# Synform

People, Trends and Views in Chemical Synthesis

2018/12

## Conference Report: ISFC-22

*Articles with focus on the 22nd International Symposium on Fluorine Chemistry (ISFC-22), July 22–27, 2018, Oxford (UK)*



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# Dear Readers,

The 22nd International Symposium on Fluorine Chemistry (ISFC-22) held from July 22–27, 2018 at the University of Oxford (UK) – brilliantly organised by Prof. Véronique Gouverneur and attended by about 450 participants – is the object of this special issue of Synform. Oxford is undoubtedly a very fascinating and inspiring venue for any scientific event, so it is not surprising that ISFC-22 was a fantastic meeting, with a very rich scientific programme, that is reflected by the excellent fluorine chemistry featured in this issue. A brief overview of the ISFC-22 opens the December issue. The second article is a Young Career Focus interview with Dr. Zhong Wang (University of Southampton, UK) – from the group of Prof. B. Linclau – who was awarded the Best Poster Prize. Third is an article highlighting the photocatalytic Minisci-type difluoromethylation of heterocycles reported in an oral communication by Prof. John Nielsen (University of Copenhagen, Denmark). This special issue wraps up with the novel approach to difluoromethylated fungicides reported in an award-winning poster presented by Yosuke Ochi and colleagues from Asahi Glass Company (Japan).

Long live fluorine chemistry. And as usual...

Enjoy your reading!!

## In this issue



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# International Fluorine Chemistry in Oxford

The 22nd International Symposium on Fluorine Chemistry (ISFC-22) was held July 22–27, 2018 in some of the most magnificent venues of the University of Oxford (UK). The opening ceremony took place in the Sheldonian Theatre, while the scientific oral sessions were held in the Examination Schools, and the poster sessions were hosted by the Oxford University Museum of Natural History. The conference was superbly organized by Professors Véronique Gouverneur (Chair, University of Oxford, UK), David O'Hagan and Graham Sandford (Co-Chairs, from the University of St. Andrews and the University of Durham, UK, respectively). The symposium was attended by about 450 registered participants.

Professor David MacMillan (Princeton University, USA) gave the opening lecture, centred on the most recent results obtained by his group in the thriving area that he has pioneered, photoredox catalysis. A very rich programme of invited and plenary speakers brought the attendees up to date about the most recent advances of fluorine chemistry in a number of areas such as materials science, energy, biomedicine and drug discovery.

The prestigious Prix Henri Moissan 2018, managed by the "Fondation de la Maison de la Chimie" (Paris, France), was awarded to Professor David O'Hagan, co-chair of the Symposium. The first Poster Prize was awarded to Dr. Zhong Wang (University of Southampton, UK) who is the subject of the Young Career Focus interview in this issue.

Thieme Chemistry was obviously present with a booth showcasing all of their journals and chemical information tools.

The next main events for fluorine chemists are the ACS Spring Conference (Orlando, USA) and the European and International Symposia on Fluorine Chemistry (Warsaw, Poland, in 2019 and Québec, Canada, in 2021, respectively).

Group photo from ISFC-22

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From left to right: Professors Bruno Linclau, Graham Sandford, Véronique Gouverneur, and Matteo Zanda

# Young Career Focus: Dr. Zhong Wang (University of Southampton, UK)

**Background and Purpose.** SYNFORM regularly meets 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 Young Career Focus presents postdoctoral researcher Dr. Zhong Wang (University of Southampton, UK). Zhong Wang was recently awarded the Best Poster prize at The 22nd International Symposium on Fluorine Chemistry (ISFC-22, July 22–27, 2018) in Oxford (UK).

## Biographical Sketch

*Dr. Zhong Wang*

**Zhong Wang** was born in 1986 in Nantong (P.R. of China) and studied at Donghua University (Shanghai, P.R. of China) and Hochschule Reutlingen (Baden-Württemberg, Germany) obtaining a BSc in chemistry with marketing in 2010. He then moved to University of Southampton (UK) where he completed his MSc (2011) in the synthesis of fluorinated 5-$HT_4$R ligands and the synthesis of rigid fluorohydrins as models for the investigation of hydrogen-bond donating capacity. In 2016, he received his PhD in chemistry under the supervision of Professor Bruno Linclau. His other experience includes an internship in 2009 at Benecke-Kaliko, Hannover (Germany), conducting research on the coating systems based on NMP-free aliphatic anionic polyurethane dispersions. In 2012 he worked as a marketing supervisor at Shanghai Rainbow Chemistry (P. R. of China), mainly working on overseas market penetration and in 2015 he completed an industrial placement at Dextra Laboratories (Reading, UK) on the synthesis of fluorinated bioactive compounds. He has also attended various conferences, where he has had poster presentations and given oral presentations, and has co-authored several academic papers.

