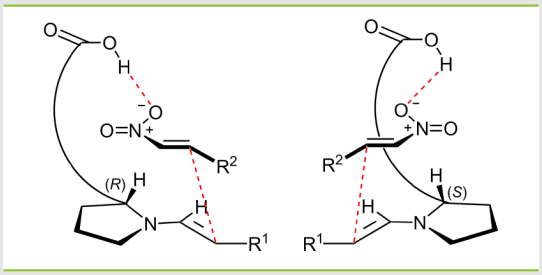
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/01

SYNSTORIES



CONTACT

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

Thieme Chemistry

Dear readers,

The "2nd EuCheMS Chemistry Congress" was held in Turin (Italy) from September 16–20, 2008. About 2100 attendees (in line with the 1st EuCheMS held in Budapest, Hungary, in 2006), including four Nobel Prize awardees, seven plenary lectures, a number of "key note" and "invited lectures", 270 oral communications and 1250 poster communications, distributed over 25 scientific sessions are the main numbers of this conference. The congress was flanked by the initiative "Chemistry Meets the Public", with many authoritative speakers, who helped informing young people and the general public about the importance of chemistry in the modern world. An exposition featuring about 40 exhibitors was also available. My personal feeling is that the EuCheMS is still far from reaching the quality and quantity of the ACS Conferences, but work is in progress and the perspectives are rather promising. This issue of ***SYNFORM*** features two ***SYNSTORIES*** reporting on communications presented at the 2nd EuCheMS. The 3rd ***SYNSTORY*** is dedicated to an important work published by the group of Professor J. Barluenga (Spain), dealing with the biocompatible modification of unprotected peptides in water. The issue is completed by a brief report on a recent symposium on fluorinated peptides that was held in Tokyo (Japan).

Enjoy your reading!!!

Matteo Zanda

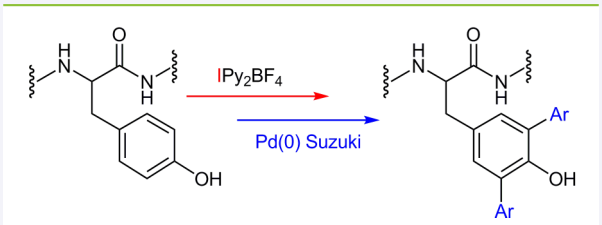
Editor of ***SYNFORM***

CONTACT

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

IN THIS ISSUE

SYNSTORIES



SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559

Synthesis of New Branched Sugars as Precursors for Labeling Proteins or Peptides Using Positron Emission Tomography (PET)

Selected Presentation from the 2nd EuCheMS Chemistry Congress, Turin (Italy), *September 16–20*, **2008**

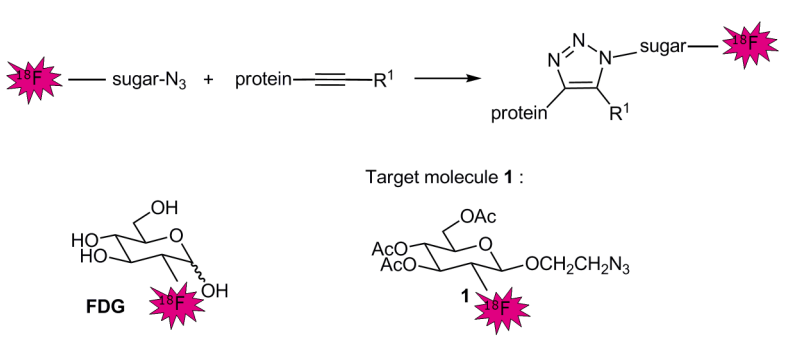
Positron emission tomography (PET) is a medical imaging technique for investigating physiological parameters, such as blood-flow studies, glucose metabolism, receptors properties, or drug distribution, in living human and animal bodies (*Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226). PET imaging involves different steps, among which is the chemical synthesis of an appropriate radiotracer. This radiotracer is a significant molecule, for example, a ligand bearing a short-lived radioisotope, like ^{18}F or ^{11}C, produced by a biomedical cyclotron. After its intravenous injection, the radiotracer fixes onto tissues, and imaging with a PET camera allows for localization of the radiotracer, and this in turn can be used for a medical diagnosis. 2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is commonly used as a radiotracer to follow glucose metabolism and hence to detect tumor cells, which have a strongly enhanced metabolism. The chemistry of this radiotracer is well developed and its use has been implemented in hospitals.

