JOC The Journal of Organic Chemistry

pubs.acs.org/joc Editorial

Fluorine: A Very Special Element and Its Very Special Impacts on Chemistry

Cite This: J. Org. Chem. 2021, 86, 16213−16219 Read Online

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Chemists love extremes and superlatives! We will thus give special credits to the element that comes up with (1) the smallest atomic radii of all non-hydrogen and non-noble-gas elements, (2) the largest electronegativity of all open-shell atoms (4.1 in the Allred−Rochow scale), and (3) the highest reduction potential of all elements (2.87 V).[1,2] We are speaking, of course, of fluorine, an element that forms the least stable, and thus most reactive, homoatomic bond of a diatomic gas existing under normal conditions (E_{diss} = 158.78 kJ mol^{-1}).[3] The manifold effects of these properties transfer onto the compounds formed with fluorine, imparting unusual stability and incredible utility in many applications.

To provide evidence to support these claims, we present this Virtual Issue dedicated to fluorine compounds and their underlying chemistry. With selected papers from *Inorganic Chemistry*, *Organometallics*, *The Journal of Organic Chemistry*, and *Organic Letters*, this collection covers the entire spectrum of chemistry from inorganic solid-state compounds and nanomaterials to purely inorganic molecules as well as a variety of fluorinated organometallic and organic compounds with bioactive properties or applications in the creation of hybrid functional materials.

Naturally, because the reactivity of elemental fluorine is so high owing to the small atomic size (r_{atom}= 50 pm)[1] producing electronic repulsions within the F_2 molecule, most of the compounds resulting from reactions with it possess outstanding thermodynamic stability. The high tendency of fluorine to reach its noble-gas configuration in compounds makes it an ideal partner for virtually all elements of the Periodic Table—with the only exceptions being helium and neon. Although its electron affinity is smaller than that of chlorine (328 vs 349 kJ mol^{-1})[1]—again because of its small atomic size—it is comfortable with an electron octet even as an isolated anion and thus forms very stable binary salts, such as the prototypical calcium fluoride, CaF_2 (fluorite). It also appears in multinary salts as a counterion of different metal ions or as a second anion besides O^{2-}, for instance. On the other hand, the fluorine anion, F^-, can readily share its electron density, which is well reflected in its strong Lewis basicity, which, in turn, produces extremely stable adducts with Lewis acids.

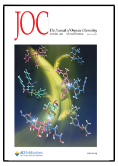
Fluorine has a relatively high abundance in the Earth's crust; at 525 ppm, it is ranked 13th among all elements and is found almost exclusively in chemically bonded forms in minerals. The only reported occurrences of elemental F_2 itself in nature are inclusions in fetid fluorite (antozonite), as a result of the radioactive decay of trace amounts of uranium salts contained in this mineral.[4] As a consequence of its frequent occurrence, fluorine has been a key element in human endeavors for nearly 500 years, and its name is the basis for designating some key properties. Hence, we will start with a brief historical flashback.

Fluorite was described as early as 1529 by Georgius Agricola, who recognized its ability to lower the melting point of solids in smelting processes.[5] He coined the element's name by defining such minerals as "fluores", from latin "fluor" = flow. Even today, fluorides (especially potassium fluoride aluminates) play an important role as fluxing agents and for the pretreatment of surfaces in the production of aluminum components. Roughly 200 years later, as of 1720, there was evidence of the use of hydrogen fluoride (HF) for glass etching. The German chemist Andreas Sigismund Marggraf in 1770 and the Swedish chemist Carl Wilhelm Scheele in 1771 described HF formation by the treatment of CaF_2 with acids.[6,7] Scheele explored the effect of HF on glass in more detail, which gave him silicon fluoride and fluorosilicic acid. He also demonstrated the fluorescent properties of CaF_2, thus laying the foundation for the term "fluorescence", which is named after this mineral.

However, it took another 100 years to finally isolate the elemental form of fluorine. This was a consequence of not only its extreme corrosiveness but also, being a strong oxidant, F_2's requirement of an electrochemical approach for isolation. This need, in turn, required a suitably conducting starting material. While pure, dry HF does not fulfill this precondition, Henri Moissan succeeded in isolating F_2 in 1886 via electrolysis of a mixture of nonconducting HF with KHF_2 as an electrolyte in a platinum vessel and platinum/iridium electrodes at −50 °C.[8] This feat earned him the Nobel Prize 20 years later.

