SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/01

SYNSTORIES

CONTACT

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Dear readers,

This first ***SYNFORM*** issue of 2014 is a concentrate of cutting-edge organic chemistry, spanning from a modern re-examination of a textbook reaction like the bimolecular nucleophilic substitution reaction (S_N2) to the development of a groundbreaking methodology for incorporating the positron emitting ^{18}Fluorine nuclide into organic molecules, which should ultimately lead to new tracers for Positron Emission Tomography (PET) imaging. The first ***SYNSTORY*** reports the discovery of a new stereocontrolled process developed by Professor R. Shenvi (USA) for converting tertiary alcohol derivatives (trifluoroacetates), which are normally refractory to standard S_N2 reactions, into the corresponding tertiary isonitriles and amines with inversion of configuration. The second ***SYNSTORY*** describes a novel method for producing unsymmetrical 'trisulfides' or trisulfanes, which are found in a number of very important natural bioactive compounds such as the anticancer calicheamicins. Thus, the strategy described by Professor D. Witt could ultimately lead to more efficient synthetic access to these compounds and a number of other molecules and materials incorporating an unsymmetrical –S-S-S– function. The third ***SYNSTORY*** covers a conceptual breakthrough for introducing an ^{18}F-labelled trifluoromethyl group into organic molecules, and produce previously unaccessible tracers for PET imaging. The method stems from a collaborative effort between Dr. J. Passchier and Professor V. Gouverneur (UK). Last but not least, a Young Career Focus on Dr. J. Deska (Germany) is completing the issue.

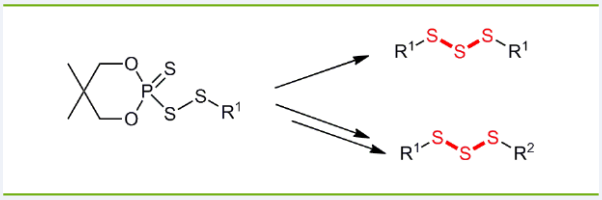
Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

IN THIS ISSUE

SYNSTORIES



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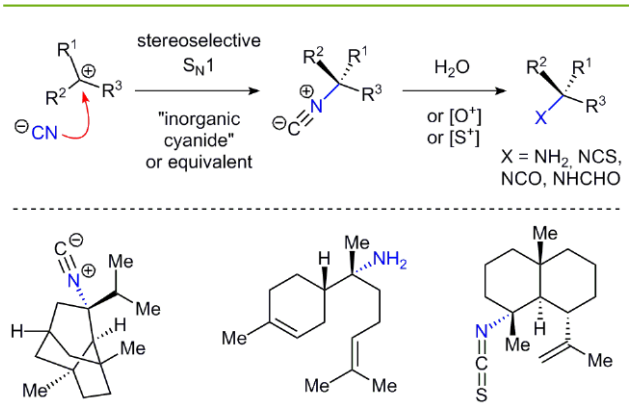
Stereoinversion of Tertiary Alcohols to Tertiary Alkyl Isonitriles and Amines

Nature **2013**, *501*, 195–199

The bimolecular nucleophilic substitution (S_N2) reaction is one of the most basic chemical transformations used in organic synthesis. A crucial feature of this transformation is the predictability of its stereochemical outcome, as the substrate always undergoes backside attack by the nucleophile, leading to inversion of configuration at the reaction center. The reaction thus allows the union of two fragments or the exchange of two functional groups in a stereospecific manner. The textbook limitation of the process is substitution of tertiary alkyl substrates, which usually fail to undergo substitution under S_N2 conditions, or lead to a mixture of products due to the intervention of alternative reaction pathways. The more typical reactivity of tertiary alkyl substrates involves the formation of intermediate carbocations, which are then trapped by nucleophiles – a monomolecular nucleophilic substitution (S_N1) reaction. This process, however, typically proceeds with scrambling of stereochemical information and thus results in mixtures of stereoisomers. "One of the few exceptions may be the postulated biosynthesis of a group of natural products called isocyanoterpenes which appear to be formed by stereoselective attack of a tertiary carbocation by cyanide (Scheme 1)" explained Professor Ryan Shenvi of the Scripps Research Institute (La Jolla, USA). "This process, however, likely takes place in a yet-to-be-identified enzymatic environment and is therefore unavailable to the synthetic chemistry community".



Scheme 1 *Stereoselective S_N1 reaction in the biosynthesis of isocyanoterpenes*

Professor Shenvi's research group has now developed an abiotic variant of this transformation, which for the first time allows stereoselective incorporation of nitrogen functionality at the tertiary alkyl stereocenter by means of nucleophilic substitution. Prior state-of-the-art approaches allowed for the incorporation of inorganic cyanide in tertiary alkyl substrates but suffered severely from the lack of chemo- and stereoselectivity. Professor Shenvi said: "We believed that Lewis acid assisted ionization of a tertiary leaving group in the presence of a large excess of a nitrogenous nucleophile would trap the carbocation prior to the dissociation of the intermediate contact ion pair and loss of stereochemical information." Indeed, screening of various Lewis acids revealed that early-transition-metal trifluoromethanesulfonates exhibited the desired catalytic activity, with the scandium(III) salt being particularly effective and promoting the desired substitution at low catalytic loadings. Perfluoroalkanoates proved to be optimal substrates as their non-fluorinated counterparts underwent substitution with increased stereochemical scrambling. The optimized reaction conditions involve solvolysis of tertiary alkyl trifluoroacetates in neat trimethylsilyl cyanide in the presence of 3 mol% scandium(III) trifluoromethanesulfonate at 3 °C (Scheme 2).