The design and synthesis of suitable radiotracers are key issues in the development of PET imaging; thus, specific radiotracers are actively sought and labeled peptides or proteins are regarded as useful tracers for the diagnosis of many diseases. At the 2nd EuCheMS conference, Christine Vala, a third-year PhD student from the University of Nancy (France), presented research results developed under the supervision of Dr. Yves Chapleur, head of the "Groupe S.U.C.R.E.S." research team, and Dr. Françoise Chretien in Nancy, and in collaboration with a team from the University of Liège (Belgium), formed by Dr. André Luxen, head of the "Centre de Recherche du Cyclotron", the radiochemists Dr. Christian Lemaire, Dr. David Thonon, and the radiopharmacist Joël Aerts, who contributed to the development of the labeling steps.

"The aim of this work was to explore new routes for labeling peptides and proteins with a fast and reliable method," explained Christine Vala. "We focused on the ligation of a labeled sugar like **1** with a derivatized peptide or protein. Such a ligation must be carried out in a short period of time, usually less than two hours, which is the half-life of ^{18}F."

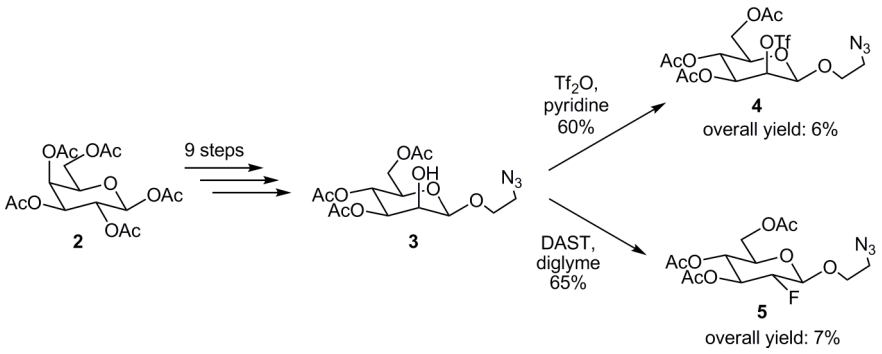
'Click chemistry' based on the Huisgen cycloaddition seemed an appropriate tool to reach this goal. "Our work started with the synthesis of an appropriate 2-*O*-triflate mannose derivative **4** equipped with a suitable arm bearing the required azido group," confirmed Ms. Vala. "Previous results from our group showed that the anomeric position was the most suitable one for the introduction of this azido arm." The synthesis of the β-anomer was achieved in nine steps from D-galactose (*J. Org. Chem.* **2007**, *72*, 3694). The key compound **3** was used to prepare the reference compound 2-deoxy-2-[^{19}F]fluoro-glucose derivative **5** using DAST as the fluorinating reagent.

In a preliminary radiochemical experiment, the introduction of the ^{18}F atom in position 2 of the sugar was carried out using the procedure routinely used for FDG synthesis. Unfortunately, under these conditions, labeling was unsuccessful. Nevertheless, the use of a new method for the preparation of reactive [^{18}F]fluoride afforded compound **1** with a significant 35% radiochemical yield (see S. Voccia et al. "Method for the preparation of reactive

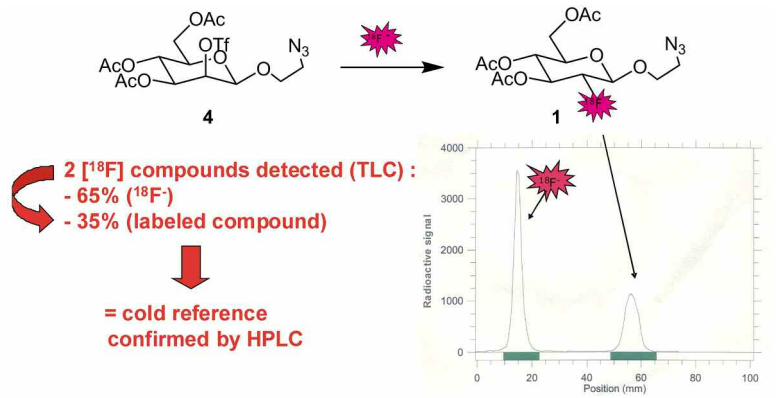


Application of 'click chemistry' in the synthesis of ^{18}F-labeled sugar derivatives

SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559



Synthesis of the key azido sugars



Radiosynthesis of ^{18}F-labeled azido sugars

[^{18}]fluoride" WO 2008128306, 20080422, **2008**). According to HPLC and TLC analyses, compound **1** was identical to reference compound **5**.