Another particularly important fluoride mineral is fluoroapatite, $Ca_5(PO_4)_3F$. Not only is it the most common phosphate mineral, but it also is a component of tooth enamel along with hydroxyapatite, $Ca_5(PO_3)_3(OH)$, bridging the inorganic and (bio)organic significance of fluorine in Nature. Regarding the latter, however, there are relatively few natural fluorinated organic compounds, only about a dozen.[9,10] The inherent stability of fluorine minerals and organofluorine compounds renders them challenging for even Nature to manipulate.

Published: November 22, 2021



https://doi.org/10.1021/acs.joc.1c02745

In the 20th century, chlorofluorocarbon compounds (CFCs), such as CCl_2F_2, were used extensively in refrigerators and as blowing agents because of their inertness and low toxicity. However, once their atmospheric-damaging effect was realized, they were banned.[11] A second product that has played a major, yet problematic, role was and is uranium hexafluoride, UF_6. Its production was originally driven by the need for uranium enrichment for nuclear weapons, during the Manhattan project, for example. UF_6 is the only volatile and at the same time stable uranium compound under ambient conditions, so it could be used in isotope separation by gas centrifuges. Depleted UF_6 waste is still stored by the ton, in tens of thousands of drums, some of which are in questionable condition because of the corrosive nature of the compound. Ironically, these activities have ignited branches of fluorine chemistry because of the need for materials that would not corrode, such as nickel membranes, liquid fluorocarbons for cooling and as lubricants, and fluoropolymers as sealing materials.

A third prominent fluorine compound that stemmed from the first half of the 20th century is polytetrafluoroethylene, commonly known as Teflon. This synthetic fluoropolymer was accidentally discovered in 1938 by DuPont's Roy J. Plunkett during his search for a new chlorofluorocarbon refrigerant. He recognized it as an inner coating on a gas bottle when he cut open the cylinder to determine why gas flow had ceased. Plunkett unwittingly used the iron interior of the gas cylinder as a catalyst for the polymerization reaction.[12]

Clearly, fluorine chemistry and fluorine chemicals are much more than the above. As a result of its reactivity toward nearly all other elements and the numerous ways to incorporate fluorine atoms into organic compounds, the element plays an exceptional role in many areas of chemistry, technology, industry, life sciences, and modern daily life. Fluoroorganic compounds are increasingly used as pharmaceuticals or blood substitutes, as biocides, anticorrosives, or paints, and as liquid crystals, surfactants, or ionic liquids. Fluorinated polymers exhibit the highest thermal stabilities; for example, sulfonated tetrafluoroethylene ionomers, such as Nafion,[13] are used in electrochemical devices, chlorine-free fluoroorganic compounds are modern replacements for CFCs, and a range of compounds with fluorocarbon chains are used as antistick and water-repellent coatings. However, despite the utility of many organofluorine compounds, their persistence in the environment and links to negative health effects in humans and animals raise a concern for how they should be used.

Concerns about potential hazards also apply to inorganic fluorides, which are (or have been) equally meaningful in terms of technical applications. Nontoxic SF_6 is still needed and employed for high voltage and power engineering owing to its outstanding inertness and isolation properties, although it is excluded from other uses because of its strong greenhouse gas effect.[14] Similar considerations apply to the use of highly corrosive and harmful HF, which is still indispensable for the production of semiconductor chips. One should also not forget the use of liquid HF or the "superacid" mixtures of HF or HSO_3F with SbF_5 as reaction media to produce otherwise inaccessible compounds, albeit of mostly academic value.[15] Electrochemical energy storage currently relys on graphite fluoride and on electrolytes comprising $[BF_4]^-$ or $[PF_6]^-$ anions, and many solid fluorine compounds are investigated and developed as innovative materials for their outstanding optoelectronic, magnetic, or catalytic properties. Last, fluorine as a mononuclidic element, with ^{19}F as its only isotope comprising a nuclear spin of $^1/_2$, plays an important role in NMR spectroscopy, and the artificial ^{18}F isotope is used in positron emission tomography.[16]

To highlight the significance of fluorine chemistry, this Virtual Issue showcases a cross section of the literature published in *Inorganic Chemistry*, *Organometallics*, *The Journal of Organic Chemistry*, and *Organic Letters* in this context since 2019. Of course, we were not able to include all of the approximately 600 papers in these journals that address fluorine chemistry during this period. Therefore, this collection is by no means comprehensive and does not cover all recent advances in the field. However, we have selected examples from the most important areas to encourage further reading.[17] In the following, we mention some of the most innovative features among the papers from our collection.