## INTERVIEW

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

**Dr. Z. Wang** Fluorine introduction is an attractive and effective strategy to modulate chemical and physicochemical properties of organic compounds. Currently, our research interest includes the investigation of the influence of fluorination on molecular lipophilicity and on hydrogen-bond donating capacity of aliphatic fluorohydrins and deoxyfluorinated carbohydrates. I am currently continuing my second postdoctoral research position on these topics in the group of Professor Bruno Linclau at University of Southampton (UK).

**SYNFORM** *When did you get interested in organofluorine chemistry?*

**Dr. Z. Wang** I already was interested in chemistry when I was in high school, and I chose chemistry and physics as optional subjects to study for national college entrance examination in P. R. of China. This was then followed by two years of studies in natural sciences in Donghua University (P. R. of China) and a further two years of training in polymer chemistry in Hochschule Reutlingen (Germany). Up until that moment, I was still a stranger to organofluorine chemistry. However, during a research project (synthesizing fluorinated serotonin 5-$HT_4$R ligands[1]) for my Master's degree at the University of Southampton (UK), I was introduced to fluorine chemistry by my supervisor Professor Linclau and was instantly amazed by fluorine's impact on molecular and biological properties. My interest in fluorine chemistry was further enhanced by our unexpected finding of the influence of fluorination on hydrogen-bond donating capacities of conformationally restricted fluorohydrins (Figure 1).[2] Since then, I have

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been exploring the surprising effects of fluorination in model compounds and in bioactive compounds.

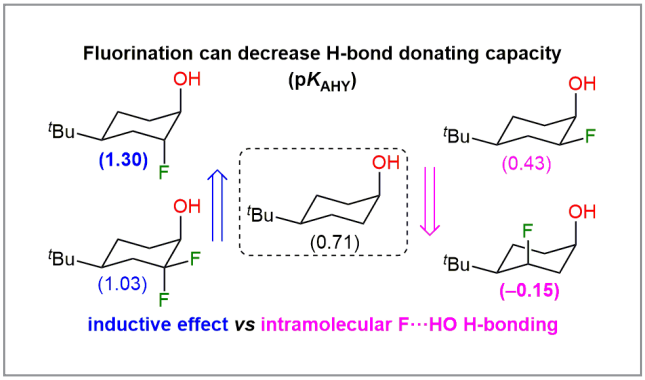


**Figure 1** Impact of fluorination on H-bond donating capacity of model compounds[2]

**SYNFORM** *What do you think about the modern role and prospects of fluorine chemistry?*

**Dr. Z. Wang** From my perspective, organofluorine chemistry is still a vibrant and thriving field. It plays an important role in chemical industry. An obvious example of its success is the application in pharmaceutical industry for drug property optimization. Fluorinated compounds also find key applications in agrochemicals, fine chemicals and materials. In addition, it is worth mentioning that $^{18}$F-labelled radiotracers are commonly used in positron emission tomography (PET) imaging for disease diagnosis and for monitoring treatment effects. During the last few decades, many new fluorinating reagents and new methodologies for the introduction of fluorine atoms and fluorinated motifs have been reported with increasing frequency. This provides even more opportunities for chemists to explore organofluorine chemistry and its applications. Therefore, I think the best era for fluorine chemistry is yet to come.

**SYNFORM** *Could you tell us more about the work that was awarded the Best Poster prize at ISFC-22?*

**Dr. Z. Wang** First of all, I would like to thank the ISFC-22 organizing committee for such an incredible conference, gathering so many great minds from the fluorine chemistry community across the globe. It was truly my honour to present our work at such a conference in Oxford (UK), and also I want to thank all the poster judges for their recognition of our work.

The work I presented in my poster regards our recent findings on the influence of deoxyfluorination on the lipophilicity (logP) of fluorinated monosaccharides and their derivatives, using a straightforward method to determine logP values based on $^{19}$F NMR spectroscopy that we have developed (Figure 2).[3] We were able to measure the lipophilicity of a wide range of fluorinated carbohydrates and their derivatives, and we identified interesting trends (comparing numbers of fluorination sites, fluorine motif, and stereochemistry) on carbohydrate lipophilicity. For the first time, we also investigated the logP differences between anomers of methyl glycosides

