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

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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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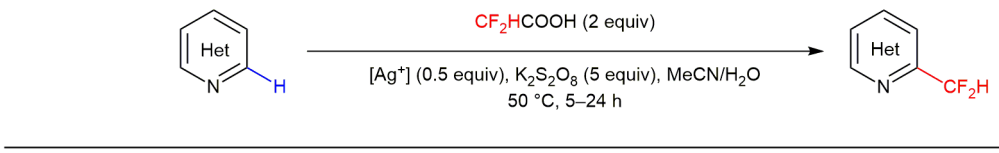
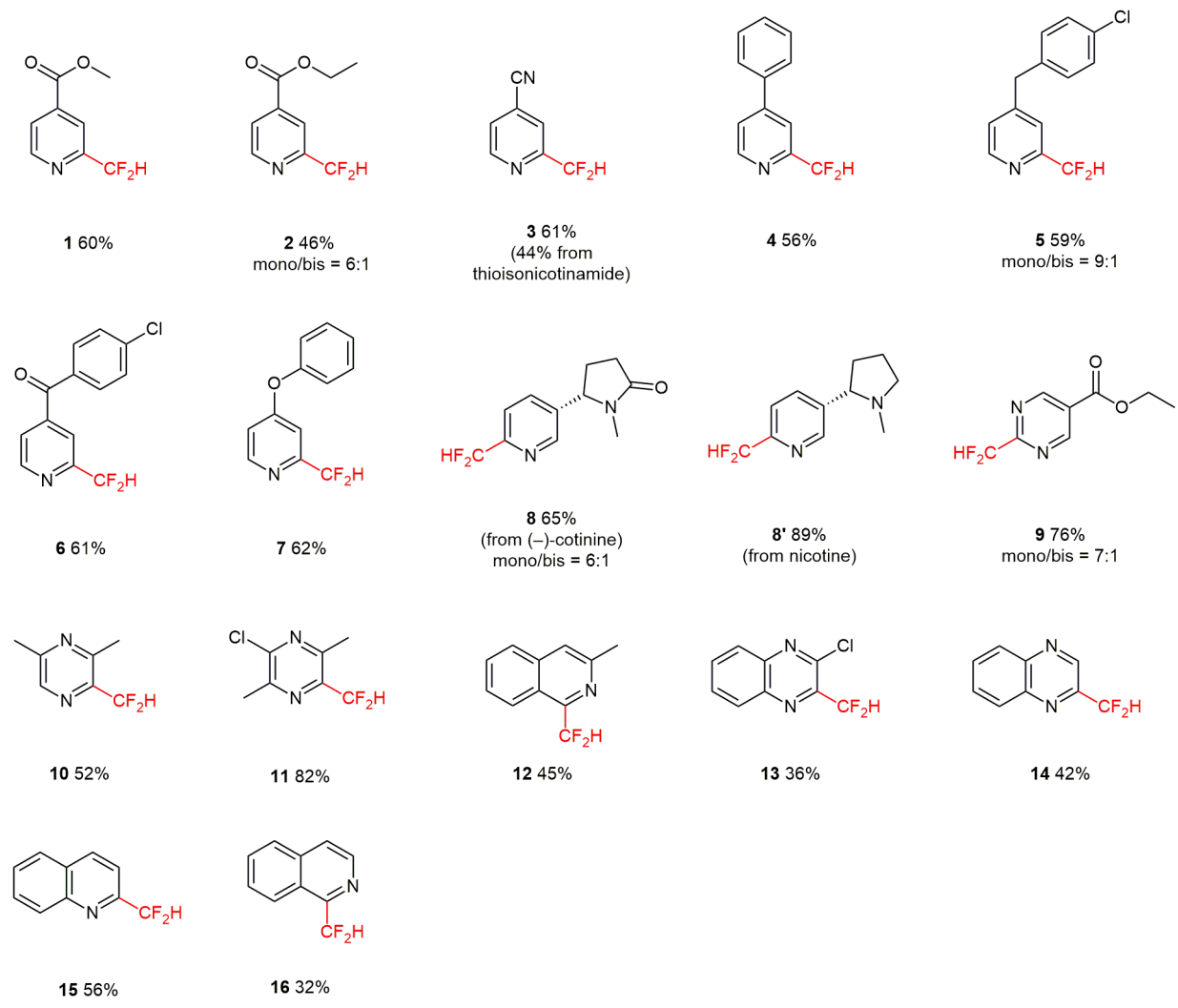