Purely inorganic fluorine compounds, those in which C−F bonds are absent or play no major role, are found with crystalline, glassy, or nanostructured morphology, in the liquid state (or solution), or in the gas phase. The fluorine atom in them causes or amplifies their chemical or physical properties in many different regards, as outlined in selected papers from *Inorganic Chemistry*

Some of the recent work on fluorides is connected with a basic question regarding superacidity versus hypercoordination or the stabilization of low-valent compounds, as well as the strength (or weakness) of OH···F bonding. Such questions are discussed, for example, in the paper by Gillian Reid and coauthors on phosphine and arsine complexes of PF_5 (DOI: 10.1021/acs.inorgchem.9b03630), in the report on the behavior of disilenes toward fluoride by Judith Baumgartner, Christoph Marschner, and coauthors (DOI: 10.1021/acs.inorgchem.9b02223), and in the work by Steven H. Strauss and coauthors describing their spectroscopic investigations of the interactions between hydrated metal ions and weakly coordinating fluoroanions (DOI: 10.1021/acs.inorgchem.9b02646).

Another fundamental area of synthetic fluorine chemistry is the use of fluorides in or as the reaction medium. While reactions in liquid HF are well-known, they still require a specific expertise and great care in handling, so they are still far beyond standard synthesis methods. A mixture of SO_2 with AsF_5 and CH_3F also requires special handling. It serves not only as a reaction medium but also as a strong methylating agent, which is shown by the formation of $[W(CNMe)_8][AsF_6]_4$ from $[NBu_4]_4[W(CN)_8]$ under supercritical conditions in the paper by Moritz Malischewski and coauthors (DOI: 10.1021/acs.inorgchem.1c00326).

Ionic liquids are a significantly more benign alternative reaction medium and often incorporate weakly coordinating fluorido anions, such as BF_4^- or PF_6^-; as solvents, they provide a low-temperature pathway to compounds that are otherwise difficult to synthesize or even inaccessible,[18,19] although issues regarding their toxicity need to be kept in mind.[20] Examples for corresponding syntheses are found in the paper by Anja-Verena Mudring and coauthors (DOI: 10.1021/acs.inorgchem.9b02028). Famous examples of even more weakly coordinating anions include perfluorinated alkyl- or arylborates of alkoxyaluminate anions, $[B(CF_3)_4]^-$, $[B(C_6F_5)_4]^-$, or $[Al[OC(CF_3)_3]_4]^-$, in which one single negative charge is distributed over 12, 20, or even 36 fluorine atoms.[21]

Other compounds with high coordination numbers include actinide fluorido complexes, the bonding properties of which are barely understood. Hence, fundamental investigations were carried out on Li_4PuF_8 by the group of Thomas E. Albrecht-Schmitt (DOI: 10.1021/acs.inorgchem.9b02466). Another actinide complex demonstrating the potential of fluoride ion

https://doi.org/10.1021/acs.joc.1c02745
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coordination for switching intramolecular conformations is a diuranyl bis(salophen) macrocycle reported by Massimo Cametti and coauthors (DOI: 10.1021/acs.inorgchem.9b02587). In another work on ligand effects, comprehensive quantum chemical studies done by Julian D. Rolfes, Maurice van Gastel, and Frank Neese serve to rule out the existence of a "fluoro wall", in contrast to the "oxo wall", which indicates the instability of six-coordinate tetragonal oxo complexes beyond Group 8 (DOI: 10.1021/acs.inorgchem.9b03474).

The optical and magnetic properties of compounds can be influenced by the presence of fluorine atoms in many ways. Luminescence can be changed by fluorination of the organic ligands of platinum complexes, as reported by Yu-Wu Zhong and coauthors (DOI: 10.1021/acs.inorgchem.0c00887). Chinna Ayya Swamy P, Pakkirisamy Thilagar, and coauthors, in turn, report how the luminescence of the famous BF_2-based BODIPY unit is affected by its chemical environment (DOI: 10.1021/acs.inorgchem.0c02739). Many fluoridic solids are also classified as phosphors—either as pure compounds, like the red phosphor Cs_2MnF_6 described by Xinyu Ye and coauthors (DOI: 10.1021/acs.inorgchem.9b02140), or upon doping with transition-metal ions. Moreover, by the introduction of fluoridic layers in solid-state structures, it is possible to engineer the band gap. In $BaF_2TeF_2(OH)_2$, for instance, UV-transparent $[BaF_2]$ layers alternate with $[TeF_2(OH)_2]$ layers to form a polar pseudo-Aurivillius structure, thereby exhibiting a balance between a wide band gap, a large second-harmonic generation response, and a suitable birefringence for solar-cell design.[22] The fluoride effect on magnetic properties can be observed for networks in which fluoride atoms directly bridge the spin centers, such as those reported by Lucy Clark and coauthors for $KFe(C_2O_4)F$ (DOI: 10.1021/acs.inorgchem.9b00571). Alternatively, organic donor ligands can be modified by the introduction of fluoride substituents, as shown for dysprosium complexes by Bing Yin, Dongfeng Li, and coauthors (DOI: 10.1021/acs.inorgchem.0c01716).