"The reaction proved general for isolated stereocenters and exhibited excellent functional group tolerance," said Professor Shenvi. "Of note is the inertness of primary and secondary alkyl trifluoroacetates towards these isocyanation conditions. Solvolysis of polyol derivatives leads to selective isocyanation of tertiary trifluoroacetates and yields the corresponding isocyanoalcohols after mild hydrolytic work-up. Thus, the reaction is complementary to the traditional S_N2 displacement but with inverse substitution requirements." Furthermore, this isocyanation allows rapid access to isocyanoterpenes such as isocyanocadinene, which is now prepared in only nine steps –

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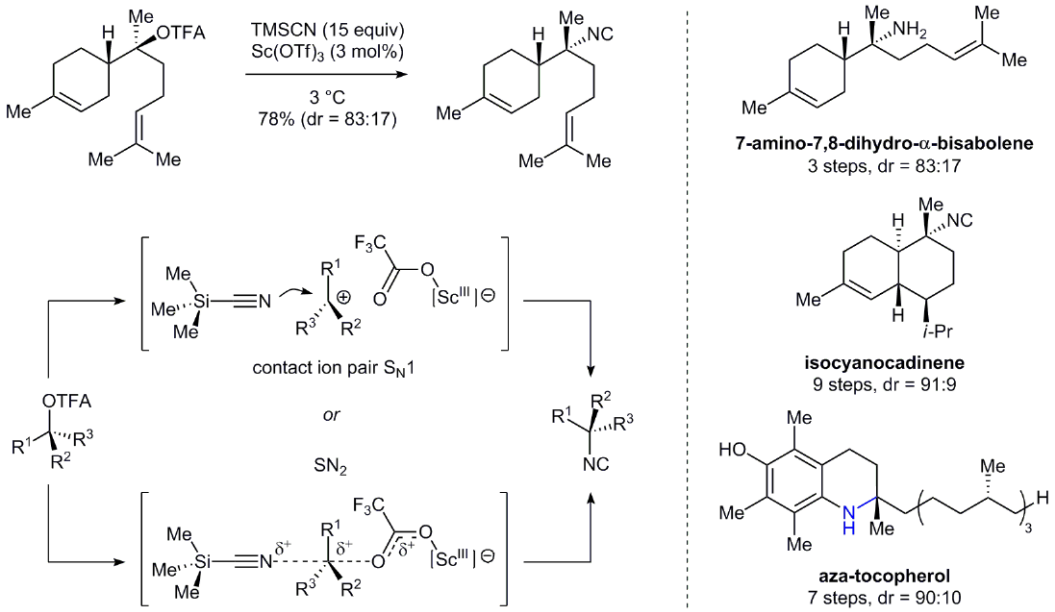

Scheme 2 *Stereoinversion of tertiary alkyl trifluoroacetates to isonitriles and amines*

twenty steps shorter than the previous synthesis. Hydrolysis of the isonitrile products allows the synthesis of the corresponding formamides and amines. For example, commercially available α-bisabolol can be converted in three steps into the corresponding tertiary alkyl amine, which is an enantiomer of a natural product. Application of this methodology also allowed a short synthesis of 'aza-tocopherol', a compound that would be difficult to access otherwise.

Professor Shenvi remarked: "The mechanism of the new isocyanation is not fully understood, but we believe that the reaction proceeds via backside attack on the intermediate contact ion pair formed by ionization of the substrate–Lewis acid complex" (Scheme 2). The alternative direct S_N2 displacement cannot be ruled out completely but is unlikely based on experimental observations. "While other nucleophiles cannot be utilized in the current transformation, we hope that future investigations will broaden the scope of this reaction and provide us with useful insights into carbocation–counteranion interactions," he concluded.

Matteo Zanda

About the authors

Prof. R. A. Shenvi

Ryan A. Shenvi was born and raised in Wilmington, DE (USA) and received his BS degree in chemistry from Penn State University (USA), where he was a research student in the laboratories of John R. Desjarlais and Raymond L. Funk. He earned his Ph.D. with Phil S. Baran at The Scripps Research Institute (USA), and then joined the laboratory of E. J. Corey at Harvard University (USA) as a postdoctoral fellow. Since 2010, he has been an Assistant Professor in the Department of Chemistry at The Scripps Research Institute.

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C. A. Reiher

Christopher A. Reiher received his BS degree in chemistry from Penn State University (USA), where he conducted research in the laboratory of Raymond L. Funk. He worked as an intern at Bristol-Myers Squibb (USA) under the guidance of Ke Chen and Martin D. Eastgate during the summer of his fourth year at Penn State. In 2012, he began graduate school at the Scripps Research Institute (USA), where he is currently a second-year student in the Shenvi lab.

Dr. S. V. Pronin

Sergey V. Pronin received his Specialist degree in chemistry from Moscow State University (Russian Federation), where he was a research student in the laboratory of Valentine G. Nenajdenko and Elizabeth S. Balenkova. He earned his Ph.D. from The University of Chicago (USA) under the supervision of Sergey A. Kozmin. In 2011 he joined the laboratory of Ryan A. Shenvi at The Scripps Research Institute (USA) as a postdoctoral associate.

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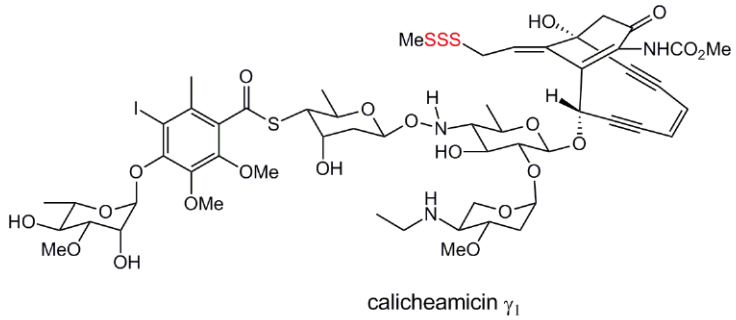
Efficient Synthesis of Functionalized Unsymmetrical Dialkyl Trisulfanes