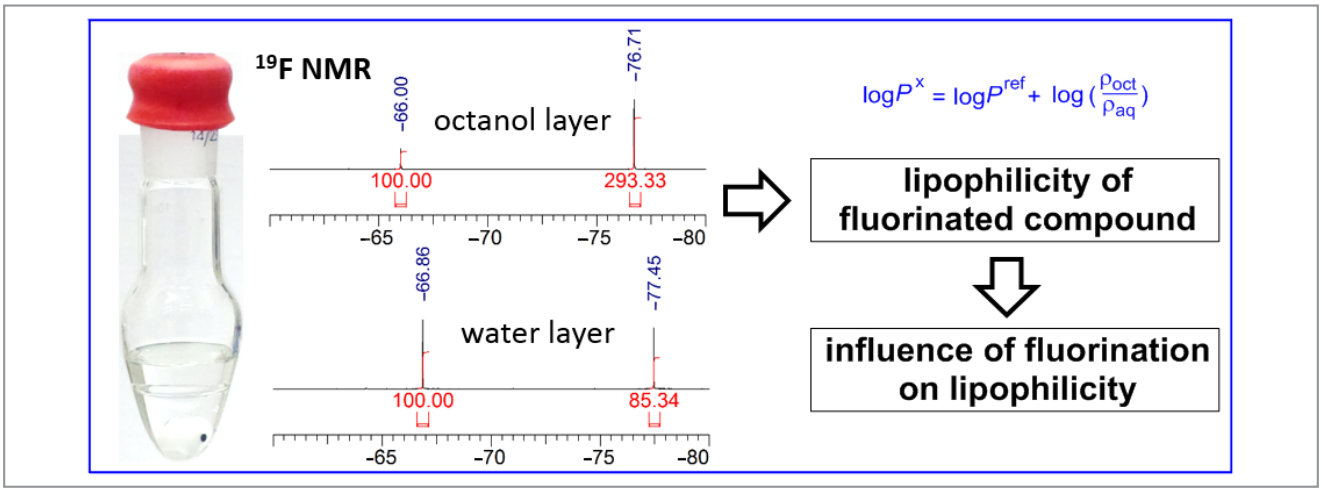


**Figure 2** Investigation of fluorination effect on lipophilicity by using a $^{19}$F NMR-based method for logP measurement.[3] Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Adapted with permission.

and glycosyl fluorides. As expected, we found that α-anomers of methyl glycosides and glycosyl fluorides are more lipophilic than their respective β-anomers. We have also been able to measure lipophilicities of equilibrating species, such as the anomers of reducing sugars. We will publish the detailed results shortly.

**SYNFORM** *What are the most important aspects of this work and why?*

**Dr. Z. Wang** Fluorinated carbohydrates have been used as probes for sugar epitope mapping, mechanism-based inhibitors and for kinetic studies of membrane transport rate in human red blood cells. However, it is difficult to properly interpret the changes in binding data without knowing the lipophilicity difference due to deoxyfluorination. Currently, there is very little information regarding the effect of deoxyfluorination on carbohydrate lipophilicity, which is cumbersome to measure due to the difficulty in quantifying concentrations of non-UV-active compounds. This is why our NMR method, which works equally as well for hydrophilic as for lipophilic compounds (within a logP ±3 range), is of interest. While carbohydrates are very hydrophilic and for this reason are perceived as of less interest in drug discovery, we show that deoxyfluorinations rapidly bring their logP to acceptable ranges: monodeoxyfluorination increases their lipophilicity by 1 logP unit, dideoxy-difluorination by 2 logP units, and dideoxy-tetrafluorination by three logP units. Interestingly, the lipophilicity difference between α- and β-anomers, including between anomers of reducing sugars, can be very large (up to ca. 1.0 logP units). The findings from this work will contribute to insights into the data interpretation of binding studies involving fluorinated carbohydrates. More broadly, together with our work on other aliphatic fluorination motifs and equilibrating species, an improved and more detailed understanding of the influence of fluorination on lipophilicity will be beneficial in general medicinal chemistry, where control of lipophilicity is one of the most important aims in the drug development process.

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(3) B. Linclau, Z. Wang, G. Compain, V. Paumelle, C. Q. Fontenelle, N. Wells, A. Weymouth-Wilson *Angew. Chem. Int. Ed.* **2016**, *55*, 674–678.

