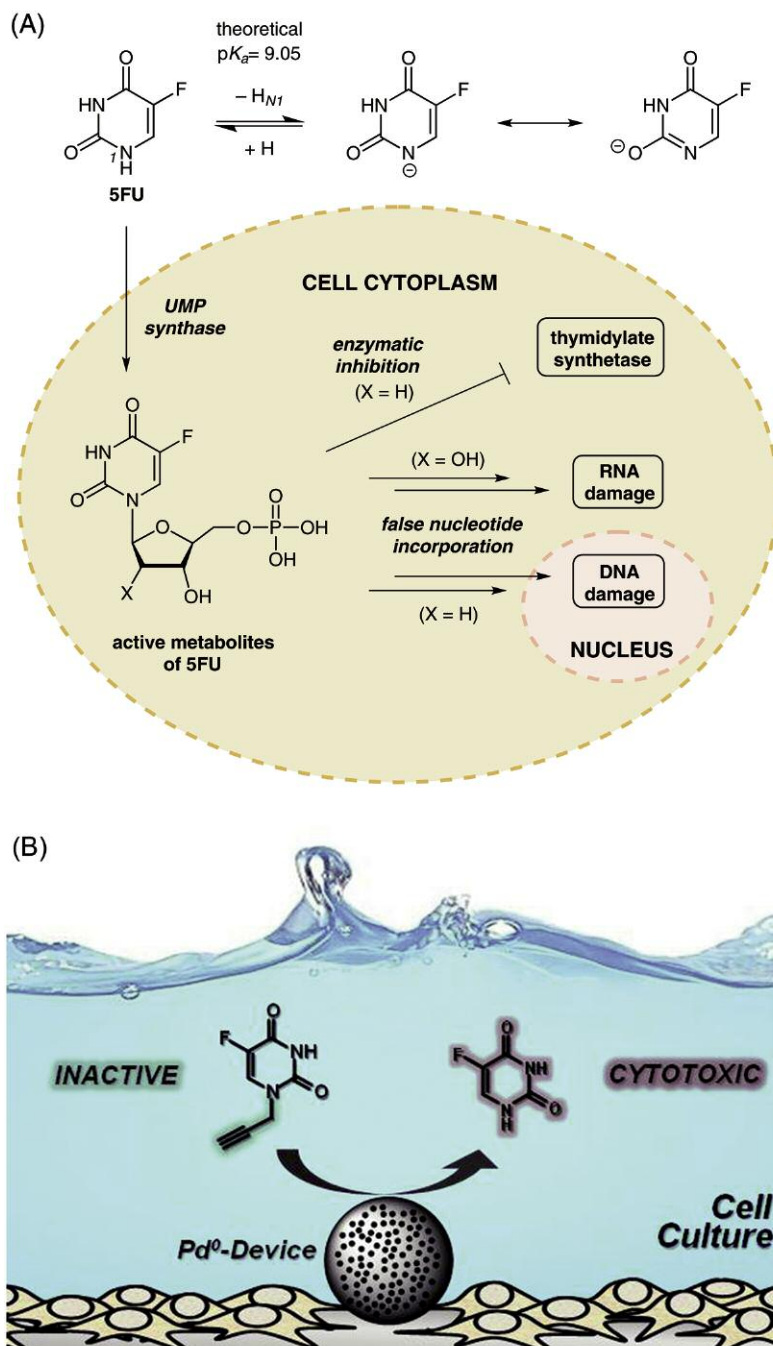


Figure (A) 5FU and its conjugate bases (top) and intracellular biofunctionalization of 5FU to generate cytotoxic metabolites (bottom).

(B) In situ transformation of an inert drug precursor into a bioactive material (5FU) by the mediation of an extracellular biocompatible catalyst in cell culture.

Matteo Zanda

About the authors



From left to right: Dr. A. Unciti-Broceta, J. Weiss, Dr. N. Carragher (other authors: J. Dawson, K. Macleod, C. Fraser, L. Patton, M. Bradley)

Jason Weiss was born in Ottawa (Canada) in 1985. He completed his Honors Bachelor of Science degree in Biotechnology at Carleton University (Ottawa). Afterwards, he worked for Nordion in the radiopharmaceutical production division as a drug production technician synthesizing medical isotopes. After two years, he went back to school to the University of Edinburgh (UK) where he obtained his MSc in Biomedical Sciences. He is currently pursuing his PhD in Molecular Medicine (Edinburgh Cancer Research UK Centre, University of Edinburgh) under the supervision of Asier Unciti-Broceta working on the development of antineoplastic prodrugs sensitive to palladium as a novel spatially controlled anticancer chemotherapy.