"The first experiments we performed in the click chemistry of sugar **5** with alkynylated amino acid (phenylalanine, tyrosine and cysteine) and gave the desired products in good yield within a few minutes," said Ms. Vala. "This can be considered as a significant advance in this field because it opens the way to the labeling of any molecule equipped with an acetylenic function. Moreover, labeling with ^{18}F does not require optimization since it is based on a simplified FDG synthetic process and this can be performed using already existing robots."

"Our current investigations," concluded Ms. Vala, "are directed toward the final ligation of labeled sugar **1** with model peptides and to the extension of this synthetic sequence to biologically significant peptides."

C. Vala

Matteo Zanda

SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559

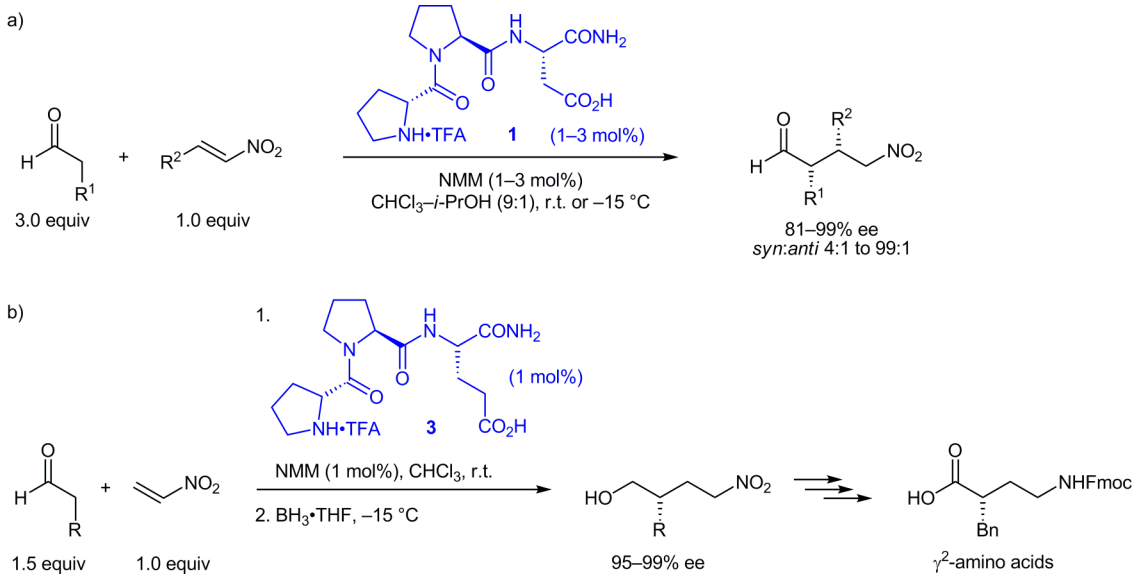
Peptides as Asymmetric Catalysts

Selected Presentation from the 2nd EuCheMS Chemistry Congress, Turin (Italy), *September 16–20*, **2008**

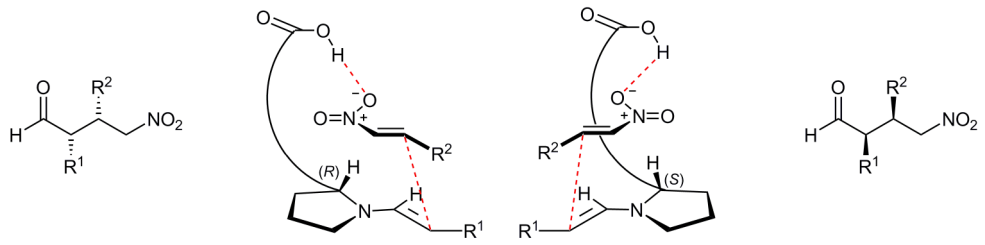
The conjugate addition reaction of aldehydes to nitroolefins has been a focus of research in recent years since it provides γ-nitroaldehydes as versatile building blocks to a plethora of other compound classes. The use of organocatalysts represents an efficient and straightforward route to perform this important process. Among the different types of organocatalysts, peptides are an attractive yet scarcely explored tool. "'It is impossible that short-chain peptides can function as catalysts' was typically heard in the last century from scientists reflecting on the possibility of applying peptides as catalysts," said Professor Helma Wennemers from the Department of Chemistry, University of Basel (Switzerland). This is not surprising since the flexibility of short-chain peptides is typically high. Thus, predicting the conformation of a peptide, and even more so its catalytic activity, is a significant challenge. Recent results from the group of Professor Wennemers, communicated at the EuCheMS congress, demonstrated that tripeptides such as H-Pro-Pro-Asp-NH_2 (**1**), H-D-Pro-Pro-Asp-NH_2 (**2**) and H-D-Pro-Pro-Glu-NH_2 (**3**) are highly effective asymmetric catalysts for aldol reactions and conjugate addition reactions of aldehydes to nitroolefins, respectively. Key to the discovery of the initial lead peptide H-Pro-Pro-Asp-NH_2 (**1**) was the use of the smart combinatorial screening technique "catalyst substrate co-immobilization" (see: *Angew. Chem. Int. Ed.* **2003**, *42*, 1722). Only small amounts of the peptide (1 mol%) are necessary to catalyze aldol reactions with good to excellent yields and stereoselectivities (see: *Org. Lett.* **2005**, *7*, 1101; *Adv. Synth. Catal.* **2008**, *350*, 1046; *Tetrahedron* **2007**, *63*, 8420; *Biopolymers (Pept. Sci.)* **2006**, *84*, 105). Conformational analysis studies then led to the development of H-D-Pro-Pro-Asp-NH_2 (**2**) as an excellent asymmetric catalyst for conjugate addition reactions of aldehydes to nitroolefins.