Both metal−organic frameworks (MOFs) with fluorinated organic linkers and neat fluoridic solids are investigated for their enhanced stability and storage properties. Functionalized linkers can serve to amplify the selectivity for alkyne adsorption relative to alkene adsorption, as reported by Qing-Yan Liu, Yu-Ling Wang, and coauthors (DOI: 10.1021/acs.inorgchem.0c00003). On another front, the group of Maria A. Kirsanova (DOI: 10.1021/acs.inorgchem.0c01961) showed that α-Na_2FePO_4F has features of a cathode material for Na^+ batteries.

Additional important aspects of fluoride chemistry are found in the context of catalysis, mostly with fluorine being part of the organic substrate but also for fluoride-containing inorganic compounds as catalysts. For instance, doping of SnO_2 nanosheets or mesoporous TiO_2 with fluoride ions boosts the electrocatalytic activity of the former, as reported in the paper by Ke Chu and coauthors (DOI: 10.1021/acs.inorgchem.9b01823), or the photocatalytic performance of the latter, as described in the paper by Chunyao Niu, Xiao Li Zhang, Rachel A. Caruso, and coauthors (DOI: 10.1021/acs.inorgchem.0c02869).

We also note that many simple binary fluorides still remain unknown or unexplored. Hence, the formation of mixed-valent solids Mn_2F_5 and Mn_3F_8 via a high-pressure/high-temperature approach and the assignment of oxidation states by means of structural considerations, CHARDI calculations, and quantum-chemical calculations by Florian Kraus and coauthors add to our collection (DOI: 10.1021/acs.inorgchem.1c01833).

The field of organometallic chemistry exploits the unique and often challenging reactivity of fluorine to realize advances in mechanistic understanding as well as to use improved syntheses to advantage in the preparation of reactive organometallic complexes poised for chemical transformations. Alternatively, fluorine can be strategically incorporated into auxiliary ligands to modulate the electronic properties of those organometallic complexes. Organometallic chemistry is also important to the field of homogeneous catalysis for the generation of fluorinated materials and organic synthetic target compounds, where unexpected C−F bond activations can result in new synthetic strategies. The papers selected from *Organometallics* delve into these topics.

Michael Whittlesey and co-workers show that diverse carbene ligands for reactive Cu−F complexes result in tunable aldehyde allylation chemistry, with concomitant Si−F side product formation (DOI: 10.1021/acs.organomet.9b00772). In related work, Richard Jordan and team show how a Pd−F precursor undergoes alkene migratory insertion to retain the fluorine in the resultant organometallic product (DOI: 10.1021/acs.organomet.9b00545). In other cases, a dative Na−F interaction, as shown by Marta Mosquera, Jesús Cano, and co-workers, is key to realizing solvent-dependent nucleophilic aromatic substitution (DOI: 10.1021/acs.organomet.8b00868).

When it comes to ligand design, fluorine has been strategically incorporated to modify the electronic properties and hence reactivity at the metal center. The ligand effects induced by fluorine cannot be readily predicted based on inductive effects alone; Noël Lugan, Vincent César, and Dmitry Valyaev show that a fluorinated carbene ($IMes^{F_2}$) is more electron-donating than its chlorinated analogue (DOI: 10.1021/acs.organomet.9b00151). Such electronic perturbations can be used as a design parameter, for example, to modify the acidity of a phenol-substituted bipyridyl manganese complex. Sheri Lense and co-workers show how this, in turn, shifts product distributions of H_2/CO in CO_2-reduction chemistry (DOI: 10.1021/acs.organomet.9b00230). The role of fluorine in a ligand may also extend beyond electronic effects and include base stabilization of metal centers. In one case, a sensitive ruthenium catalyst for cross metathesis, with a Ru−F interaction, characterized by the team of Won-Jin Chung and Sukwon Hong, has high ethanolysis reactivity with a fatty acid ester (DOI: 10.1021/acs.organomet.9b00469). Such metal−fluorine direct interactions can result in ligand modification by C−F bond activation and fluorine transfer to an electrophile, as shown in the collaboration of Graham Saunders, Andrew Marr, and Peter License (DOI: 10.1021/acs.organomet.0c00176).