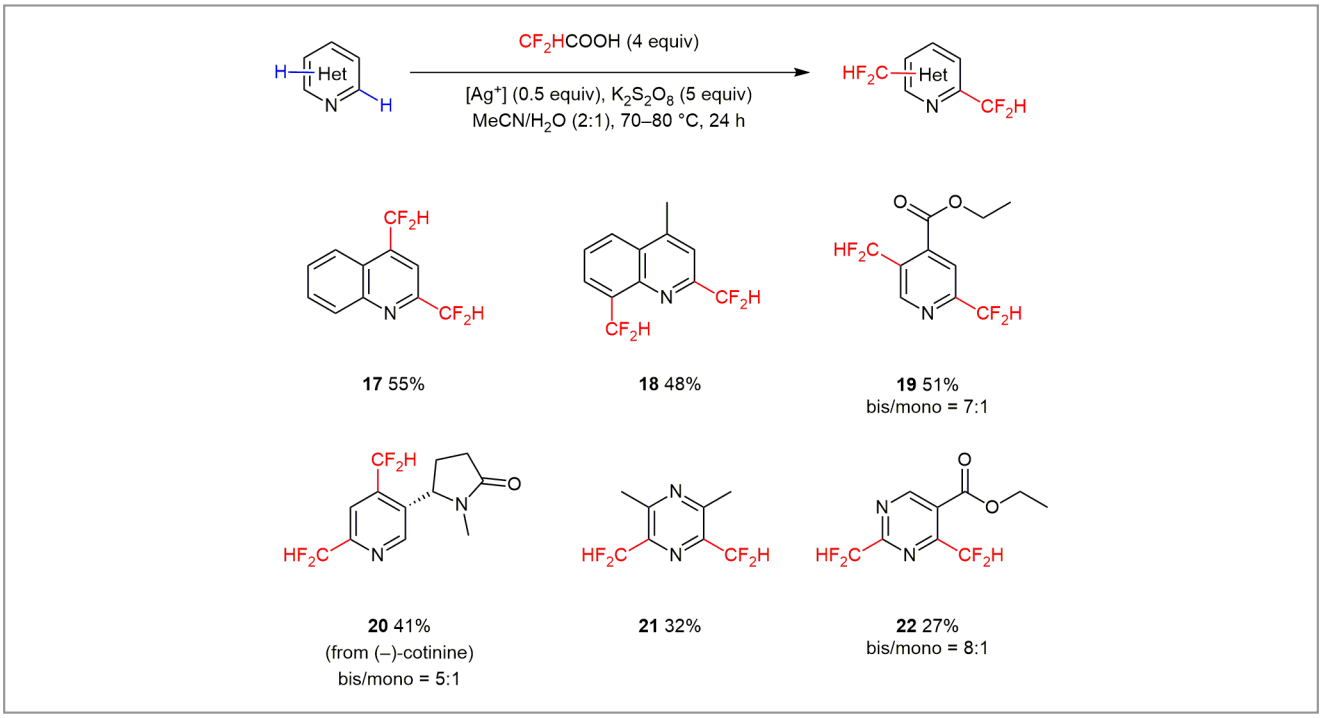




Scheme 1 Examples of difluoromethylation of various heterocycles

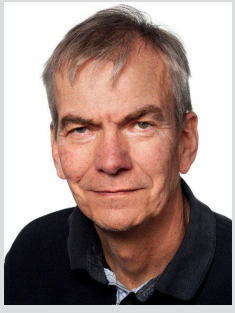


Scheme 2 Bis-difluoromethylation

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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