Neil Carragher was born in Uphall, Scotland (UK) in 1970. He studied 'Cell and Immunobiology' at the University of Aberdeen (UK) prior to accepting a position at the Yamanouchi Research Institute, Oxford (UK) where he obtained his PhD in 1996. He held consecutive postdoctoral positions within the Department of Pathology, University of Washington, Seattle (USA) and at the

Beatson Institute for Cancer Research, Glasgow (UK). In 2004 Neil returned to the pharmaceutical industry as Principal Scientist with the Advanced Science and Technology Laboratory at AstraZeneca where he pioneered early multiparametric high-content phenotypic screening approaches. In 2010 he returned to academia and took up the post of Principal Investigator at the University of Edinburgh where he leads a research group and is currently co-director of the Edinburgh Cancer Discovery Unit. Current research interests include advancing high-content analysis, phenotypic screening, reverse-phase protein array technology and cancer drug discovery.

Asier Unciti-Broceta was born in La Linea (Spain) in 1976. After studying 'Pharmaceutical Sciences' at the University of Granada (Spain), he completed his PhD in Medicinal Chemistry under the supervision of Professor A. Espinosa and sponsored by the Ramón Areces Foundation in 2004. He then moved to the University of Edinburgh (UK) to join the group of Professor M. Bradley (School of Chemistry) as a postdoctoral fellow. Following a Scottish Enterprise Proof of Concept Award in 2008, which resulted in the foundation of the spin-out company Deliverics Ltd, in 2010 he became the first chemistry group leader of the Edinburgh Cancer Research UK Centre (MRC Institute of Genetics and Molecular Medicine, University of Edinburgh). His research interests lie on the interface of medicinal chemistry and chemical biology, with particular emphasis on the design and development of innovative anticancer prodrugs and kinase inhibitors. Among his awards, highlights include being the recipient of the Nexxus Young Life Scientist Award of 2010 and the RSC Young Industrialist Award of 2012. In 2013 he was appointed co-director of the Edinburgh Cancer Discovery Unit and member of the RSE Young Academy of Scotland.

Nickel-Catalyzed Reductive and Borylative Cleavage of Aromatic Carbon–Nitrogen Bonds in *N*-Aryl Amides and Carbamates

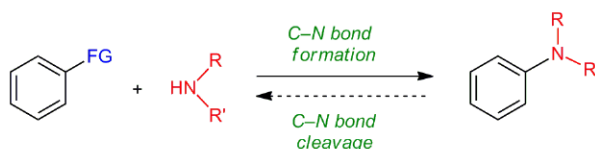
J. Am. Chem. Soc. **2014**, *136*, 5587–5590

■ Although substantial progress has been made in the development of catalytic C(aryl)–N bond-formation reactions for the construction of aryl amine derivatives, reports pertaining to the reverse process, namely the catalytic cleavage of C(aryl)–N bonds, remain scarce. C(aryl)–N bond cleavage of aniline derivatives normally requires the use of highly reactive cationic intermediates, such as diazonium and ammonium salts, in which the elimination of electronically neutral dinitrogen and amine moieties facilitates the C–N bond-cleavage process. A notable exception to this is the ruthenium-catalyzed C–N bond activation of electronically neutral aniline derivatives, although applicable substrates are limited to compounds that contain ortho-directing groups. Recently, the group of Professor Naoto Chatani and Associate Professor Mamoru Tobisu at Osaka University (Japan) reported on a

catalytic method for cleavage of C(aryl)–N bonds of electronically neutral, simple aryl amine derivatives, including amides and carbamates. The process involves the nickel-catalyzed conversion of inert C(aryl)–N bonds into C(aryl)–H and C(aryl)–B bonds.