# Difluoroacetic Acid as a New Reagent for Direct C–H Difluoromethylation of Heteroaromatic Compounds – Scope, Limitations and Perspectives

*Oral Communication A-OC-13, 22nd International Symposium on Fluorine Chemistry (ISFC-22), July 22–27, 2018, Oxford, UK*

Fluorine is the 13th most abundant element in the earth's crust. In spite of this, fluorine is present in very few organic natural products. This can be rationalized by three factors: Firstly, fluorine is almost exclusively found in poorly soluble minerals like fluorspar (fluorite, $CaF_2$) and cryolite ($Na_3AlF_6$). The poor solubility prevents the presence of fluorine in aqueous biological media. Secondly, fluorine is very unstable in oxidation levels higher than –1. Other halogens are incorporated in natural products from high oxidation states. Finally, fluoride ions are highly solvated in aqueous biological media, hampering their instalment in organic natural products by substitution. Professor John Nielsen from the University of Copenhagen (Denmark) explained: "Since no fluorinated organic natural products were discovered before 1943, no drug designers or developers envisioned using this element in drugs. In the 1950s, however, it was discovered that introduction of fluorine at C-9 of hydroxycorticosterone increased hormone activity about 10 times compared to the parent hormone. A few years later, a fluorine-containing analogue of one of the DNA bases was found to be highly cytotoxic, which led to development of the prodrug 5-fluorouracil, which still remains an important chemotherapeutic drug today." These discoveries resulted in an increased number of fluorine-containing drugs, so today 20–25% of drugs contain fluorine. In agrochemicals, the number is as high as 40%. Incorporation of fluorine into drugs often improves physiochemical properties, pharmacodynamics and pharmacokinetics, and most of all increases the stability towards metabolic degradation.

"The difluoromethyl group, in addition to the above-mentioned advances, can also function as a lipophilic bioisostere of hydroxyl, amino or sulfanyl groups," explained Professor Nielsen. He continued: "A remarkable example is the replacement of the thiol group of cysteine, which has led to the design of inhibitors of the viral HCV NS3 protease. However, the principle has not yet been used in any registered drug. The introduction of the difluoromethyl moiety in drug candidates is hampered by the limited number of synthetic methods." Early methods consisted of converting aldehyde groups into difluoromethyl groups. Unfortunately, very toxic, corrosive, volatile or explosive reagents had to be used for these transformations. "An alternative procedure involved generation of difluormethyl radical, which can be used for substitution of hydrogen on heteroaromatic rings," remarked Professor Nielsen, continuing: "A commercially available reagent, zinc bisdifluoromethanesulfinate, $Zn(SO_2CF_2H)_2$ (DFMS), has been marketed. Drawbacks of this reagent are its price and the difficulty in controlling the numbers of difluoromethyl groups introduced in the molecule."

Difluoroacetic acid is an inexpensive and off-the-shelf reagent. Professor Nielsen said: "In our research (*Chem. Eur. J.* **2017**, *23*, 18125–18128), we have successfully performed the late-stage C–H mono- and bis-difluoromethylation of several pharmaceutically interesting heteroaromatic scaffolds using difluoroacetic acid. This method provides access to the hitherto untapped substituent for drug discovery. In particular, difluoroacetic acid, at low temperature (50 °C), can be used for mono-difluoromethylation of heteroaromatic rings under silver-catalyzed oxidative decarboxylation mechanism (Scheme 1)."

Professor Nielsen concluded: "An additional feature of this methodology is that by increasing the temperature, we can enable the synthesis of bis-difluoromethyl heteroaromatic compounds (Scheme 2)."