Synlett **2013**, *24*, 1927–1930

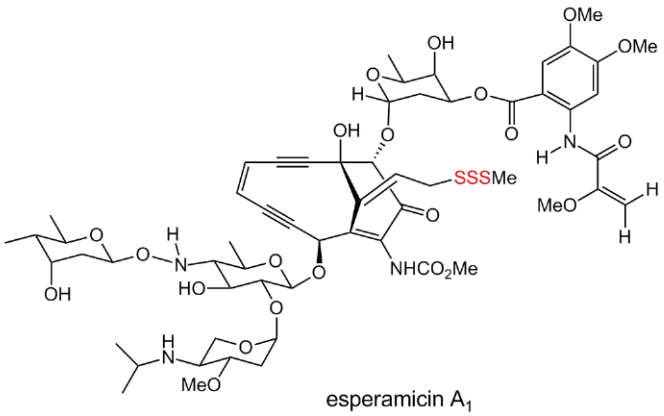
Not only do organic trisulfanes play an important role in basic research and in industry, they are also found as natural products in organisms. Calicheamicin (from *Micromonospora echinospora*) and esperamicins (from *Actinomadura verrucosospora*), members of the enediyne class of antibiotic with very potent antitumor activity, are well-known examples.

There are several preparative methods that can be used to obtain symmetrical organic trisulfanes. Although preparation of unsymmetrical trisulfanes is more complex, there are known procedures based on the coupling of chlorodisulfanes with *N*-arylamidothiosulfites (*J. Org. Chem.* **1961**, *26*, 2482) or thiols (*Justus Liebigs Ann. Chem.* **1958**, *617*, 62; *J. Sulfur Chem.* **2006**, *27*, 15) or the sequential coupling of two thiols using sulfur dichloride (*Tetrahedron Lett.* **1994**, *35*, 5381). Other procedures involve the desulfurization of unsymmetrical dialkanesulfonic thioanhydrides (*Chem. Pharm. Bull.* **1967**, *15*, 1310), or the use of (often) unstable hydrodisulfanes (*Chem. Ber.* **1960**, *93*, 380).

The group of Professor Dariusz Witt at the Gdansk University of Technology (Poland) noticed, when they analyzed these published procedures, that moderate yields and/or the formation of undesirable polysulfane side products were the major drawbacks. Moreover, the scopes of the presented methods are limited by the availability of reagents and the chemical reactivity of the additional functional groups. Professor Witt said: "In fact, our research starts at this point. We decided to select activation of the thiol functionality by its conversion into the disulfanyl derivatives **1** of phosphorodithioic acid." He continued: "We intended to develop a new synthetic protocol for formation of S–S bonds with very high yield and chemoselectivity, so that protection of additional functional groups (hydroxy, carboxy or amino) would not be required." Professor Witt noted that the beginning was tough. Preparation of phosphorodithioic acid was straightforward but its purification by vacuum distillation resulted in two explosions and the laboratory had to be renovated! "We did not give up," said Professor Witt, "and the purification was accomplished by crystallization." Then an appropriate solvent or mixture of solvents needed to be found. Finally, after a month of searching, carbon tetrachloride was the only one to provide



calicheamicin γ_1



esperamicin A_1

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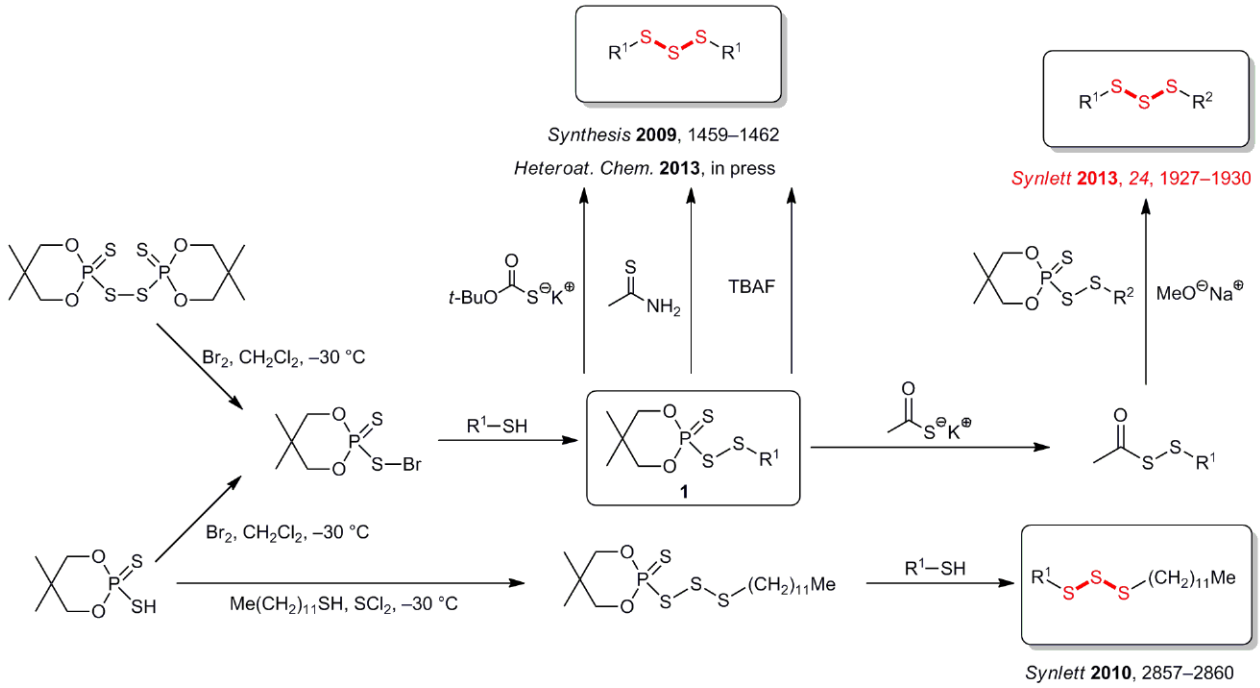

Scheme 1 *Preparation of dialkyl trisulfanes*

phosphorodithioic acid in acceptable crystallization yield and purity. Professor Witt commented: "The rest of the research was accomplished by the hard work of my graduate and PhD students. They demonstrated the ability to work independently with great creativity and enthusiasm. I am really grateful for that." The electrophilic properties of phosphorodithioic acid disulfanyl derivatives **1** were very useful in the preparation of various symmetrical and unsymmetrical trisulfanes (Scheme 1).