Professor Chatani said: “Our research group has focused on the development of new catalytic methods that can be used for the direct transformation of strong σ -bonds, including C–H, C–C and C–O bonds. In this context, we previously reported a series of nickel-catalyzed cross-coupling reactions using anisole derivatives as aryl halide surrogates (for a review, see: *Top. Organomet. Chem.* **2013**, *44*, 35). We wondered whether the low-valent nickel species could be used for the transformation of even stronger σ -bonds.” After selecting C(aryl)–N bonds as the target for cleavage by nickel

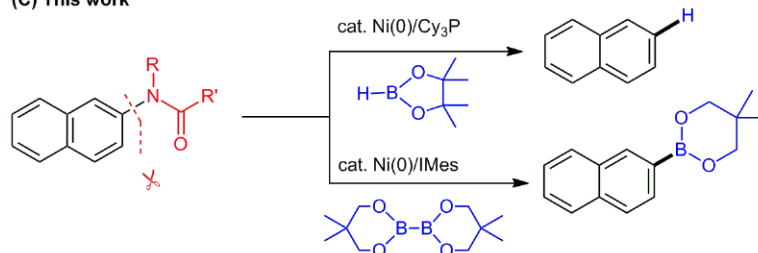
(A) C–N bond cleavage: A challenging task

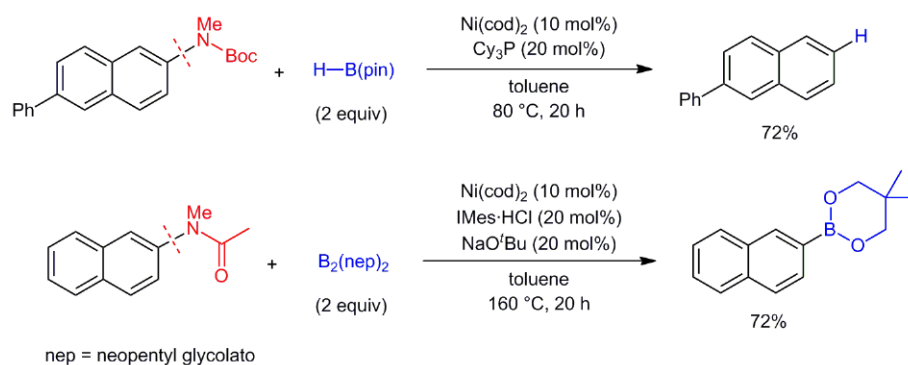


(B) Chatani's previous work: C–OMe activation using Ni(0)



(C) This work

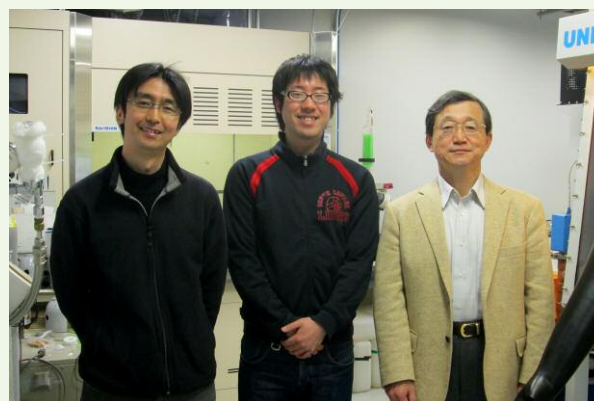




catalysis, the Osaka-based researchers examined a series of reagents, ligands and reaction conditions. “The first promising result was obtained just after Keisuke Nakamura joined the group as an undergraduate researcher,” revealed Associate Professor Tobisu. “He examined the nickel-catalyzed reaction of 1-(naphthalen-2-yl)pyrrolidin-2-one with hydrosilane and found that naphthalene, a C–N bond-cleavage product, was formed in 7% yield. He dedicated his master’s degree studies to further developing this intriguing C–N bond-cleavage reaction.” After considerable study, the reductive cleavage of C–N bonds was revealed to proceed in synthetically useful yield when hydroborane was used as the reducing agent. Professor Chatani concluded: “What excited us even more was that substitution of an amide group by a boryl group was also possible when a diboron reagent was used. Although the mechanism responsible for this new C–N activation process is unclear at present, we conclude that the C(aryl)–N bond cleavage reaction can now be considered to be a viable methodology for enabling a nonconventional synthetic strategy.” ■

Matteo Zanda

About the authors



From left to right: Prof. M. Tobisu, K. Nakamura, Prof. N. Chatani

Mamoru Tobisu received his PhD from Osaka University (Japan) in 2001 under the direction of Professor Shinji Murai. During the course of his PhD studies, he also worked with Professor Gregory C. Fu at the Massachusetts Institute of Technology (USA) as a visiting scientist (1999). Following a period of employment with the Takeda Pharmaceutical Company, Japan (2001–2005), he began his academic career at Osaka University in 2005 as an Assistant Professor. He then moved to the Frontier Research Base for Global Young Researchers at Osaka University as a lecturer in 2006 and was appointed as an Associate Professor at the Center for Atomic and Molecular Technologies at Osaka University in 2011.