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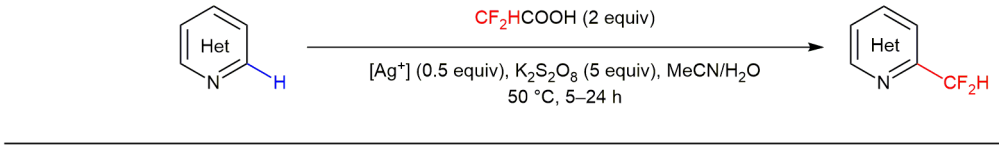
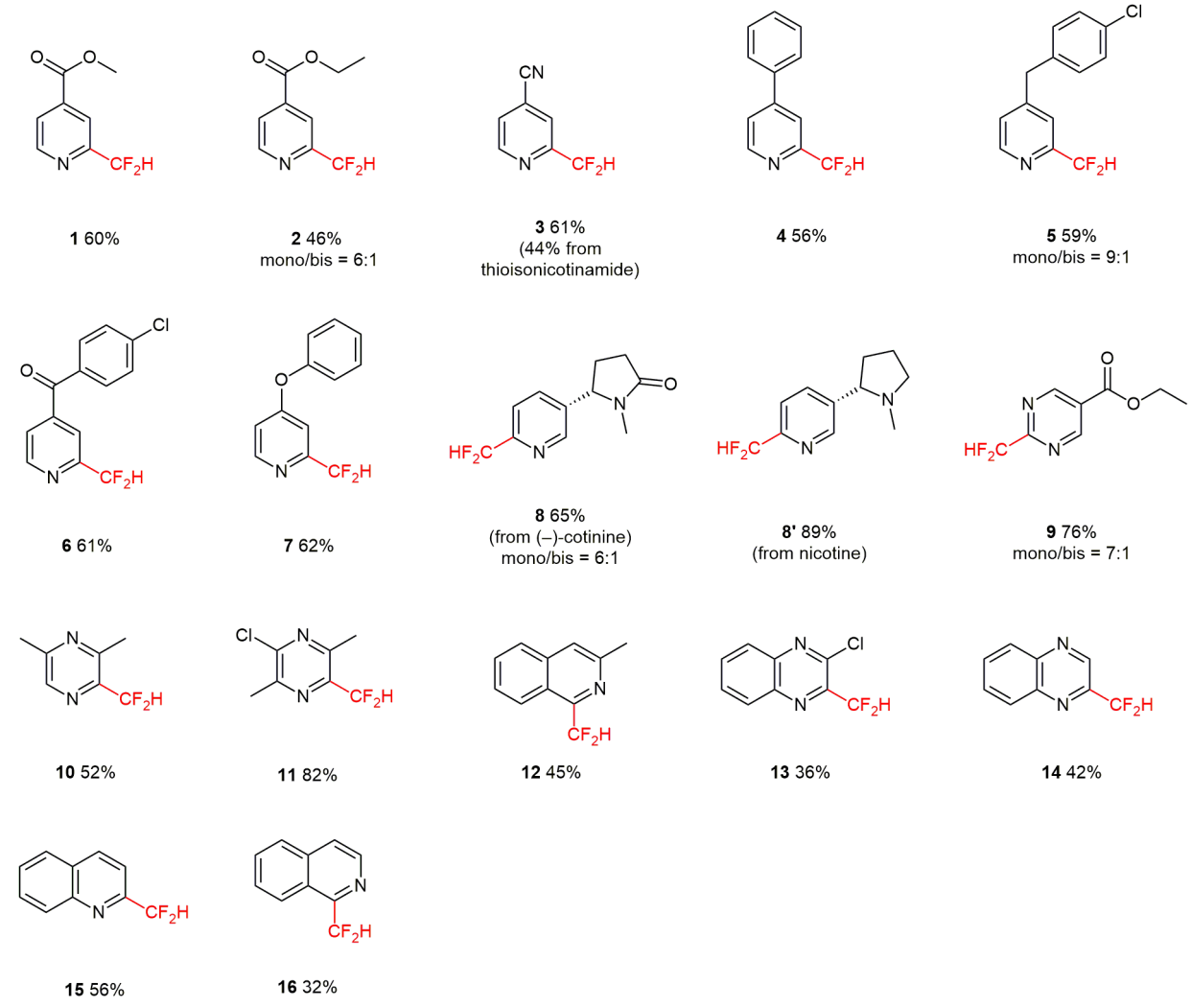
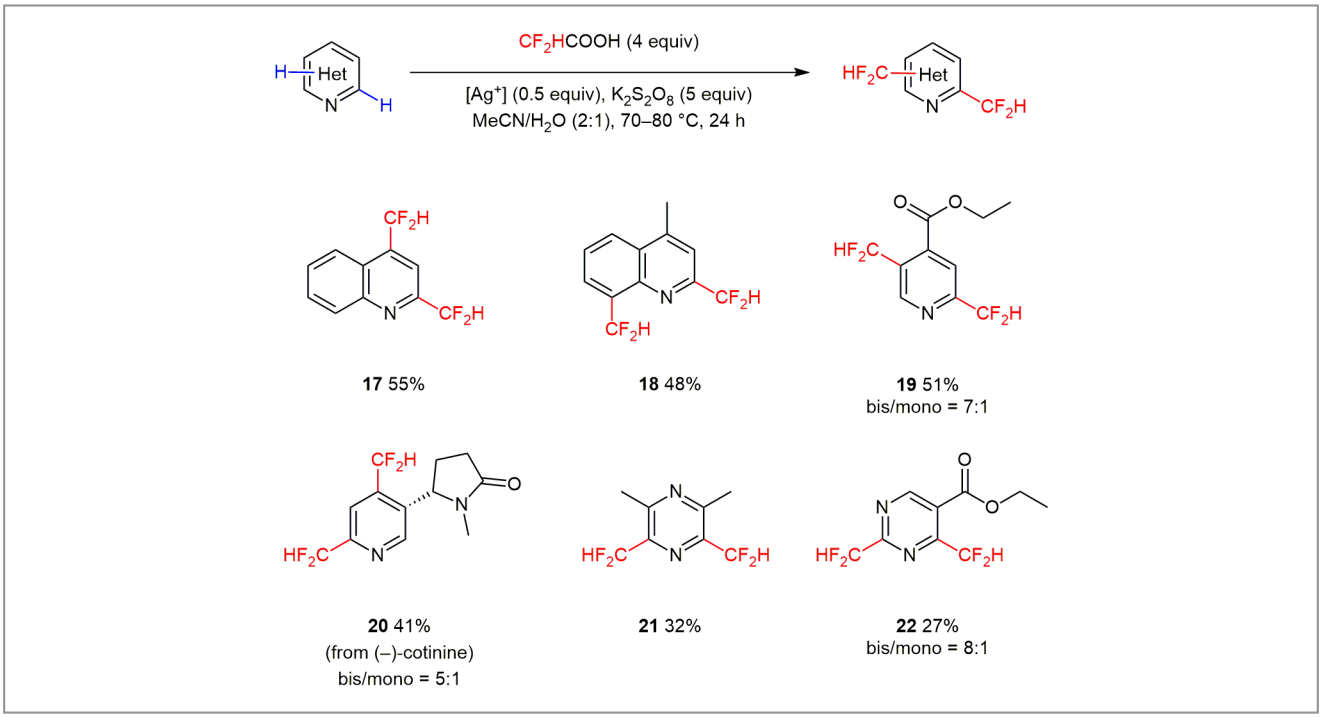