"The peptidic catalyst H-D-Pro-Pro-Asp-NH_2 (**2**) provided solutions to challenges encountered in this reaction," explained Professor Wennemers (see: *Angew. Chem. Int. Ed.* **2008**, *47*, 1871; *J. Am. Chem. Soc.* **2008**, *130*, 5610). "First of all, catalyst loadings of as low as 1 mol% suffice for effective catalysis. Secondly, only a small excess of the aldehyde (1.5–3.0 equiv) is necessary for effective catalysis. And last but not least, a broad substrate scope including functionalized aldehydes, aliphatic nitroolefins and nitroethylene is tolerated, and products are obtained in excellent yields and stereoselectivities."

Even the simplest of all nitroolefins, nitroethylene, known for its high tendency to polymerize, reacts readily with aldehydes in the presence of the peptidic catalysts. This reaction provides monosubstituted γ-nitroaldehydes that can be readily converted into the corresponding γ-amino acids. "γ-Amino acids are useful building blocks for the development of medi-



SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559



H-D-Pro-Pro-Asp-NH_2 (**2**) as catalyst

H-Pro-Pro-Asp-NH_2 (**1**) as catalyst

cinally relevant compounds and in foldamer research and have previously only been accessible using chiral auxiliaries," said Professor Wennemers. "Since a wide range of aldehydes react with nitroethylene, many different monosubstituted γ-amino acids are available using this protocol."

In a comment to this work, Professor Karl Gademann from the EPF Lausanne (Switzerland), who prepared monosubstituted γ-amino acids during his PhD thesis with Professor Dieter Seebach, said: "When I think about how much hard work went into the synthesis of these γ-amino acids, the peptidic catalyst provides a very elegant solution to facilitate their synthesis."

Organocatalysis is a highly competitive research field. The group of Professor Samuel Gellman (University of Madison, Wisconsin, USA) also worked on the idea of using conjugate addition reactions of aldehydes to nitroethylene to access monosubstituted γ-amino acids efficiently. The Gellman group took advantage of a prolinol derivative in combination with stoichiometric amounts of an acid cocatalyst to achieve this goal. "After the initial mutual shock when we found out about our common research interests, Sam and I were pleased that our research was published back to back," said Professor Wennemers (see: *J. Am. Chem. Soc.* **2008**, *130*, 5608 and *J. Am. Chem. Soc.* **2008**, *130*, 5610).

The peptidic catalysts are easy to use since no additives such as additional acids are necessary. "For practical reasons we typically use the TFA salts of the catalysts and add the equivalent amount of N-methylmorpholine to liberate the secondary amine," said Professor Wennemers. "However, the desalted peptide (the 'inner salt') has the same catalytic efficiency in the conjugate addition reactions. Another advantage of short-chain peptidic catalysts is their facile synthesis. A tripeptide can be prepared on a multigram scale within one day!"

An additional benefit of the peptidic catalysts is the facile tunability of their stereoselectivities; for example, the diastereomeric catalysts H-Pro-Pro-Asp-NH_2 (**1**) and H-D-Pro-Pro-Asp-NH_2 (**2**) exhibit opposite enantioselectivities. "Based on molecular modeling studies, this can be attributed to the fact that both peptides adopt turn-like conformations that are very similar apart from their N-terminal proline residues which point in opposite directions with respect to the turn," said Professor Wennemers. "Further conformational analyses suggest that the conformation of the peptides is not entirely rigid but allows for conformational freedom. It is intriguing to speculate that the 'right degree of flexibility' is the key to the effectiveness of the peptides as asymmetric catalysts."