Contributions to *Organometallics* provide critical insight into understanding elementary steps in catalytic or stoichiometric sequences, and monitoring the reactivity of elementary reactions often requires the preparation and isolation of reactive intermediates. Ryan King in the laboratory of Stephen Buchwald developed a route to access an air- and moisture-stable acetonitrile adduct of Pd−CF_3 as a general precursor for exploring elementary steps in catalytic trifluoromethylation sequences (DOI: 10.1021/acs.organomet.9b00516). An example of such investigations relevant to catalytic cycles includes ligand effects in aryl carbonylative trifluoromethylation (DOI: 10.1021/acs.organomet.9b00849), as completed by the team of Troels Skrydstrup. Expanding the investigation of elementary steps to include nickel catalysis inspired an evaluation of the oxidatively induced aryl−CF_3 coupling step by the group of Melanie Sanford (DOI: 10.1021/acs.organomet.9b00678). Such insightful foundational work into these elementary steps provides critical insight for developing new and/or improved catalytic transformations.

Alternatively, density functional theory mechanistic investigations provide key details into how reactions can proceed and have been used to advantage for reactions involving reactive fluorinated intermediates. For example, computational approaches by Bruno Amèduri and Rinaldo Poli reveal an α-F elimination route that is thermally accessible in Mn-CF_3 species (DOI: 10.1021/acs.organomet.8b00721). In addition, Pėter Pál Fehėr and András Stirling completed a theoretical study of the nickel-catalyzed decarbonylation of acyl fluorides (DOI: 10.1021/acs.organomet.0c00387) to complement recent advances in modified Suzuki−Miyarua coupling methods.

Such insights can then be leveraged to realize synthetic advances in the preparation of organofluorine products. For example, Yohei Ogiwara and Norio Sakai have developed a palladium-catalyzed route for the preparation of acyl fluorides from anhydrides using commercially available benzoyl fluoride as the fluorine source (DOI: 10.1021/acs.organomet.0c00028). In another example, fluorosulfonylvinylation of arenes has been achieved by Gqwetha Ncube and Malcolm P. Huestis using a Cp*Rh^{III} catalyst (DOI: 10.1021/acs.organomet.8b00327). The development of flexible catalytic routes to access organofluorine compounds efficiently is an important challenge in synthesis.

Many important reactions and synthesis developments address the activation or formation of the C−F bond itself or, alternatively, exploit prepositioned C−F bonds in reactants. This latter strategy is gaining in prominence, with difluoro- and trifluoromethylation becoming more important. A parallel thrust is represented in the physical organic chemistry of fluorine: the properties of new fluorinated species, unusual bonding arrangements, fluorine as a hydrogen-bond acceptor, nonbonding interactions of fluorine with other atoms, and the inevitable consequences to mechanisms. The bioorganic chemistry of fluorine is a salient example of the primacy of a fascinating spectrum of nonbonding interactions between fluorine atoms and other functional groups in complex biomolecules that have evolved from simplistic concepts of "hydrophobic effects". On all of these fronts, the synthesis of organofluorine compounds has benefitted tremendously in recent years by the evolution of fluorinating reagents, from stoichiometric methods involving traditional reagents F_2 gas, HF, SF_4, and hard-to-handle derivatives to catalytic methods that employ new generations of mild, commercially available reagents. The two outlined synthesis and physical thrusts as outlined in *The Journal of Organic Chemistry* work in concert in such diverse areas as catalysis (catalytic organofluorination, including asymmetric variants) and the chemistry of bioactive compounds for pharmaceuticals and agricultural chemicals (the substitution of hydrogen by fluorine has become a staple of drug discovery).

In the realm of C−F bond formation, Cynthia Hong, Aaron Whittaker, and Danielle Schultz published a new approach to the "halex" reaction that exploits the cooperative catalytic action of 18-crown-6 ether and tetramethylammonium chloride to enable the use of tetramethylammonium fluoride. This combination permits aryl fluorinations under mild conditions and with straightforward separation (DOI: 10.1021/acs.joc.0c02845). This new method readily converts heteroaryl chlorides and aryl triflates to their corresponding (hetero)aryl fluorides in high yields and purity. In synthetic chemistry, intact C−F bonds can be incorporated from starting materials; for example, Mang Wang and coauthors report a trifluoromethylation of alkenes, employing $PhICF_3Cl$ as a bifunctional reagent (DOI: 10.1021/acs.joc.9b01901). The chemoselectivity of the reaction is dependent on the nature of the alkene substrate. Nonconjugated alkenes afford chlorotrifluoromethylated products, whereas vinyl C−H trifluoromethylated products were obtained by the formal elimination of hydrogen chloride in conjugated alkene substrates. The wide scope of the reaction indicates the potential for use in late-stage tranformations in drug discovery.