>>

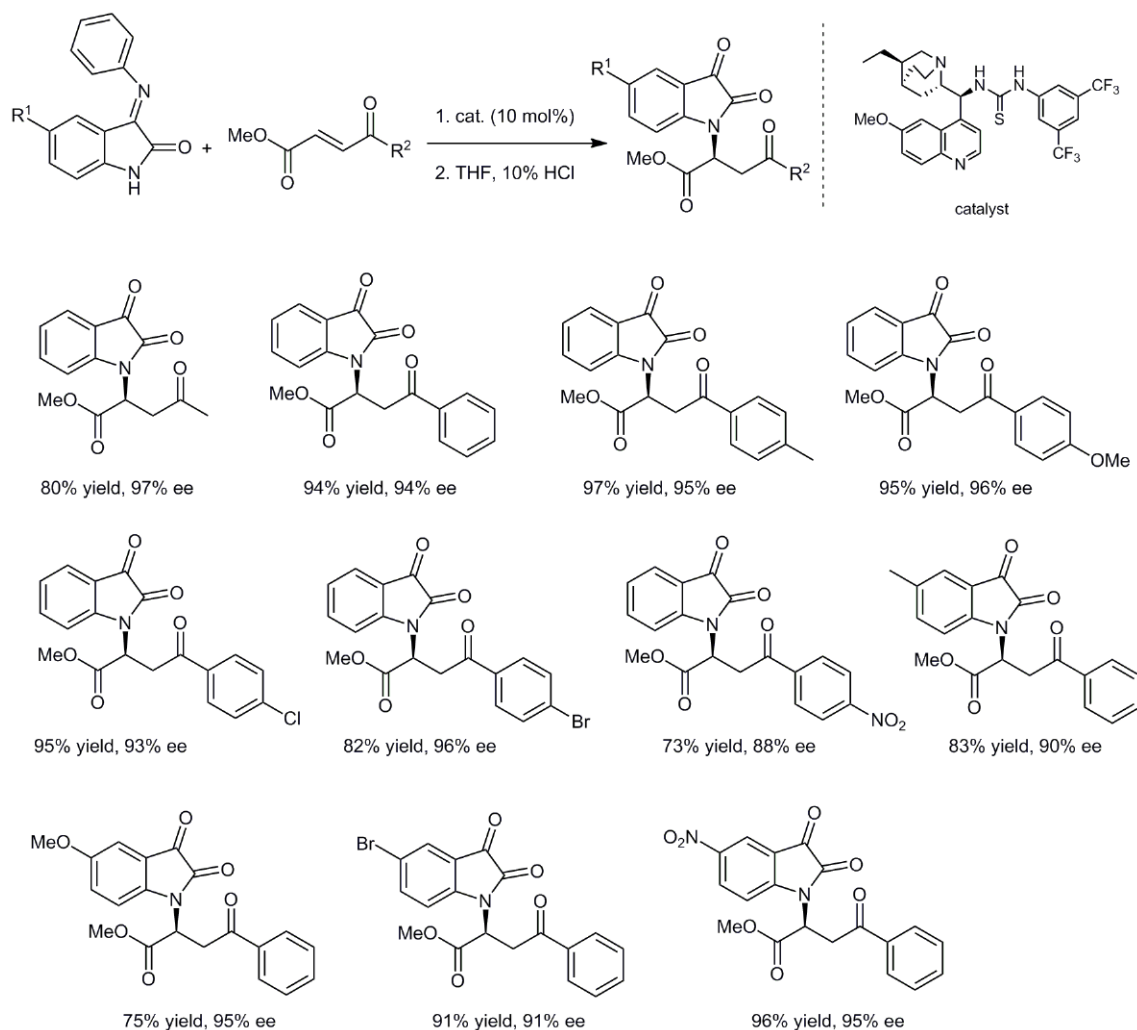
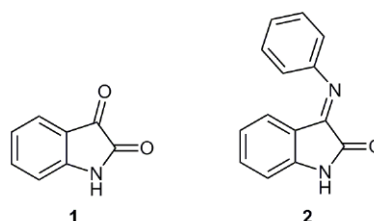
Keisuke Nakamura graduated from Osaka University (Japan) in 2011 and obtained his MSc from the same university in 2013. He is currently pursuing his PhD under the supervision of Professors Chatani and Tobisu at Osaka University.