A convenient method for the preparation of symmetrical and unsymmetrical dialkyl trisulfanes bearing hydroxy, carboxy, methyl ester, or *tert*-butoxycarbonylamino groups on either or both sides of the trisulfane has been developed. Reactions of **1** with a variety of reagents were generally complete within 30 minutes and gave exclusively the dialkyl trisulfanes in very good yields after purification. Because the reactions proceeded with a small excess of **1** under mild reaction conditions and in a short time, thiol–trisulfane exchange and sulfur extrusion did not occur during the reaction. Professor Witt noted: "This is very important because separation of disulfanes from trisulfanes and symmetrical from unsymmetrical products is very often impossible by column chromatography. The simplicity and very good yields of this method make it one of the most attractive approaches for the preparation of functionalized dialkyl trisulfanes."

He continued: "Currently, in our opinion, advanced organic synthesis is focused on the development of new catalysts and reagents which allow the required transformation to be accomplished efficiently, without protective groups, and from inexpensive starting materials and solvents. We believe that both economic and environmental aspects are crucial for the future of organic synthesis." From this point of view, the synthetic application of disulfanyl derivatives **1** should not be limited exclusively to the formation of trisulfanes. Indeed, a wide range of disulfanes, phosphorothioates, α-sulfonylated carbonyl compounds, selenenylosulfanes, vinylic and acetylenic sulfanes, and sulfenylamides can be obtained from disulfanyl derivatives **1** (Scheme 2).

The researchers were able to demonstrate the great synthetic potential of electrophilic derivatives **1** in the reaction with sulfur, carbon, nitrogen and phosphorus nucleophiles. Although all these transformations were performed in an

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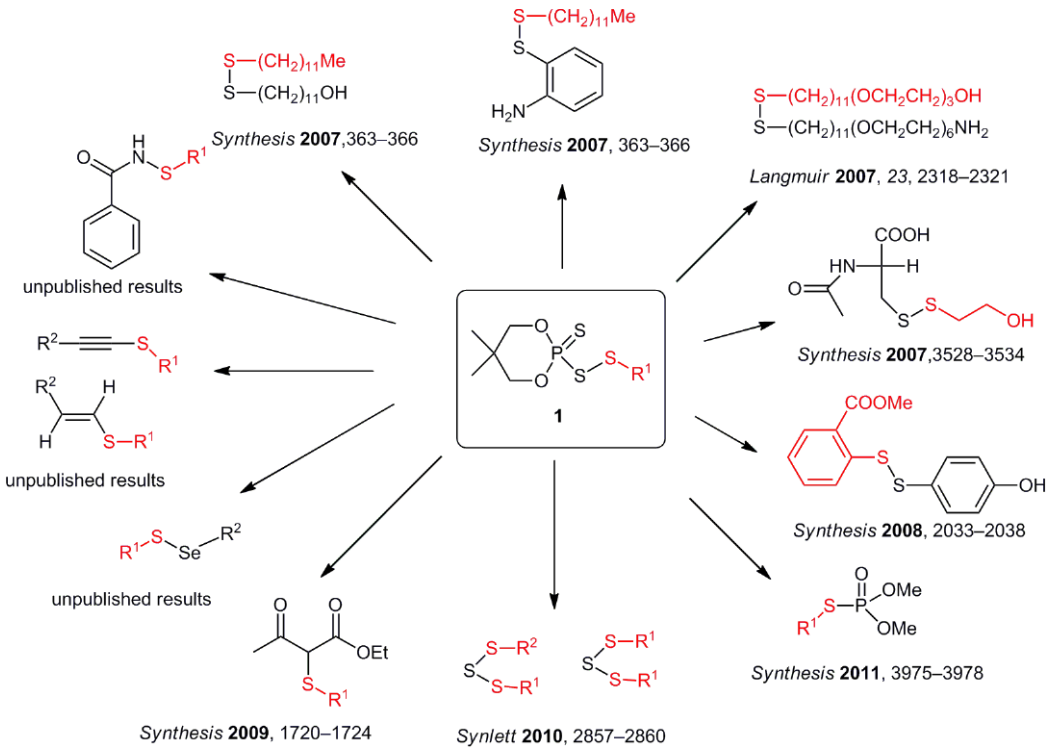

Scheme 2 *Synthetic application of disulfanyl derivatives* ***1***

organic solvent, they have recently been able to obtain water-soluble derivatives **1**. This opens new possibilities for attachment of non-radioactive reporter groups to important water-soluble biomolecules such as proteins and oligonucleotides (possessing thiol functionality) directly under aqueous conditions. Professor Witt said: "We also expect that preparation of new prodrugs and immunotoxins can be achieved with this approach."

