RESEARCH PAPER

Green Chemistry Strategies for the Synthesis of Fluorinated Bioactive Molecules: Recent Advances and Future Directions

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Abstract

Fluorination of bioassay molecules has proven to be a unique strategy in recent drug discovery, agrochemical, and materials sciences. The unique properties of fluorine, such as its high electronegativity, small atomic size, and high bond energy of the C–F bond, bring remarkable metabolic stability, increased membrane permeability and pharmacokinetic optimization to drug candidates. But the existing methods of fluorination suffer from the use of dangerous reactants, volatile organics as solvents, extreme reaction temperatures, and good amount of chemical waste, which would bring critical environmental and safety issues. The principles of green chemistry, as stated by Anastas and Warner, are a very good guiding tool to design alternative approaches to fluorination chemistry that are more environmentally friendly while not compromising on synthetic efficiency and yields. This review brings together all the key approaches that have been applied to the design and synthesis of fluorinated bioactive molecules in a panoramic way. Solvent-free fluorination reactions, aqueous-phase fluorination strategies, photocatalytic, electrochemical, renewable fluorine sources, biocatalytic C–F bond formation, microwave- and flow chemistry-assisted fluorinations and computational tools for designing greener fluorination processes are discussed. Besides that, we explore the concepts of atom economy, catalytic fluorination and waste minimization in the synthesis of pharmacologically significant scaffolds of fluorine. Recent developments in the introduction of PET imaging 18F-radiolabeling under green conditions, sustainable trifluoromethylation reactions, and incorporation of machine learning for prediction of optimal green pathways for fluorination reactions will receive special attention. The review presents and summarises the evidence that sustainable industry development for pharmaceuticals and agrochemicals is possible with green fluorination chemistry while simultaneously being economically viable and technologically cutting-edge.

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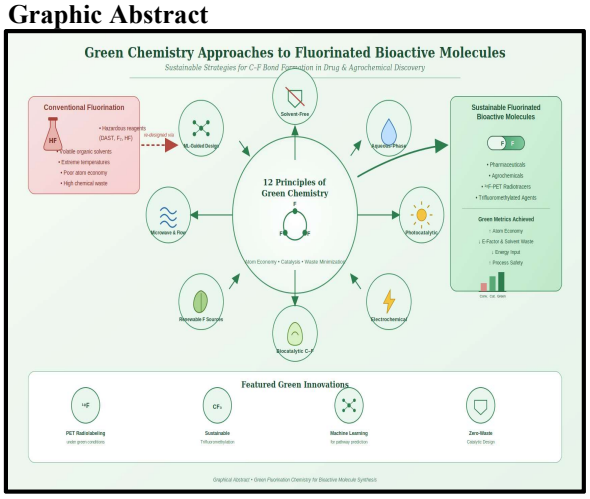
Graphic Abstract



1. Introduction

The most electronegative element in the periodic table, fluorine, stands out as a special element in medicinal chemistry and drug design. Although fluorine is a relatively uncommon element in natural products, synthetic molecules containing fluorine have become so common in the pharmaceutical world. Previously, in the statistical analysis based on FDA-approved drugs, about 20-25% of all the marketed drugs and nearly 30% of the top-selling drugs were found to contain at least one fluorine atom. Medicines such as atorvastatin (Lipitor), fluoxetine (Prozac), ciprofloxacin, sorafenib, sitagliptin and many antifungal, antiviral and antipsychotic medicines are among the many well-known medicines that interact with food. In the agrochemical industry, the amount of fluorine in pesticides and herbicides marketed has grown even higher, with over 30% of new active ingredients now containing it.

There are many reasons for introducing fluorine into bioactives. The C–F bond (bond dissociation energy ~130 kcal/mol) is much stronger than most popular bonds, e.g., the C–H bond (bond dissociation energy ~99 kcal/mol) and the C–C bond (bond dissociation energy ~83 kcal/mol), enabling the bond to resist oxidation much more effectively by P450-cytochrome in the metabolic process. Second, the introduction of a fluorine substitution can substantially influence the acidity or basicity of the neighbouring functional groups, which can affect their ionization essential for receptor interactions. Third, although the fluorine atom is highly electronegative, it is a truly inefficient hydrogen bond acceptor and a very effective orthogonal multipolar C–F•••H–N and C–F•••H–O protein-binding interactant. Fourth, the strategic positioning of the fluorine atom increases the lipophilicity in an atomism-dependent manner, in some cases reduces the lipophilicity in others (an aliphatic fluorination is known to increase the lipophilicity, whereas an aromatic fluorination is known to decrease it, depending upon the situation). Fourth, the introduction of a fluorine atom in a strategic position increases the lipophilicity in some cases and reduces the lipophilicity in others (in some cases, it makes it more lipophilic, whereas in others, it makes it less lipophilic). Lastly, the introduction of fluorine is isosteric to the hydrogen or hydroxyl group, which allows for fine-tuning of steric and/or electronic features without significantly changing the geometry of the molecule.