Along similar lines, Jianbo Wang and co-workers recently reported a cycloaddition of difluoroketenimine with alkenes or alkynes (DOI: 10.1021/acs.joc.0c01120). Difluoroketenimine is generated from the reaction of *tert*-butyl isocyanide and difluorocarbene; the ketenimine is thus formed in situ in the presence of alkenes or alkynes to afford fluorinated pyrrolidines or pyrroles. In yet another eexample, Jingyu Zhang, Yingsheng Zhao, and coauthors achieved a meta-selective difluoromethylation of phenol derivatives using ruthenium as a catalyst and pyrimidine as the directing group (DOI: 10.1021/acs.joc.0c01909). This synthetic scheme provides an efficient method for the syntheses of fluorine-containing phenols.

In work that bridges the gap between synthesis and mechanism, Yan Liu and co-workers report a study of a new Lewis/Bronsted acid activation process to augment the generally accepted "double-activation" mode (DOI: 10.1021/acs.joc.8b02741). Different from the generally proposed iodine(III)iranium S_N2 mechanism, the hypervalent difluoroiodoarene-promoted fluorocyclization of unsaturated alcohols undergoes the key metathesis steps through an iodine(III)-π intermediate. The importance of this discovery lies in the critical role that activation plays in hypervalent iodine reagent-mediated reactions. In a similar vein, Olesya V. Khoroshilova, Aleksander V. Vasilyev, and coauthors found a way to employ Brønsted superacids (CF_3SO_3H and FSO_3H) to generate short-lived and reactive trifluoroalkyl-thiophenyl carbocations (DOI: 10.1021/acs.joc.0c00170). The cations react with (hetero)aromatic π-nucleophiles in various ways, depending on the structure as well as reaction temperature and time, leading to the formation of novel, more complex fluorinated thiophenes. Another notable interdisciplinary study reports a stereochemical milestone. Christian Roussel, Osamu Kitagawa, and coauthors synthesized several configurationally stable ortho-fluorinated *N*-aryl atropisomers. Notably, even a small fluoro group can enforce configurational stability when the steric demand of the flanking substituents is sufficient (DOI: 10.1021/acs.joc.8b03043).

In the realm of medicinal chemistry, wherein fluorinated carbohydrates are of ever-increasing interest, Denis Giguère and coauthors have developed syntheses of novel trifluorinated glucopyranose analogues employing levoglucosan as a starting material and a microwave glycosylation method as a key step (DOI: 10.1021/acs.joc.9b00795). In an interesting forensic medicinal chemistry angle, "designer" benzodiazepines have recently appeared in forensic cases as legal alternatives to federally scheduled drugs such as diazepam (Valium) and alprazolam (Xanax). Although current forensic techniques are often sufficient for identifying novel psychoactive substances, they may not easily differentiate between positional isomers. In a new study, Daniel V. Reinhardt, Stefan France, and coauthors synthesized and characterized flubromazepam, which is a recognized designer benzodiazepine that entered the marketplace in 2012 and without FDA approval has an uncertain legal status within the United States (DOI: 10.1021/acs.joc.9b01433). A practical synthetic scheme was developed to prepare purified reference materials for each positional isomer of flubromazepam in which bromine and fluorine substituents were varied. Medicinal chemistry, mechanism, and synthesis all come into play in work by Pavel K. Mykhailiuk and coauthors, who devised an efficient synthetic approach to difluoro-substituted bicyclo[1.1.1]pentanes (DOI: 10.1021/acs.joc.9b01947). Their key step is an addition of difluorocarbene (:CF_2) to electron-rich bicyclo[1.1.0]butanes. The resultant difluorobicyclo[1.1.1]-pentanes have potential as saturated bioisosteres of benzene rings for drug discovery projects.

Under the aegis of the physical organic chemistry of organofluorine compounds, perfluorination of keto−enol systems has long been known to shift the equilibrium toward the enol tautomer. Ronald Raines, Kendall Houk, and coauthors have now performed quantum mechanical calculations that reveal that the equilibrium shift is a consequence of the stabilization of the enol tautomer by hyperconjugative $\pi \rightarrow \sigma^*$CF interactions and the destabilization of the keto tautomer by the electron withdrawal induced by the neighboring fluorine atoms (DOI: 10.1021/acs.joc.9b00825). In an interesting observation, this classical fluorination effect apparently overrides the effect of the ring size that controls the equilibrium in nonfluorinated compounds.