Naoto Chatani received his PhD in 1984 under the guidance of Professors Noboru Sonoda and Shinji Murai. In 1984 he joined the Institute of Scientific and Industrial Research at Osaka University (Japan) and was involved in research in the laboratory of Professor Terukiyo Hanafusa. After postdoctoral studies (1988–1989 under Professor Scott E. Denmark at the University of Illinois, Urbana-Champaign, USA), he moved back to Osaka University and was promoted to Associate Professor in 1992 and to Full Professor in 2003.

Remote Activation of the Nucleophilicity of Isatin

Org. Lett. **2014**, *16*, 1740–1743

■ Isatin (**1**) is a versatile compound whose derivatives have a part to play in different branches of chemistry, varying from dyes to efficient antibacterial agents. Its chemistry has been studied thoroughly and electrophilic substitution in an aromatic ring, dipolar cycloaddition and especially the nucleophilic addition to the C3 carbonyl function of isatin are well-described reactions (for references, see the *Org. Lett.* article).



Scheme The new aza-Michael reaction and its scope

The multifunctionality of isatin makes it an attractive target for various cascade reactions with other multifunctional compounds, a topic that the group of Professor Tõnis Kanger at the Tallinn University of Technology (Estonia) has been working on for some time. “Our first idea was to contribute to the organocatalytic asymmetric synthesis of N-heterocyclic spiro-oxindoles,” said Professor Kanger. “We planned to derivatize isatin to imine **2** and perform a Mannich–aza-Michael cascade reaction using enolizable 1,4-unsaturated dicarbonyl compounds. However, no one could predict that instead of this contribution we would get a new topic to study and that a single HPLC analysis done ‘out of interest’ would, over time, lead to a new method for using isatin as a nucleophile in aza-Michael reactions.” This new methodology represents an efficient and straightforward approach to the synthesis of highly enantiomerically enriched N-substituted isatins and also opens the possibility of achieving new cascade reactions. According to Professor Kanger, in fact, this is the first example of remote activation of nucleophilicity in an organocatalytic reaction.

Professor Kanger remarked: “While isatin itself efficiently reacts in this aza-Michael reaction, its simple derivatization is the key step for achieving high enantioselectivity and at the same time blocking possible side reactions.” He concluded: “Moreover, additional studies showed that you can’t simply derivatize isatin with just any primary amine for this positive effect to take place: aniline provides the best combination of high yields and excellent enantiocontrol. We are still working on understanding the mechanism by which the imine aromatic ring makes the reaction efficient by combining experiments with NMR studies and theoretical calculations and expanding the range of suitable Michael acceptors.” ■

Matteo Zanda

About the authors



Prof. T. Kanger

Tõnis Kanger received his BSc in 1982 from Tartu University (Estonia) and PhD in 1990 from the Estonian Academy of Sciences. After postdoctoral studies at the Pierre et Marie Curie University (France), under the supervision of Professor Alexandre Alexakis, he returned to Estonia, where he is currently professor at Tallinn University of Technology. His research interests are focused on methodology of organic synthesis, chemical asymmetric synthesis and organocatalysis.



S. Žari

Sergei Žari was born in Tallinn (Estonia) in 1987. He started his studies at Tallinn University of Technology in 2005 and joined Professor Tõnis Kanger’s group during his first year of bachelor’s studies. He received his BSc in chemistry and biotechnology in 2009 followed by an MSc in 2011. He is currently a third-year PhD student under the supervision of Professor Tõnis Kanger. His main research interest is the application of asymmetric organocatalysis for the synthesis of biologically active chiral compounds.

Young Career Focus: Dr. Arturo Orellana (York University, Canada)

■ **Background and Purpose.** *SYNFORM* will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This *SYNSTORY* with a Young Career Focus presents Dr. Arturo Orellana, York University, Canada.

BIOGRAPHICAL SKETCH



Dr. A. Orellana

Arturo (Art) Orellana was born in El Salvador and emigrated to Ottawa (Canada) in 1986. He obtained a B.Sc. (Honours) degree from the University of Ottawa in 1997, where he conducted undergraduate research with Professor Alex Fallis. He carried out graduate studies at the University of British Columbia (Canada) with the late Professor Edward Piers on the synthesis of terpene natural products.