**Scheme 1** Examples of difluoromethylation of various heterocycles

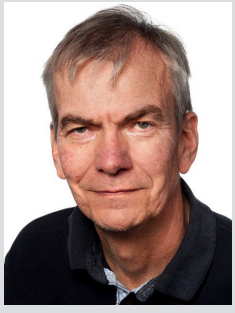



**Scheme 2** Bis-difluoromethylation

## About the authors

*Prof. J. Nielsen*

**John Nielsen** holds a Ph.D. in organic chemistry from the University of Copenhagen (Denmark) and completed postdoctoral studies with Prof. Marvin H. Caruthers at the University of Colorado at Boulder (USA). Afterward, he obtained an assistant professorship at University of Copenhagen. After a few years in a biotech company, he returned to the USA as a senior research associate at The Scripps Research Institute in La Jolla working out the encoded combinatorial chemistry with Professors Richard Lerner, Sydney Brenner and Kim Janda. He returned to Denmark as an associate professor at the Technical University of Denmark and eventually, in 2002, moved up the ranks to his current professorship in medicinal chemistry at the University of Copenhagen. He has been a visiting professor at the University of Regensburg (Germany), Stanford University (USA) and the Tokyo Institute of Technology (Japan). Moreover, he is a cofounder of three biotech/pharma startups.



*Prof. S. B. Christensen*

**Søren Brøgger Christensen** was born in Denmark in 1947. He received his M.S. and Ph.D. from the Royal Danish School of Pharmacy (Denmark), where he was employed in 1975. When the School was merged with the University of Copenhagen (Denmark), he became a professor in pharmacognosy. The main work has been in the discovery of bioactive natural products and optimization of drugability. He discovered thapsigargin, which has since become the standard tool for measuring calcium homeostasis. He was involved in the development of mipsagargin, which has been in phase 2 clinical trials. He was involved in the investigation of the antimalarial effects of licochalcone A and a cofounder of Lica Pharmaceuticals. He retired in 2016 and is now Professor Emeritus at the University of Copenhagen.

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*Dr. T. T. Tung*

**Truong Thanh Tung** earned his M.S. degree at Seoul National University (South Korea) in 2014 where he developed new Diversity-Oriented Synthesis (DOS) and Privileged Substructure-Based Diversity-Oriented Synthesis (pDOS) pathways under the guidance of Prof. Seung Bum Park. In early 2018, he received his Ph.D. from the University of Copenhagen (Denmark) where he developed a new drug design method (LEGO-inspired drug design) and discovered a new fluorination reaction under the supervision of Prof. John Nielsen and Prof. Søren B. Christensen. Tung is now finishing his first postdoctoral studies at Aarhus University (Denmark) with Prof. Alexander N. Zelikin and will soon be heading to his second postdoctoral research position at the University of Pittsburgh (USA).