According to Professor Witt, self-assembled monolayers (SAMs) of alkyl phosphonothioic acids are underexploited in nanoscience. They adsorb strongly onto the oxides of aluminum, titanium, zinc and other metals to form SAMs that are more closely packed and exhibit greater oxidative and thermal stability than alkylthiolate-based monolayers. "We noticed that wide application of these compounds is limited by their synthetic availability," said Professor Witt. "That is why we decided to develop a method that may be applied for conversion of a wide range of thiols with interesting terminal groups like maleimide, biotin, NTA and the peptide Gly-Arg-Gly-Asp, etc., into the corresponding phosphorothioates (*Synthesis* **2011**, 3975)." He concluded: "SAMs formation with precisely designed properties can be very useful for functionalization of metal oxide nanoparticles, nanotips, nanorods and nanowire surfaces and further application of these materials for development of chemical nanoscaled sensors, optoelectronic devices, solar cells, chemically modified electrodes, and boundary lubricants, etc., can be expected."

Matteo Zanda

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About the authors

Prof. D. Witt

Dariusz Witt was born in 1968 in Gdynia (Poland). He graduated from the Gdansk University of Technology (GUT, Poland) in 1992. His Ph.D. work in the group of Prof. Janusz Rachon at GUT was focused on the elucidation of reaction mechanisms of various classes of organosulfur and organophosphorus compounds. He obtained his Ph.D. in 1996. From 1998 to 2000 he was a post-doctoral fellow in the group of Prof. Lyle Isaacs at the University of Maryland (USA). His general research interests comprise organic chemistry at the interface to HPLC, molecular self-assembly and nanotechnology. Special focus is placed on the various aspects of organic synthesis methodology based on organophosphorus reagents.

Dr. S. Lach

Slawomir Lach was born in 1984 in Bytow (Pomerania, North Poland). He received his Ph.D. in 2013 from the Gdansk University of Technology (Gdansk, Poland) under the supervision of Dariusz Witt. He then took up a position at University of Gdansk (Gdansk, Poland) as Postdoctoral Fellow with Professor Sylwia Rodziewicz-Motowidlo. His research focuses on modern organic synthesis, and the design and study of anticancer therapeutics.

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A Broadly Applicable [^{18}F]Trifluoromethylation of Aryl and Heteroaryl Iodides for PET Imaging

Nat. Chem. **2013**, *5*, 941–944

The high cost of drug development combined with low return on investment and low productivity in R&D activities is leading to profound change in the pharmaceutical industry, with extensive restructuring and the evolution of new business models. Notwithstanding these changes, the risks of drug development and, more importantly, late-stage drug candidate failure remain. Positron emission tomography (PET) is a non-invasive, quantitative molecular imaging technique with nano- to picomolar sensitivity that, through the use of tool compounds or drugs or drug candidates appropriately labelled with a positron-emitting isotope (such as ^{18}F or ^{11}C), can allow for the determination of, for example, biochemical changes in the body, drug–target interactions and drug candidate tissue distribution.[1] PET imaging provides a wealth of information on the injected radiolabelled probe, making it ideally suited to applications in drug discovery.[2] Medicinal chemists can assess at an early stage of a drug's development whether it reaches the target of interest, as well as efficacy and pharmacokinetics. Thus, timely use of imaging at the translational phase can provide invaluable information in humans on drug–target interactions, and dosing and candidate selection, as well as improve the definition of clear 'go' or 'no-go' decision points to facilitate 'fast-to-fail'.

Despite these benefits, imaging is frequently not integrated into the drug development process and its potential is thus not fully realized – in part due to limited knowledge of the benefits and a lack of suitable tools, but also due to a lack of chemical transformations within the unique space that is called PET radiochemistry. The unnatural isotope fluorine-18 is often considered as an ideal PET isotope due to its favorable physical properties.[3] The progress of PET in the clinic and for drug discovery is dependent on the ability to synthesize radiolabelled target compounds in an efficient and selective manner within the time constraints of a radiochemical synthesis. While new methods for the incorporation of [^{18}F]fluorine have seen a resurgence in the mainstream chemical literature, a general method for [^{18}F]trifluoromethylation of arenes had not been addressed.[4] This synthetic group is of interest to medicinal chemists as it provides a convenient way to modify physicochemical properties of potential drug candidates and can be found in many drugs currently on the market. Recent work directed by Professor Veronique Gouverneur, at the University of Oxford (UK), and Dr. Jan Passchier, at Imanova Ltd. (UK), has resulted in a general method for the [^{18}F]trifluoromethylation of (hetero)aryl iodides by [^{18}F]$CuCF_3$.[5] Existing methods for [^{18}F]trifluoromethylation were typically based around halogen-exchange reactions, where the key C–^{18}F bond is formed by the displacement of a halide leaving group of a difluorinated benzylic precursor. These reactions suffered from a limited substrate scope and required harsh reaction conditions.

Professor Gouverneur and Dr. Passchier pursued a fundamentally different approach, whereby they considered a multicomponent strategy that would allow construction of both the aryl–$CF_2{}^{18}$F and the arylCF_2–^{18}F bonds in a single transformation. Building on the work of Burton and Chen, who pioneered the use of methyl chlorodifluoroacetate, they used a combination of this reagent with a fluoride source and copper iodide, and thereby generated a reactive Cu-CF_3 species for the trifluoromethylation of aryl iodides.[6] Professor Gouverneur said: "We recognized that if the proposed difluoromethyl carbene could be intercepted with [^{18}F]fluoride, this would lead to the in situ generation of [^{18}F]$CuCF_3$, which could undergo cross-coupling with (hetero)aryl iodides." Validation of this [^{18}F]trifluoromethylation strategy was realized after extensive optimization efforts which identified methyl chlorodifluoroacetate in combination with copper iodide and tetramethylethylenediamine (TMEDA) as the conditions of choice. "Interestingly, 1,10-phenanthroline, a ligand commonly employed for copper-catalyzed trifluoromethylation, was unsuccessful in this radiochemical transformation," remarked Professor Gouverneur. The methodology was applied to a wide variety of aryl and heteroaryl iodides giving the desired [^{18}F]trifluoromethylated products within 30 minutes at 150 °C. A protected dipeptide, a carbohydrate and a uracil derivative were also successfully labelled using the optimized protocol, demonstrating the broad applicability of this new radiochemical technique. "Notably, we were also able to develop the methodology for the direct C–H functionalization of a C3-substituted *N*-methylindole substrate, an exciting avenue that we are pursuing further," said Professor Gouverneur. "The utility of this procedure for drug develop-