On a different topic, Josefredo R. Pliego and coauthors published a study on the activation of potassium fluoride for nucleophilic fluorination of alkyl halides (DOI: 10.1021/acs.joc.0c02229). The problem is challenging because of the high lattice energy of the salt contributing to its low solubility in many polar aprotic solvents. In this work, theoretical methods were employed to design a cooperative combination of bulky diols with crown ethers. The calculations indicate that the bulky diol 1,4-bis(2-hydroxy-2-propyl)benzene is able to catalyze nucleophilic fluorination in combination with 18-crown-6 via two hydrogen bonds to the S_N2 transition state. In contrasting work in which fluoride is sequestered rather than liberated, Bradley Smith and coauthors synthesized a neutral tetralactam macrocycle in one pot and at high concentration using commercially available starting materials. The lactam shows a remarkable affinity for fluoride-ion binding (DOI: 10.1021/acs.joc.9b00042). NMR titration studies in dimethyl sulfoxide revealed an anion affinity order of $F^- > AcO^- > Cl^- > Br^-$. The receptor affinity for F^- is high because of the formation of a self-complementary dimer comprised of two "saddle-shaped" complexes. Experiments showed that the stabilization of F^- as a supramolecular complex curtailed its ability to participate in elimination and substitution chemistry. Practical applications include the idea of using tetralactam macrocycles to stabilize fluoride-containing liquid electrolytes within redox devices such as room-temperature fluoride-ion batteries.

In a purely physical organic study, Thomas Lectka and coauthors have investigated hydrogen bonding between the amide N−H and a C−F bond in peri-substituted naphthalenes (DOI: 10.1021/acs.joc.0c00553). Of special note is the ability of C−F···H−N interactions to influence such diverse qualities as bifurcation, crystal packing, and π-stacking, all of which have relevance for biomolecular chemistry.

The collection of fluorine chemistry papers from *Organic Letters* is the most extensive of all four journals. Correspondingly, selecting 15 of them for this Virtual Issue was no easy task. Thus, while the chosen ones reflect a remarkable breadth of methods, reactions, catalysts, and reaction conditions that make them so typical for modern dynamic organic chemistry, they have also been chosen because they have already shown to be impactful, as judged by the number of online views and citations.

The photocatalytic activation of SF_6, a compound recognized as being otherwise very stable and kinetically inert, has been used by Pavel Nagorny and co-workers in the synthesis of glycosyl fluorides. The anomeric hydroxyl group of a series of otherwise protected carbohydrates is thereby smoothly replaced by a fluorine atom (DOI: 10.1021/acs.orglett.0c03915). Hypervalent iodine reagents have also played a significant role in organofluorine chemistry in recent years, and it is not surprising that such polyvalent reagents continue to inspire researchers around the world. The enantioselective difluorination of cinnamamides catalyzed by a chiral enantiopure iodoarene, which is oxidized in situ in the presence of a fluoride source, has been reported by Eric Jacobsen and co-workers (DOI: 10.1021/acs.orglett.9b00938). Difluoroaryliodanes, this time electrochemically generated, serve as reagents in the formation of 5-fluoromethyloxazoles starting from *N*-propargylamides by Siegfried Waldvogel and co-workers (DOI: 10.1021/acs.orglett.9b02884), and the classical Togni's reagents have been used by Huiying Zeng, Chao-Jun Li, and co-workers for the C-trifluoromethylation of hydrazones (DOI: 10.1021/acs.orglett.9b02072).

A variety of different catalysts play a central role in various studies facilitating partly known reactions. In this regard, phosphines efficiently catalyze the 1,2-addition of perfluoroalkyl iodides to alkenes with or without irradiation at 461 nm, as shown by Constantin Czekelius and co-workers (DOI: 10.1021/acs.orglett.9b02812) and Ling Zhao et al. (DOI: 10.1021/acs.orglett.9b02314), copper catalysts are used in C−H activation and fluorination followed by further functionalizations by Shannon Stahl and co-workers (DOI: 10.1021/acs.orglett.0c02238), and a $CoBr_2$-derived catalyst is central to diastereoselective difluoroalkylation/Giese addition domino reactions by Lutz Ackermann, Jie Li, and co-workers (DOI: 10.1021/acs.orglett.9b01400). On another front, the hydration of trifluoromethyl- and pentafluorosulfanylalkynes is efficiently catalyzed by Au(I) complexes described by Jean-François Paquin and co-workers (DOI: 10.1021/acs.orglett.9b01379), and $Ca(NTf_2)_2$ is used to activate sulfamoyl and sulfonyl fluorides as well as fluorosulfates for their reaction with amines to generate the corresponding sulfamides, solfonamides, and sulfamates, respectively, by Christopher am Ende, Nicholas Ball, and co-workers (DOI: 10.1021/acs.orglett.0c01397). Rounding out our selected papers, Emmanuel Magnier, Guillaume Dagousset, Luca Dell'Amico, and coauthors report a new α-trifluoromethoxylation of ketones starting from the corresponding enol carbonates (DOI: 10.1021/acs.orglett.1c02494). The OCF_3 radical involved in this reaction is generated from a known pyridinium reagent under photocatalytic conditions.