Matteo Zanda

About the authors

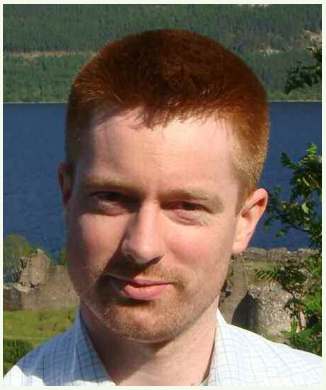
Helma Wennemers studied chemistry at the Johann Wolfgang Goethe Universität in Frankfurt (Germany) and obtained her Ph.D. from Columbia University (New York, USA) under the direction of Professor W. Clark Still in 1996. Following postdoctoral studies at Nagoya University (Japan) with Professor Hisashi Yamamoto, she moved to the University of Basel where she is currently Associate Professor of organic chemistry. She was awarded Kekulé and Liebig fellowships from the "Fonds der Chemischen Industrie" and the Hammet Award for excellence in research from Columbia University. In 2004 she was the Goering Visiting Professor at the University of Wisconsin at Madison and she currently holds the Bachem endowed professorship at the University of Basel. Her research focuses on utilizing the large structural and functional diversity of peptides for the development of asymmetric catalysts and selective molecular receptors that find applications as building blocks of supramolecular assemblies.

Markus Wiesner studied chemistry at the University of Basel and is currently a Ph.D. student in the group of Professor Helma Wennemers. His research focuses on the development of peptides as asymmetric catalysts.

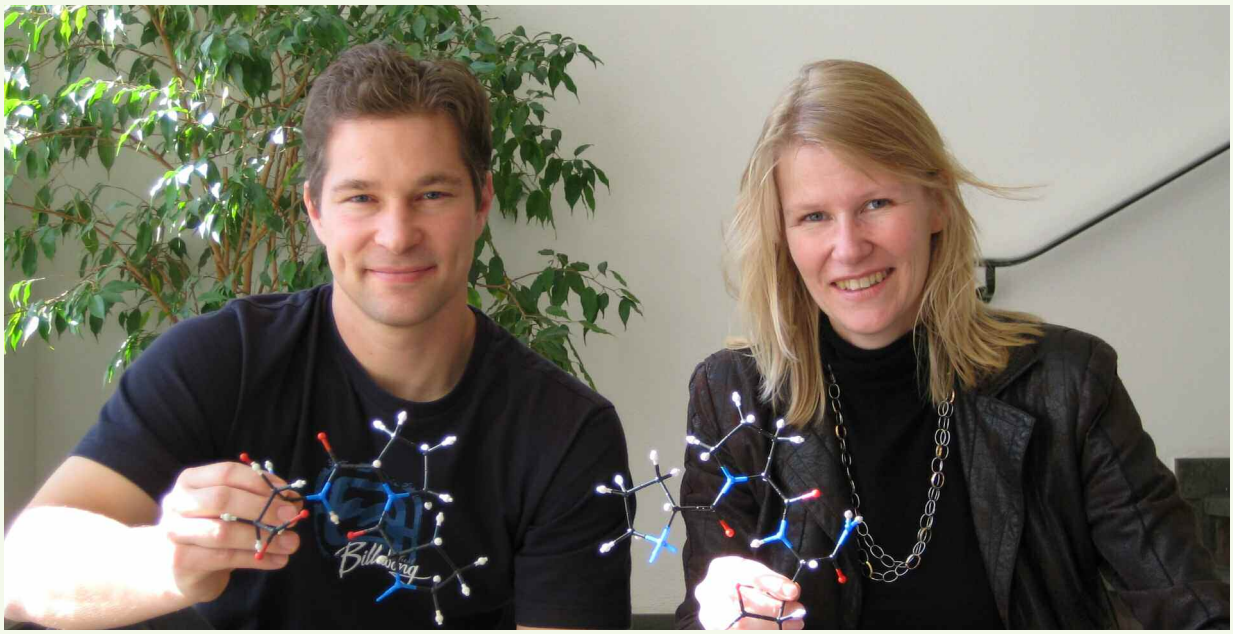
>>

SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559

Jefferson D. Revell received his Ph.D. in 'Organic and Combinatorial Chemistry' in 2004 from the University of Southampton (UK) under the guidance of Dr. Arasu Ganesan. He then accepted a postdoctoral position investigating the 'Development of Peptides as Efficient Asymmetric Organocatalysts' at the University of Basel under the supervision of Professor Helma Wennemers. He is currently working on the development of peptides as therapeutics at Medimmune Ltd (Cambridge, UK).