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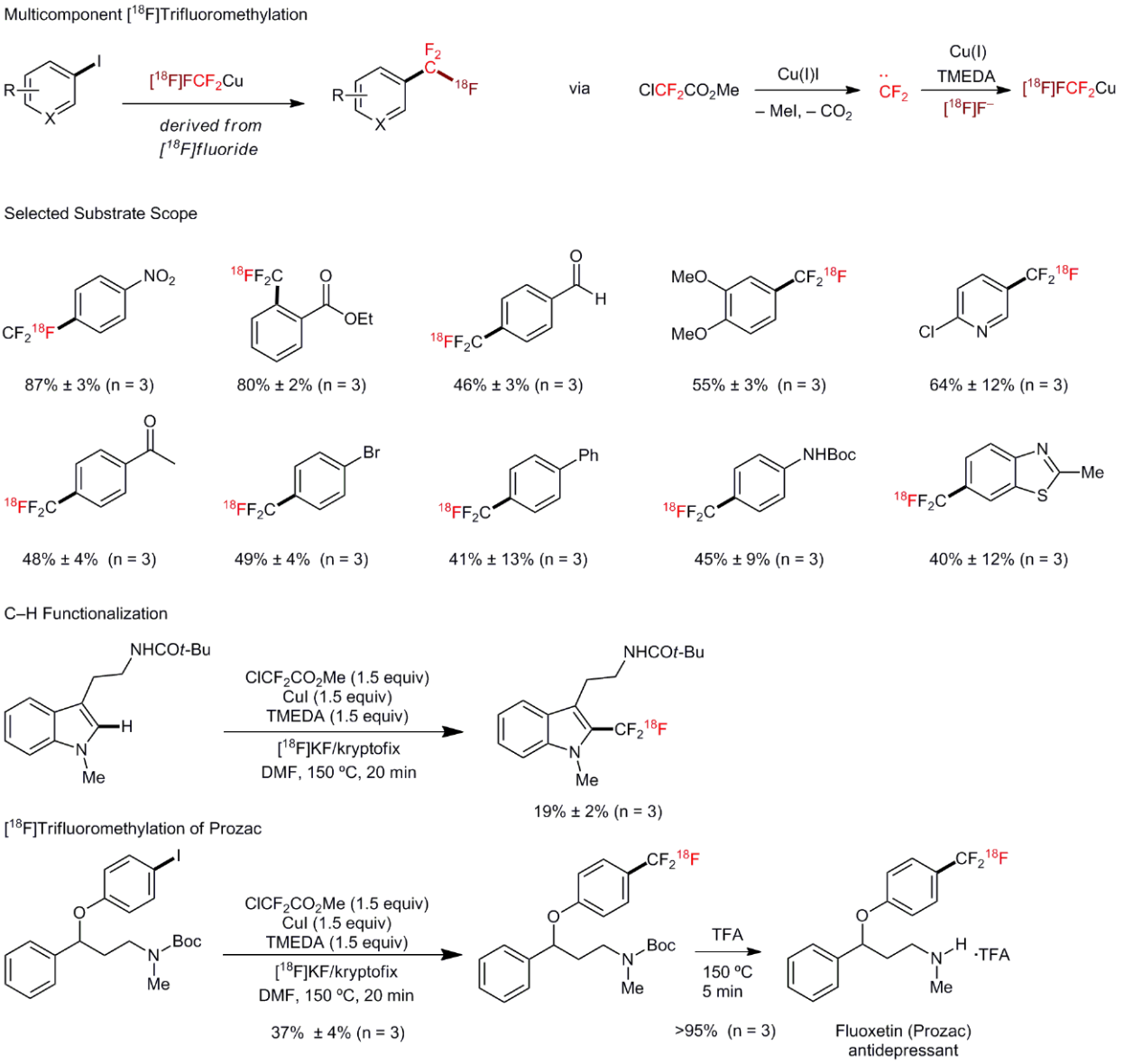

ment is highlighted by the [18F]trifluoromethylation of the antidepressant Prozac."

Professor Gouverneur continued: "The reaction conditions employ [18F]fluoride and are operationally very simple and readily applicable for use on automated synthesis units, making this procedure accessible and implementable in the hundreds of PET centers the world over. This is a key aspect any new radiochemical transformation needs to adhere to in order for the protocol to be widely adopted and employed outside of an academic environment."

This [18F]trifluoromethylation is an exciting development in the field of radiochemistry, bridging the gap between fundamental discoveries in catalysis and clinical applications. Tantalizing opportunities emerge for the preparations of 18F-labelled biomarkers and drugs or drug candidates that are currently difficult to access. Professor Gouverneur concluded: "Beyond the preparation of [18F]trifluoromethylated (hetero)-arenes, one could now also consider using a new range of [18F]CF_3-prosthetic groups for the labelling of complex peptides and proteins through orthogonal ligation chemistry."

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Matthew Tredwell obtained his D.Phil. from the University of Oxford (UK), under the supervision of Professor Gouverneur, before moving to the University of Cambridge (UK) for postdoctoral studies with Professor Matthew Gaunt. He returned to the University of Oxford in 2009 to undertake postdoctoral studies with Professor Gouverneur.