Subsequently, although there are many benefits associated with overhauling the synthetic methods available for the generation of fluorinated bioactive molecules, these methods have been historically plagued by drawbacks and are unsuitable for sustainable chemistry principles. Classical electrophilic fluorination is achieved by using reagents like elemental fluorine (F_2), xenon difluoride (XeF_2), and N-fluoropyridinium salts under severe conditions. Previously, nucleophilic fluorination was accomplished with potassium fluoride in highly polar aprotic solvents like dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), which have reproductive toxicity and prohibitively high amounts of waste. Owing to the high temperatures (>150°C) and the long reaction times needed for halogen exchange (halex) reactions, inorganic waste in the form of stoichiometric amounts of salt is produced. $TMSCF_3$, known as a Ruppert-Prakash reagent or similar species, is a powerful reagent for trifluoromethylation, but can create by-products containing silicon and requires anhydrous conditions. These options have a high environmental cost, suggesting the need for a shift towards more environmentally friendly alternatives.

There is a set of twelve principles of green chemistry, which Professor Paul Anastas and John Warner first introduced in 1998, that give us something to do. All of these principles include the concepts of waste prevention, atom economy, and less hazardous synthesis, designing safer chemicals, safer solvents and auxiliaries, design for energy efficiency, use of renewable feedstocks, reduced derivatization, catalysis, design for degradation, real-time analysis for pollution prevention, and inherently safer chemistry. Applied to the field of fluorination chemistry, the principles can be translated into specific targets: to replace stoichiometric fluorinating agents with catalytic reactions, to use water or supercritical CO_2 as reaction media, to use electrochemistry and photocatalysis as less polluting inputs for the reactions, to design biomimicking enzymes capable of C–F bond formation and to apply flow chemistry for the safe handling of hazardous fluorine species and to

use the computational prediction approach for the selection of greener reaction conditions.

The objective of this review is to comprehensively and critically address the synthetically developed green chemistry approaches for the preparation of fluorinated bioactive molecules during the last ten years. The principal classes of fluorination reactions (aromatic, aliphatic C–F bond formation, trifluoromethylation, difluoromethylation and radiofluorination) are discussed, and possible application of the principles of green chemistry to these reactions is explored. These are among the emerging technologies: machine learning-guided synthesis planning, microreactor technology, and biocatalysis, that has the potential to further aid the development of sustainable fluorination chemistry. We wish to bring together the present knowledge, highlight gaps, and suggest research avenues to fill the gaps that will contribute to the safe development of fluorinated therapeutics and agrochemicals.

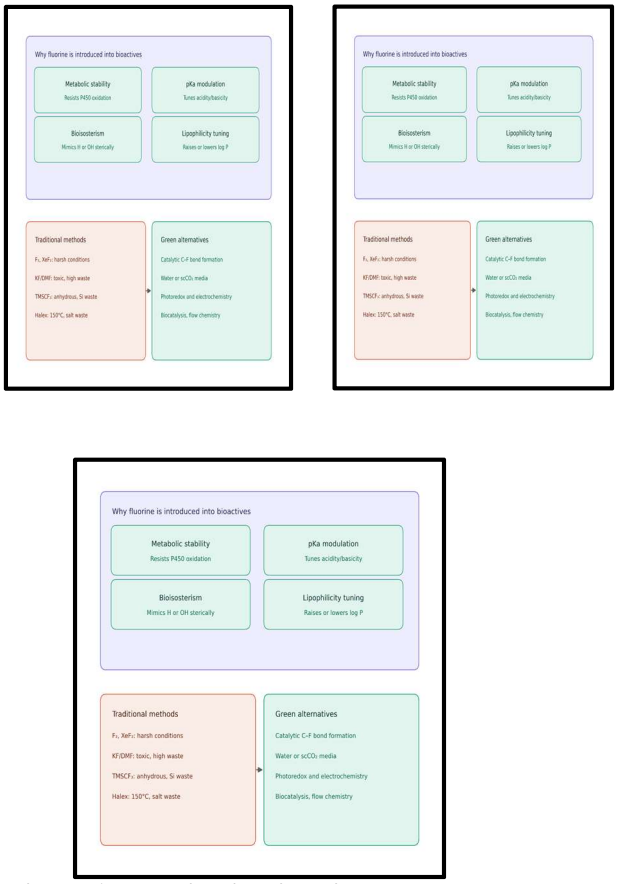


Figure 1. Fluorine in bioactive molecules and the shift toward green fluorination chemistry

2. The Role of Fluorine in Bioactive Molecules

2.1 Physicochemical Effects of Fluorine Substitution

The substitution of a fluorine atom with an organic molecule dramatically affects its physicochemical characteristics and has, in fact, occasionally synergistic effects. The steric substitutions of fluorine have a small van der Waals radius (1.47 Å compared with hydrogen (1.20 Å), which makes repairs simple. The impacts of the electronic are not short-term, though. The polar C–F bond carries fluorine with a large partial negative charge, which can affect the electrostatic potential surface of the whole molecule. This electron-donating or withdrawing effect is transmitted through the molecular framework known as the inductive effect, which affects the electron density at distant points, affecting pKa values, dipole moments, and reactivity.