Dr. J. D. Revell



From left: M. Wiesner, Prof. H. Wennemers

SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559

Arylation of Phe and Tyr Side Chains of Unprotected Peptides by a Suzuki–Miyaura Reaction in Water

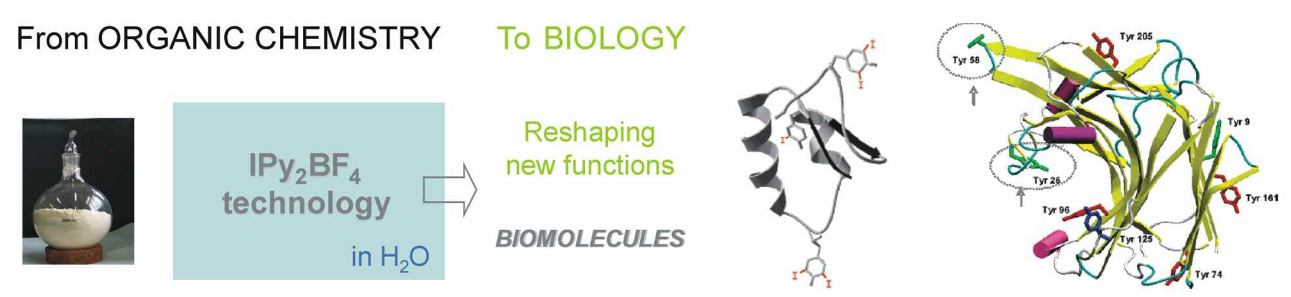
Org. Lett. **2008**, *10*, 3243–3245

Site-selective chemical modification of peptides and proteins is an important tool for understanding the function of these ubiquitous compounds. Among the possible structural variations, modification of aromatic amino acids would be particularly desirable, but few efficient methods are available to functionalize aromatic groups in peptides or proteins. Recently, the group of Professor José Barluenga from the University of Oviedo (Spain) in collaboration with Dr. Gregorio Valencia and Dr. Gemma Arsequell from the CSIC of Barcelona (Spain), reported a novel methodology for the functionalization of phenylalanine and tyrosine aryl groups of unprotected peptides through a Suzuki–Miyaura reaction taking place in water as solvent.

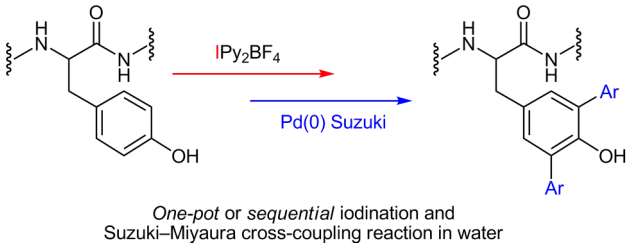
"The reference paper is the latest result of a long ongoing collaboration between our groups," said Professor Barluenga. "The main goal was to explore if the wide applications we have unveiled for the IPy_2BF_4 reagent in organic chemistry (*Pure Appl. Chem.* **1999**, *71*, 431) could be applied to solve unmet medicinal chemistry and biochemical issues. In the first case," he continued, "we have used the reagent to design and prepare a new class of potent transthyretin fibrillogenesis inhibitors (*Biochem. J.* **2004**, *381*, 351). In the latter case, the stability and reactivity of our reagent seemed a good alternative for performing electrophilic aromatic iodinations on biological molecules such as peptides and proteins that always require mild reaction conditions. This initial idea has led us to conduct a rather exhaustive exploration of the use of the reagent in peptide chemistry (*Tetrahedron Lett.* **1998**, *39*, 7393; *Tetrahedron Lett.* **1999**, *40*, 7279; *Chem. Commun.* **2000**, 1307) and a successful attempt to halogenate functional proteins (*Biochemistry* **2006**, *45*, 5957)."