Prof. S. Mizuta

Satoshi Mizuta was born in Saga (Japan) in 1981. He received his Ph.D. in 2008 from Nagoya Institute of Technology under the supervision of Professor N. Shibata. He moved to The Scripps Research Institute of Technology (USA), where he worked as a postdoctoral fellow with Professor Carlos F. Barbas III in 2009. In 2010, he was appointed as a research fellow of Dr. K. Hirai's group at The Sagami Chemical Research Institute (Japan). He then worked at the University of Oxford (UK) with Professor V. Gouverneur as a postdoctoral fellow until May 2013. He is currently an assistant professor at Nagasaki University. His research interests are fluorine chemistry and innovative drug development.

Dr. J. Passchier

Jan Passchier received his M.Sc. in organic chemistry and Ph.D. in medicinal sciences from Groningen University in The Netherlands. In September of 2000, he joined GlaxoSmithKline in Cambridge (UK) as a PET radiochemist. In this capacity, he was responsible for many PET ligand development and drug labelling activities across the drug development portfolio. He currently serves as director of operations and head of radiochemical sciences for Imanova Ltd.

Dr. M. Huiban

Mickael Huiban received his M.Sc. (2001) in chemistry of biomolecules from the University of Montpellier (France). He obtained his Ph.D. (2004) in synthetic organic chemistry from the University of Caen (France) under the guidance of Dr. Louisa Barré. In 2005, he joined the GSK Clinical Imaging Centre in London (now Imanova Ltd) as a PET radiochemist. He currently serves as the Head of Clinical Chemistry at Imanova.

Dr. Z. Wan

Zehong Wan received his B.Sc. (1990) from the University of Science and Technology of China (P. R. of China), M.S. (1995) in organic chemistry from Iowa State University (USA), and Ph.D. (2000) in synthetic organic chemistry from the University of Pennsylvania (USA) under the guidance of Professor Amos B. Smith III. He then joined GSK R&D in King of Prussia, Pennsylvania (USA) and transferred to GSK R&D in Shanghai (P. R. of China) in 2008. Currently he serves as Director and Head of Medicinal Chemistry for Neurodegeneration Discovery Performance Unit in the Neurosciences Therapy Area Unit of GSK.

Dr. X. Zhang

Xiaomin Zhang received his B.Sc. (1991) from Lanzhou University (P. R. of China), Ph.D. (1997) in inorganic chemistry from Nanjing University (P. R. of China), and second Ph.D. (2007) in synthetic organic chemistry from ETH Zurich (Switzerland) under the guidance of Professor A. Vasella. He joined GSK R&D Shanghai (P. R. of China) in 2007, and currently works in the Neurodegeneration Discovery Performance Unit of GSK as a principal scientist.

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Prof. V. Gouverneur

Véronique Gouverneur has been Professor of Chemistry at the University of Oxford (UK) since 2008 and a Fellow of Merton College. She entered the Faculty of Chemistry at Oxford in 1998 as a University Lecturer. She was educated in Belgium at the Université Catholique de Louvain, having completed her M.Sc. and Ph.D. in chemistry with Professor L. Ghosez. She pursued her postdoctoral studies at the Scripps Research Institute (USA) under the mentorship of Professor R. A. Lerner. She started her research career in 1994 at the Université Louis Pasteur in Strasbourg (France) prior to moving to Oxford. Her research is centered on fluorine chemistry and [^{18}F]radiochemistry for PET. Her work, published in more than 140 peer-reviewed publications and presented at over 100 international conferences, has been recognized with various awards. At present, she holds the "Chair Blaise Pascal" and is a recipient of a Royal Society Wolfson Research Merit Award.

Dr. L. Collier

Dr. Lee Collier received his Ph.D. (1989) from Carleton University (Canada) under the guidance of Professor John ApSimon. Two industrial post-doc positions were a great learning experience: the first, with the environmental analysis company Paracel Laboratories (Canada), then the second started his research in radiochemistry for use in medical imaging at the University of Tennessee Medical Center at Knoxville (USA) as part of a joint program with CTI Inc (USA). Dr. Collier has been involved in the design, development and automation of radiotracers for medical imaging over the past 20 years. He has held various senior research and academic positions while at ANSTO (the Australian Nuclear Science and Technology Organisation), Columbia University Medical Center (USA), Siemens Molecular Imaging (USA), and Advion Inc. (USA). For the past 10 years, his research has included the use of microfluidics for radiochemistry and this work continued when he moved to Advion Inc. (USA) about five years ago. Dr. Collier currently holds a senior scientist position at Advion Inc., as well as visiting research positions at the University of Tennessee Medical Center at Knoxville (USA), Harvard Medical School (USA) and Massachusetts General Hospital (USA), where his research is involved in furthering the applications of microfluidics and radiochemistry in medical imaging.

REFERENCES

(1) M. E. Phelps *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226.

(2) P. M. Matthews, E. A. Rabiner, J. Passchier, R. N. Gunn *Br. J. Clin. Pharmacol.* **2012**, *73*, 175.

(3) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee *Angew. Chem. Int. Ed.* **2008**, *47*, 8998.

(4) M. Tredwell, V. Gouverneur *Angew. Chem. Int. Ed.* **2012**, *51*, 11426.

(5) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur, J. Passchier *Nat. Chem.* **2013**, *5*, 941.

(6) (a) J. G. MacNeil Jr., D. J. Burton *J. Fluorine Chem.* **1991**, *55*, 225. (b) J.-X. Duan, D.-B. Su, Q.-Y. Chen *J. Fluorine Chem.* **1993**, *61*, 279.

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Young Career Focus: Dr. Jan Deska (University of Cologne, Cologne, Germany)

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 Professor Jan Deska, University of Cologne, Cologne, Germany.