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# Development of a New Route to 3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic Acid (DFPA) – A Key Building Block for Novel Fungicides

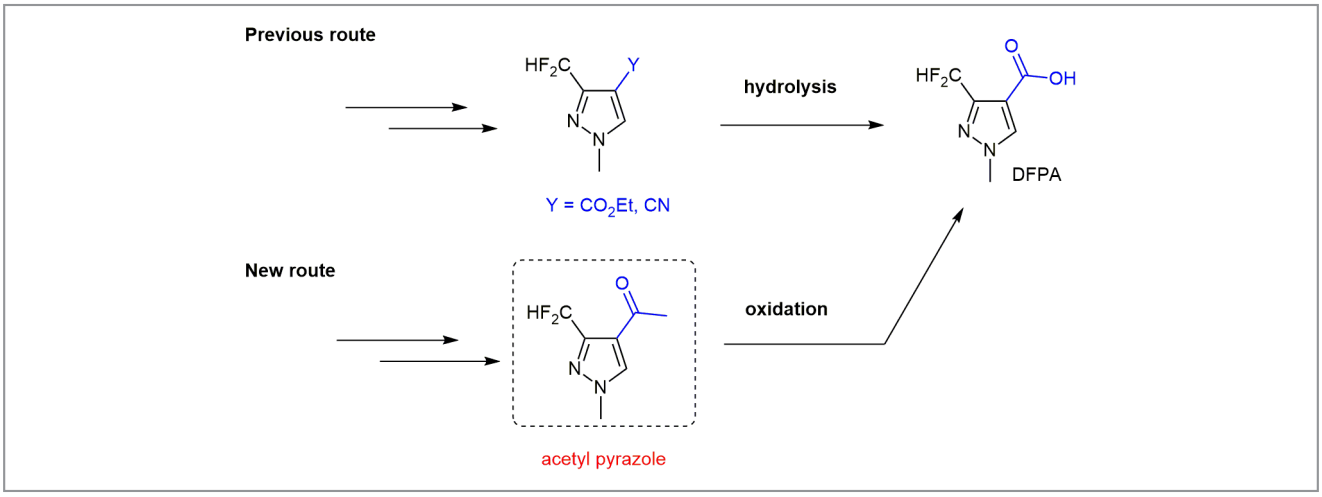
Poster #36 (Poster Award Winner), 22nd International Symposium on Fluorine Chemistry (ISFC-22), July 22–27, 2018, University of Oxford (UK)

3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (DFPA) is a key intermediate in the synthesis of succinate dehydrogenase inhibitors (SDHI), a new class of fungicides: six recently marketed compounds and four compounds currently in development have the same DFPA scaffold. Therefore, the global demand for this key intermediate is growing rapidly. For this reason, Yosuke Ochi and co-workers at the Asahi Glass Company (currently AGC Inc.) (Japan) started to develop an original route. Mr. Ochi said: "In most of the conventional routes (for a recent review, see *J. Fluorine Chem.* **2013**, *152*, 2–11), DFPA is synthesized by hydrolysis of a pyrazole ester (or nitrile), and there was no report on the preparation of DFPA from an acetyl pyrazole. Thus, we developed the new route using an acetyl pyrazole as a key intermediate of DFPA (Scheme 1)."

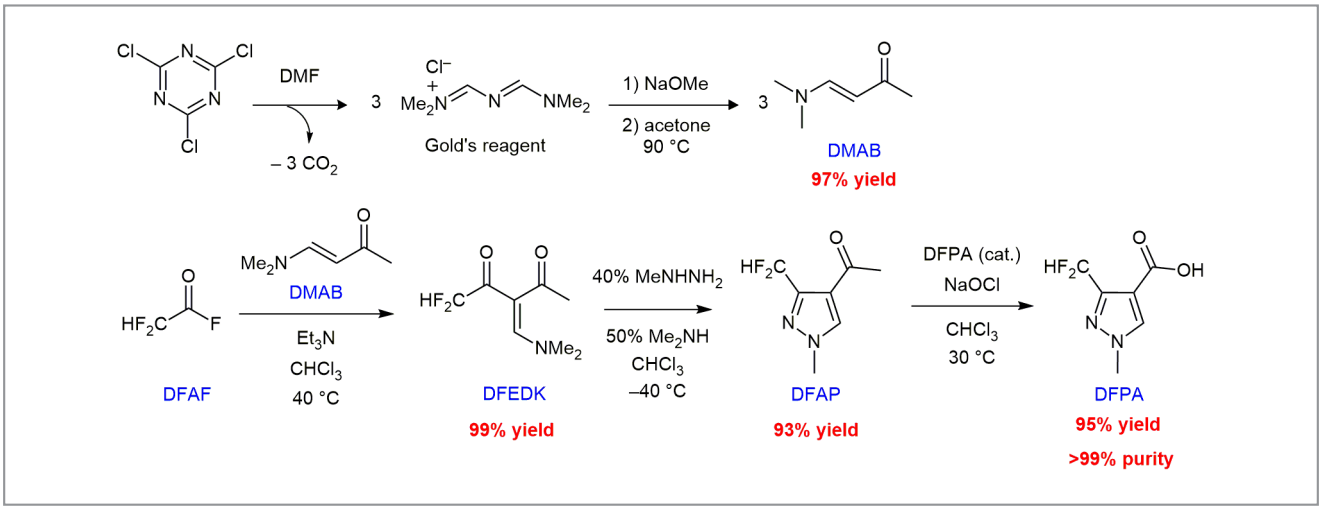
Mr. Ochi explained: "In our new route, each step of the reaction proceeds quantitatively and DFPA is obtained with very high purity. Moreover, we can utilize our in-house raw materials and technologies, such as difluoroacetyl fluoride (DFAF), chloroform, and NaOCl." The starting material, dimethylaminovinyl methyl ketone (DMAB), is prepared via a well-known method using acetone, ethyl formate, and dimethylamine. However, the group developed an alternative route to DMAB using Gold's reagent. "The new route is more cost-effective compared with the previous one (patent application WO2018074411)," remarked Mr. Ochi. He continued: "The difluoroacetylation of DMAB proceeds quantitatively using $Et_3N$ to trap HF. In the cyclization step, the addition of $Me_2NH$ controls the formation of several isomers and the trace amount of isomers generated can be removed efficiently by crystallization. The oxidation of an acetyl pyrazole with NaOCl is a very clean reaction, and DFPA is obtained in up to 99% purity. In this reaction, we use DFPA as a phase-transfer catalyst to make the reaction proceed smoothly (Scheme 2)."