The concept that these iodinated peptide entities could be transformed by metal-catalyzed cross-coupling reactions seemed straightforward, according to Professor Barluenga. "We could preliminarily confirm this assumption by applying conventional Suzuki coupling conditions to a small model peptide (*Angew. Chem. Int. Ed.* **2004**, *43*, 325)," he said. "On further analysis, these and other conditions reported in the literature for amino acid derivatives and small peptides for the Suzuki and other cross-coupling reactions seemed rather inadequate for the vast majority of peptides, which are larger, water-soluble and thermolabile substances. In addition," continued Professor Barluenga, "it is important to bear in mind that free peptides are polyfunctional molecules which also carry a variety of metal-chelating groups that may give rise to a range of side reactions and considerable loss of metal catalyst through substrate coordination."

According to Professor Barluenga, when the work was started, there were few references on Suzuki couplings in water and even fewer on transforming biological water-soluble molecules. "However," he confirmed, "we made important progress after paying attention to the pioneering and independent work of the groups of Beletskaya (*J. Organomet. Chem.* **1989**, *371*, 397) and Calabrese (*J. Am. Chem. Soc.* **1990**, *112*, 4324). A relevant experimental detail was the use of helium- or argon-degassed water."



SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559



One-pot or *sequential* iodination and Suzuki–Miyaura cross-coupling reaction in water

One-pot or sequential iodination and Suzuki–Miyaura cross-coupling reaction in water

Professor Barluenga explained that for the optimization part of the work it was important to test potassium aryltrifluoroborate derivatives and to carefully assess the influence of the base; eventually, they found that K_3PO_4 outperformed the other bases. "We also realized that the catalytic mixture $Pd(OAc)_2$/TPPTS (1:3), in degassed water, is fairly stable, and fully active aliquots can be withdrawn from frozen stock solutions. Evidence for the active catalytic species was obtained using ^{31}P NMR spectroscopy," added Professor Barluenga.

"In assessing the influence of the different parameters on the reaction outcome," continued Professor Barluenga, "our aim was not to dissect every factor but to show that the procedure can be applied to a range of real biological peptides. Size and diversity in the sequence were some of the criteria in making the choice." The most complex peptide Professor Barluenga and coworkers have used was the adrenocorticotropin hormone, ACTH (entries 11 and 12 of Table 1 in the original article) where the side chains of all residues, except Gly, are reactive functions of differing nature. "We expected to encounter trouble, but considering that the desired product is to be obtained in the presence of all seven other reactive functional groups, even the modest yield observed for this reaction was regarded as a success," explained Professor Barluenga. "This fact also illustrates that the systematic examination of the influence of the different side chains and relative position of the amino acids of a given peptide on the performance of these reactions is a huge task. Therefore, the value of the proposed methodology should be evaluated case by case. In spite of these uncertainties," he continued, "we believe that this reaction is perfectly suited for parallel synthesis or other combinatorial approaches leading to libraries of peptide analogues."

"The one-pot iodination–Suzuki coupling experiment reported in the paper is unique in its class," explained Professor Barluenga. "However," he said, "it should be pointed out that the order of the different reaction operations is important for success. Minor modifications to the reported protocol always probed to be less effective." Thus, shorter iodination times or lower IPy_2BF_4 proportions led to mixtures of mono- and di-iodinated Leu-enkephalins, rendering further mixtures with low proportions of Suzuki products. Poor results were also recorded when IPy_2BF_4 was added to starting reaction mixtures containing the peptide and the Suzuki reagents, probably because the trifluoroborate is rendered partially unreactive by iodination (*Tetrahedron Lett.* **2004**, *45*, 343). "We are in the process of learning and properly characterizing these processes and applying them to protein chemistry," concluded Professor Barluenga.

Matteo Zanda

M. Vilaró

Prof. J. Barluenga

SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559

FOCUS on the International Meeting on Fluorinated-Peptide Chemistry, November 4th, 2008, Ochanomizu University, Tokyo (Japan)