BIOGRAPHICAL SKETCH

Prof. J. Deska

Jan Deska (born in 1979) grew up in the Franco-German border town of Saarbrücken where he studied chemistry and received his diploma in 2004. Under the direction of Professor Uli Kazmaier, he spent the following years of doctoral studies in the field of palladium catalysis to obtain his Ph.D. in organic chemistry in 2007 from the Saarland University (Germany). Subsequently, Jan took the opportunity to join the group of Professor Goverdhan Mehta at the Indian Institute of Science, Bangalore (India) to broaden his expertise on natural product synthesis. In 2008, he returned to Europe for another postdoctoral stint which he spent in the lab of Professor Jan-E. Bäckvall at Stockholm University (Sweden), developing novel dynamic kinetic resolution systems. Since April 2010, Jan has been working as an independent junior group leader (Habilitation mentor: Professor Albrecht Berkessel) at the Department of Chemistry of the University of Cologne (Germany). His work has been recognized by a Liebig fellowship and a Thieme Chemistry Journals Award and is currently funded by the German Research Foundation (DFG) as well as the Fonds der Chemischen Industrie.

INTERVIEW

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

Prof. J. Deska | As a central theme, all our research projects currently deal in one way or another with the synthesis of complex heterocyclic systems. Our main focus herein lies in the development of novel strategies for the implementation of biocatalysis into contemporary organic synthesis. The identification of new and structurally valuable enzyme substrates plays an important role in this process. In concert with other methods of modern catalysis that help us to further increase molecular complexity, we are aiming for the design of multicatalytic routes towards highly functionalized building blocks. Moreover, we are constantly looking to find as-yet-undiscovered applications for biocatalysts where we try to exploit a certain reactivity profile in order to catalyze non-natural transformations. Ultimately, our goal is to bring together some of those methods and utilize them in the preparation of structurally intriguing and biologically active natural products.

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

Prof. J. Deska | Thanks to some great teachers in the early stages of my undergraduate studies, I quickly realized that organic synthesis would most likely play an important role in my professional life. I was always stunned by the great and diverse structural architectures that Nature provides us with, and likewise fascinated by the vast repertoire of transformations that have been developed by chemists in order to find ways to emulate Nature and come up with man-made alternative synthetic routes. Synthesis represents a very creative discipline which makes it so appealing to me. Watching the great players in the field constructing most complex natural products, from the first dash on a plain paper to real life in the flask, is simply art on a molecular level.

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

Prof. J. Deska | There will always be challenging target structures that ask for novel strategies and the development

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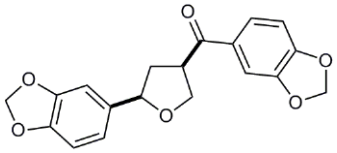
of new methodologies. However, with the tools available nowadays, I believe that the future questions posed to organic chemists will not only be whether or not one can synthesize a certain molecule but also how such a goal can be achieved. Moving into a post-fossil era, synthetic strategies might have to adapt to redesigned value chains providing sustainable solutions based on renewable biogenic sources and greener processes, with all their technological and ethical issues.

SYNFORM | *Your research group is active in the area of biocatalysis and asymmetric synthesis. Could you tell us more about your research and its aims?*

Prof. J. Deska | The use of biological catalysts has some very strong benefits when it comes to the preparation of stereochemically defined building blocks. However, for most synthetic chemists the implementation of enzymatic transformations into their synthesis planning still represents more of an *ultima ratio* rather than a natural thing to do. We are trying to expand the synthetic portfolio of enzyme catalysts in order to counterproof some common prejudices such as the often-quoted limited substrate scope of biocatalysis. Thus, one part of our research program focuses on the development of enzymatic processes for the preparation of optically active compounds bearing nonclassical stereogenic elements such as axially chiral allenes (*Angew. Chem. Int. Ed.* **2011**, *50*, 9731) and biaryls or N-stereogenic Tröger's bases (*ChemPlusChem* **2013**, DOI: 10.1002/cplu.201300295). With my background in metallo-organic chemistry, we are not limited to biological catalysts but always aim to bring those enzymatic transformations into a synthetic context by combining biocatalysis with transition-metal-catalyzed follow-up chemistry. The interplay of different catalytic processes offers great potential for the concise and efficient generation of molecular complexity. Recently, we were able to deliver a first showcase for such a multicatalytic scenario by stringing together various bio- and metal-catalyzed transformations in the total synthesis of the hyperione norlignanes (*Org. Biomol. Chem.* **2013**, *11*, 1376).



(+)-hyperione A

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

Prof. J. Deska | Having spent most of my scientific life in the field of organometallics and transition-metal catalysis, I am still in the process of learning when it comes to my self-imposed new field of interest – enzymes. So I am pretty convinced the important achievements are yet to come. Nonetheless, I have really enjoyed the first few years in Cologne where our research brought up some intriguing and encouraging results. Designing enzymatic processes with the eyes of an organic chemist, we, for example, recently succeeded with the first catalytic resolution of derivatives of Tröger's base, a molecule that has been fascinating people for more than a century. Currently, our main effort to demonstrate the synthetic power of enzymes by biocatalytically performing non-natural transformations that have so far been solely attributed to transition-metal catalysis seems to bear fruit, so I hope our work – and of course the work of others in this field – will convince more and more synthetic chemists to consider natural catalysts as a potential solution for their problems.

Matteo Zanda

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In the next issues:

SYNSTORIES

Component-Based Syntheses of Trioxacarcin A, DC-45-A1 and Structural Analogues
(Focus on an article from the current literature)

Substrate-Directable Electron-Transfer Reactions. Dramatic Rate Enhancement in the Chemoselective Reduction of Cyclic Esters Using SmI_2–H_2O: Mechanism, Scope, and Synthetic Utility
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS

Review on: Catalytic Asymmetric aza-Diels–Alder Reactions: The Povarov Cycloaddition Reaction
(by M. Fochi, L. Bernardi, L. Caruana)

SYNLETT

Account on: Flashback Forward: Reaction-Driven de novo Design of Bioactive Compounds
(by T. Rodrigues, G. Schneider)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": Total Synthesis of Indoxamycins A, C, and F

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