This new method is practical and cost-effective for large-scale production. The group has already conducted pilot-scale production with this method.

Mr. Ochi concluded: "We would like to thank the R&D division in Chiba and Yokohama for their help in the process optimization and scale-up, and the analytical science team for identifying impurities. Finally, we are grateful to the manufacturing group in the Wakasa plant for their support during pilot-scale production."




**Scheme 1** Approaches to the preparation of DFPA




**Scheme 2** Preparation of DFPA using Gold's reagent

## About the authors

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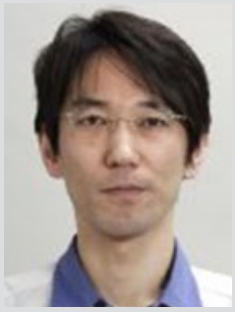
**Yosuke Ochi** was born in Hyogo, Japan in 1986. He received his Bachelor's (2009) and Master's (2011) degrees from Kyoto University (Japan) under the guidance of Professor Seijiro Matsubara. Currently, he is working at AGC Inc. (Japan). He has been engaged in the development of a manufacturing route for organic compounds in the field of specialty chemicals.



*Dr. M. Sawaguchi*

**Masanori Sawaguchi** was born in Hokkaido, Japan in 1974. He received his Bachelor's (1997) and Master's (1999) degrees, and his PhD, from Hokkaido University (Japan) under the guidance of Professor N. Yoneda in 2001. From 2000 to 2002, he worked at Hokkaido University as a JSPS Research Fellow. Currently, he is working at AGC Inc. (Japan).

*Y. Ishibashi*

**Yuichiro Ishibashi** was born in Chiba, Japan in 1977. He received his Bachelor's (2000) and Master's (2002) degrees from the University of Tokyo (Japan) under the supervision of Professor Koichi Narasaka. Currently, he is working at AGC Inc. (Japan).

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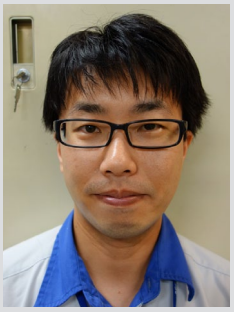

*S. Shimizu*

**Shota Shimizu** was born in Saitama, Japan in 1988. He received his Bachelor's (2012) and Master's (2014) degrees from the University of Tokyo (Japan) under the guidance of Professor Shū Kobayashi. Currently, he is working at AGC Inc. (Japan). He has been engaged in the development of a manufacturing route for organic compounds in the field of specialty chemicals.

## Coming soon

Literature Coverage

**Acceptorless Dehydrogenative Coupling Using Ammonia: Direct Synthesis of N-Heteroaromatics from Diols Catalyzed by Ruthenium**

Literature Coverage

**Approaching Sub-ppm-Level Asymmetric Organocatalysis of a Highly Challenging and Scalable Carbon–Carbon Bond-Forming Reaction**

Literature Coverage

**Exploring the Performance of Nanostructured Reagents with Organic-Group-Defined Morphology in Cross-Coupling Reaction**

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