He was a Chateaubriand post-doctoral fellow under Professor Andrew E. Greene at the Université Joseph Fourier in Grenoble (France), and also conducted post-doctoral research with Professor Tomislav Rovis at Colorado State University (USA). He began his independent career at York University (Canada) in 2007. In 2012, he received the Boehringer-Ingelheim Young Investigator Award for Organic Chemistry in Canada.

INTERVIEW

SYNFORM | *What is the focus of your current research activity?*

Dr. Arturo Orellana | For the last few years we have been exploring the palladium-catalyzed chemistry of tertiary alcohols. We have focused most of our work on strained tertiary alcohols because they display very unique reactivity. Many of these substrates in fact undergo base- or acid-catalyzed reactions leading to ring-opened products; using palladium catalysis we have been able to control their reactivity such that they can participate in carbon-carbon bond-forming reactions.

SYNFORM | *When did you get interested in synthesis?*

Dr. Arturo Orellana | I was first exposed to organic chemistry in a large undergraduate class taught by Professor Tony Durst at the University of Ottawa. This is the kind of organic chemistry class that all science majors take and that is populated by many students with medical school ambitions. Before actually sitting in class, I was a bit intimidated by the subject's reputation, but Professor Durst did an amazing job at teaching this course and it all made perfect sense, it was like a new language with its own logical rules. A year or so later I became aware of natural product synthesis as a discipline. The idea of building complex molecular structures really appealed to me and is what I pursued with Professor Alex Fallis as an undergraduate student, and with the late Professor Ed Piers (at the University of British Columbia) for graduate school.

SYNFORM | *What do you think about the modern role and prospects of organic synthesis?*

Dr. Arturo Orellana | I think organic synthesis is as important as ever, there will always be a need to build molecular structures on demand. That is not to say that the same kind of research that was being carried out 10 or 20 years ago is held in the same high regard now as it was then.

Specifically, total synthesis as an end in itself, using known technology, is not going to add very much to the field. That said, there is some excellent research in synthesis being done today that is extremely impressive and inspiring. Generally, this research tackles the challenges of molecular complexity and synthetic efficiency (step and redox economy, etc.) head on, and will likely benefit the field the most. I expect that there is still a lot of work to be done before we can confidently say that we can make any molecule efficiently and on scale.

SYNFORM | Your research group is active in the areas of total synthesis and development of new synthetic methodology. Could you tell us more about your research and its aims?

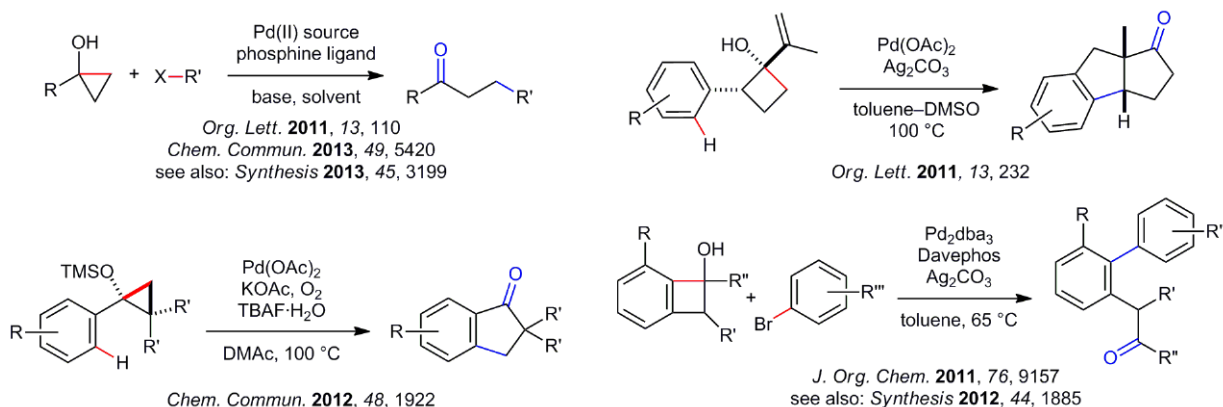
Dr. Arturo Orellana | We have been using tertiary alcohols in palladium-catalyzed reactions, where they can be used as surrogates for oxidative addition partners or organometallic reagents. The attractive aspect of this kind of cross-coupling reaction is that a new functional group (a ketone) is revealed as a new carbon–carbon bond is formed (see Scheme). This is in contrast to most cross-coupling reactions, which generally result in a net reduction of functional group content in the product. Obviously, this has important synthetic implications. In some instances, the new ketone can parti-

cipate in downstream reactions in the same pot, leading to some interesting and efficient synthetic strategies. There are a number of researchers working on very similar themes with related substrate classes, so we have been careful in terms of substrate choice and focused mostly on cyclopropanols and benzocyclobutenols.