In summary, the selected papers in this fluorine chemistry collection clearly illustrate how broad and vigorous research has become in the field. What used to be an imperative for innovation, that is new reagents, is being eclipsed by the development of milder conditions that leverage developed fluorinating reagents in an even broader range of transformations. This Virtual Issue aims to showcase this diversity of fluorine chemistry across the chemical disciplines, especially with regard to the potential for many different applications. The element fluorine has caused excitement in chemical laboratories over the centuries and continues to do so today. We wish everyone an interesting read and much inspiration for their own work.

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https://pubs.acs.org/10.1021/acs.joc.1c02745

Notes

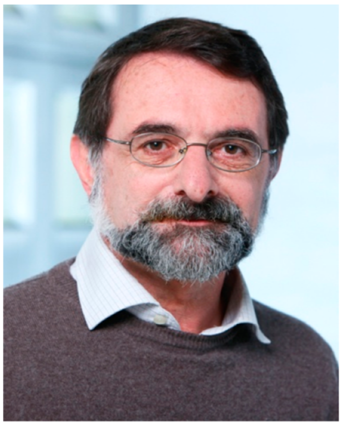
Views expressed in this editorial are those of the authors and not necessarily the views of the ACS. This Editorial is jointly published in *Inorganic Chemistry*, *Organometallics*, *The Journal of Organic Chemistry*, and *Organic Letters*.

Biographies

Stefanie Dehnen obtained her diploma in 1993 and her doctoral degree in 1996 from the University of Karlsruhe. After a postdoctoral stay in theoretical chemistry (1997), she completed her habilitation in inorganic chemistry in 2004. As of 2006, she has been Full Professor of Inorganic Chemistry at Philipps-Universität Marburg. Among many other honors, she was elected a full member of the European Academy of Sciences (EurASc) and of Leopoldina German National Academy of Sciences. Her current research is focused on the synthesis and experimental as well as quantum chemical investigation of compounds with multinary, in particular multimetallic, molecular nanoarchitectures, which possess potential as innovative catalysts, white-light emitters, or battery materials.

Laurel Schafer completed her B.Sc. at the University of Guelph and then her Ph.D. at the University of Victoria (1998) before becoming an NSERC PDF at the University of California, Berkeley. She began her independent career at the University of British Columbia in 2001 and has risen through the ranks to Professor. In 2019, she was appointed a Canada Research Chair in Catalyst Development (Tier 1). She is a Fellow of the Royal Society of Canada and has received numerous research awards for her work in the catalytic synthesis of amines, N-heterocycles, and amine-containing materials. This work has resulted in several patents, and she is a cofounder for the start-up company a2o Advanced Materials.

Thomas Lectka is a native of Detroit, MI, who graduated with a B.A. in Chemistry from Oberlin College in 1985. He then pursued his Ph.D. at Cornell University with Prof. John McMurry, finishing in 1990. He undertook postdoctoral studies as an Alexander von Humboldt Fellow at Heidelberg University in 1991 with Rolf Gleiter, followed by an NIH Fellowship at Harvard University with Prof. David Evans. He joined the Johns Hopkins chemistry faculty in 1994, where he is now Jean and Norman Scowe Professor of Chemistry. His research interests span a broad spectrum of organofluorine chemistry, physical organic chemistry, catalysis, and synthetic methodology.



Antonio Togni, born 1956 in Switzerland, studied chemistry at the Swiss Federal Institute of Technology (ETH Zurich), where he completed his Diploma (M.Sc.) in 1979 and his Ph.D. in 1983, working with the late Luigi M. Venanzi. After a postdoctoral stay (1983−1984) at California Institute of Technology in John E. Bercaw's group, he joined the Central Research Laboratories of the former Ciba-Geigy in Basel, Switzerland, where he worked seven years as a research scientist and group leader in the field of asymmetric catalysis. In 1992, he was appointed Assistant Professor at the Laboratory of Inorganic Chemistry at ETH Zurich and became a Full Professor of Organometallic Chemistry in 1999. His main research interests are in the field of homogeneous asymmetric catalysis and organofluorine chemistry. He retired in January 2021.

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