The Ochanomizu University of Tokyo, one of the two national women's universities in Japan, recently hosted "The International Meeting on Fluorinated-Peptide Chemistry", held in conjunction with the "Ishikawa-Kobayashi Fluorine Symposium", named after the two Japanese fluorine chemists Professor Nobuo Ishikawa (1926–1991) and Professor Yoshiro Kobayashi (b. 1924). The event was organized by Dr. Tomoko Yajima of Ochanomizu University, supported by Professor Koichi Mikami from the Tokyo Institute of Technology (Japan) and by the "Career Opportunity Support Model from Ochanomizu Scientists". The one-day symposium featured a good scientific program with an international group of speakers, who gave an overview of the current status of the emerging field of fluorine-containing peptides and proteins, and contiguous areas of research. Among the speakers was Professor G. K. Surya Prakash from the Loker Hydrocarbon Research Institute, University of Southern California (USA), who presented new fluoroalkylation methods developed by his group, mainly using sulfur-based reagents. Professor Koichi Mikami (see above) presented new strategies in fluorous chemistry, and specifically new fluorous tags and their influence on helical chirality control. Professor E. Neil G. Marsh from the University of Michigan, Ann Arbor (USA) discussed his work on "teflon proteins", obtained through the incorporation of fluorous amino acids into proteins. Dr. Peer Kirsch from Merck Ltd. Japan revealed new insights into super-fluorinated liquid crystals and their applications for LCD. Professor Iwao Ojima from the State University of New York (USA) presented some of the work of his group in the field of fluorine-containing taxoids and their use in targeted cancer therapy. Professor Takashi Yamazaki from the Tokyo University of Agriculture and Technology (Japan) presented the most recent results from his group on the synthesis and structural properties of fluorinated enkephalins. Professor Takeo Taguchi from the Tokyo University of Pharmacy and Life Sciences (Japan) disclosed some new Lewis acid catalyzed Diels–Alder reactions involving fluorinated esters. The symposium also featured an interesting poster session, with a "Best Poster Award" that was given for the poster "Fluorinated Johnson Reagent for Electrophilic Trifluoromethylation Reaction" presented by Shun Noritake from the group of Professors Norio Shibata and Takeshi Toru (Nagoya Institute of Technology, Japan).

The program concluded with a brief speech by Emeritus Professor Yoshiro Kobayashi, who thanked the participants and officially started the final party with the traditional "Kanpai!". The symposium organizer, Dr. T. Yajima, pointed out that the conference had a special flavor and meaning because it was hosted by Ochanomizu University: "Opportunities for females in physical sciences are still fewer than those for men," said Dr. Yajima, "and these kinds of events are also important for emphasizing gender issues in Japan's scientific community."

Matteo Zanda

Dr. T. Yajima

Prof. K. Mikami

SYNFORM, 2009/01
Published online: 22.01.2009, **DOI**: 10.1055/s-0028-1087559

COMING SOON ►► COMING SOON ►►

SYNFORM 2009/02 is available from February 19, 2009

In the next issues:

SYNSTORIES

- **[4+2] Cycloadditions of *N*-Alkenyl Iminium Ions**
(Focus on an article from the current literature)
- **Functionalizing Glycine Derivatives by Direct C–C Bond Formation**
(Focus on an article from the current literature)
- **Stereoretentive Halogenations and Azidations with Titanium(IV)**
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Reviews on: Intermolecular Addition Reactions of *N*-Acyliminium Ions (Parts I and II)
(by S. G. Pyne)

SYNLETT

Account on: The Art of the Soluble: Synthetic Problems from Industry as a Springboard for the Discovery of New Chemical Reactions
(by S. Z. Zard)

SYNFACTS

Synfact of the Month in category "Organo- and Biocatalysis":
Chiral Brønsted Acid–Base Pyridinium Disulfonate Catalysts

CONTACT

Matteo Zanda,
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare,
Via Mancinelli, 7, 20131 Milano, Italy,
e-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor
Matteo Zanda, C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Synform@chem.polimi.it
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
- Assistant Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
- Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Assistant: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 929
- Production Assistant: 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: Thomas Krimmer, thomas.krimmer@thieme.de, phone: +49 711 8931 772
- Postal Address: SYNTHESIS/*SYNLETT*/*SYNFACTS*, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
- Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 11 times in 2009 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*
Americas: Thieme New York, 333 Seventh Avenue, New York, NY 10001, USA. To order: customerservice@thieme.com or use the Web site facilities at www.thieme.com, phone: +1 212 760 0888
Order toll-free within the USA: +1 800 782 3488
Fax: +1 212 947 1112

Airfreight and mailing in the USA by Publications Expediters Inc., 200 Meacham Ave., Elmont NY 11003. Periodicals postage paid at Jamaica NY 11431.

All other countries: Thieme Publishers, Rüdigerstraße 14, 70469 Stuttgart, Germany. To order: customerservice@thieme.de or use the Web site facilities at www.thieme.com.
For further inquries please contact Mrs. Birgid Härtel:
Phone: +49 711 8931 421; Fax: +49 711 8931 410

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

Online Access via Thieme-connect
The online versions of *SYNFORM* as well SYNTHESIS, *SYNLETT* and *SYNFACTS* are available through Thieme-connect (www.thieme-connect.com/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:

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

All other countries: eproducts@thieme.de, phone: +49 711 8931 407

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.