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

Dr. Arturo Orellana | I think we have made some valuable contributions to synthetic methodology that could prove very useful in the right context, but I always try to be careful not to overstate their importance. That said, I think that extending the cyclopropanol-homoenolate idea (first developed by Kuwajima) to a broader scope will prove valuable (Professor Patrick Walsh has also made important recent contributions in this area). We were also the first to control the ring-opening reactions of benzocyclobutenols, and since our first report other researchers have begun to explore this substrate class as well. ■

Matteo Zanda



COMING SOON ►► COMING SOON ►►

SYNFORM 2014/08

is available from July 18, 2014

In the next issues:

SYNSTORIES ■ ■ ■ ■

■ SnAP Reagents for the One-Step Synthesis of Medium-Ring Saturated N-Heterocycles from Aldehydes

(Focus on an article from the current literature)

■ Amide Synthesis by Nucleophilic Attack of Vinyl Azides

(Focus on an article from the current literature)■ A Reagent-Controlled S_N2 Glycosylation for the Direct Synthesis of β-Linked 2-Deoxy-Sugars*(Focus on an article from the current literature)*

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Lewis Base Catalysis of Three n-p* Mediated Reactions with N-Heterocyclic Carbenes (NHCs), Isothioureas, Bicyclic Tertiary Amines, and Electron-Rich Pyridyls

(by D. W. Lupton)

SYNLETT

Account on: [2,8-Diheterobicyclo\[3.2.1\]octane Ring Systems: Natural Occurrence, Synthesis and Properties](#)

(by M. F. Flores, D. Díez)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Total Synthesis of \(-\)-Filiformin](#)

CONTACT + + + +

Matteo Zanda,
 NRP Chair in Medical Technologies
 Institute of Medical Sciences
 University of Aberdeen
 Foresterhill, Aberdeen, AB25 2ZD, UK
 and
 C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,
 Via Mancinelli, 7, 20131 Milano, Italy,
 e-mail: synform@outlook.com, fax: +39 02 23993080

Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and

C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
 Via Mancinelli, 7, 20131 Milano, Italy
 Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office

- Managing Editor: Susanne Haak,
susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editor: Selena Boothroyd,
selena.boothroyd@thieme.de
- Scientific Editor: Stefanie Baumann,
stefanie.baumann@thieme.de, phone: +49 711 8931 776
- Assistant Scientific Editor: Michael Binanzer,
michael.binanzer@thieme.de, phone: +49 711 8931 768
- Assistant Scientific Editor: Christiane Kemper,
christiane.kemper@thieme.de, phone: +49 711 8931 785
- Senior Production Editor: Thomas Loop,
thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Helene Ott,
helene.ott@thieme.de, phone: +49 711 8931 929
- Production Editor: Thorsten Schön,
thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller,
sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing Manager: Julia Stötzner,
julia.stoetznern@thieme.de, phone: +49 711 8931 771
- Postal Address: SYNTHESIS/SYNLETT/SYNFACTS, Editorial Office,
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: www.thieme-chemistry.com

Publication Information

SYNFORM will be published 12 times in 2014 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to SYNTHESIS, SYNLETT and SYNFACTS

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

To order: customerservice@thieme.com or use the Web site facilities at www.thieme-chemistry.com, phone: +1 212 760 0888

Order toll-free within the USA: +1 800 782 3488

Fax: +1 212 947 1112

Periodicals postage paid at Hanover, PA 17331.

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.

To order: customerservice@thieme.de or use the Web site facilities at www.thieme-chemistry.com.

Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access

The online versions of SYNFORM as well SYNTHESIS, SYNLETT and SYNFACTS are available through Thieme-connect (www.thieme-connect.com/products/ejournals) where you may also register for free trial accounts. For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695

Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407

India: eproducts@thieme.in, phone +91 120 45 56 600

Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to SYNTHESIS and SYNLETT

Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com. Use of the Word template helps to speed up the refereeing and production process.

Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.