The effect of fluorine on lipophilicity is more interesting. Generally, replacing the C–H bond with the C–F bond leads to an increase in lipophilicity (ΔlogP is approximately +0.14 per fluorine) due to the hydrophobic surface area gain and the small amount of dipole moment from the C–F bond being exposed to the solvent. However, aliphatic fluorination may result in more prominent variation of the lipophilicity, as it is possible to get an increased value of logP with respect to the parent CH_2 or CH_3 group in the case of gem-difluoro and trifluoromethyl groups. These changes in lipophilicity have direct effects on passive membrane permeability, volume of distribution, protein binding, and oral absorption. These effects are used by drug designers to fine-tune the balance between the permeability of the membranes and the aqueous solubility necessary for oral bioavailability.

Metabolic stability may be the most quoted reason in favour of a strategy of fluorination in drug design. The oxidative metabolism of most marketed drugs is catalyzed by cytochrome P450 enzymes, of which CYP3A4, CYP2D6 and CYP2C9 are most relevant. The enzymes react with the aromatic ring and aliphatic chain through a reactive carbocation or radical intermediate. By introducing FC at metabolically sensitive sites, both steric and electronic deactivation (loss of electron density at the aromatic ring) barriers to oxidation are provided. The half-life, clearance and oral exposure for fluorinated analogs have consistently been found to be significantly longer, lower and higher, respectively, than their non-fluorinated counterparts in comparative pharmacokinetic studies.

2.2 Fluorine in Clinical Drug Molecules

Fluorine-containing drugs are used to treat virtually every disease type. In oncology, fluorine is an essential element of EGFR inhibitors (gefitinib, erlotinib), BRAF inhibitors (vemurafenib) and CDK4/6 inhibitors (palbociclib). Antiviral drugs

represent a large proportion of the HIV drug scene, particularly the fluorinated nucleosides and non-nucleoside reverse transcriptase inhibitors, like two emerging drug stars, emtricitabine and efavirenz. The atypical antipsychotics, like haloperidol and risperidone, and the selective serotonin reuptake inhibitors (SSRIs), fluoxetine, fluvoxamine and paroxetine, all have key fluorine atoms as part of their structure in central nervous system therapeutics. The C-6 fluorine mediates resistance to bacterial topoisomerases; another large class of antibiotics that relies on this same property for activity is the fluoroquinolones.

It is important to note that there exists one fluorine-containing motif in pharmaceutical chemistry much more important than any other trifluoromethyl group (–CF_3). Because of its high potential as an electron-withdrawing group, high lipophilicity and metabolic inertness, this group has been used in blockbuster drugs such as celecoxib, fluoxetine, efavirenz and sorafenib. Overall, the CF_3 group was found to have a profound effect on the metabolic half-life of most drug candidates, as well as enhancing blood-brain barrier penetration in CNS drug candidates. Recently, the difluoromethyl group (–CHF_2) has been a bioisostere of CF_3 that has an intermediate lipophilicity and also a hydrophobic hydrogen bond donor (through the C–H bond).

3. Principles of Green Chemistry Applied to Fluorination

3.1 Atom Economy and Waste Prevention

Trost's definition of Atom economy is the efficiency of using atoms in the starting material in the product. The situations of poor atom economy in traditional fluorination reactions are numerous. For instance, the production of an electrophilic fluorination reagent, Selectfluor (F-TEDA-BF_4), produces a side product of a reduced version of TEDA, a tetrafluoroborate-anion salt, for each product molecule formed. Likewise, the Balz-Schiemann reaction of diazonium salts affords the corresponding nitrines in addition to stoichiometric amounts of N_2 and either BF_3 or HF. In the pharmaceutical sector, the E-factor, for the process greenness criteria, is typically in the range of 25 to >100 kg of waste per kg of product and a number of the least green unit operations are steps involving fluorination.

The overall goal of green fluorination approaches is to increase atom economy through catalytic rather than stoichiometric fluorine transfer. Transition metal-catalyzed C–F bond formation, where the metal catalyst is the mediator of transferring fluorine atoms, is a fundamental breakthrough in the field of atom-economical fluorination, one in which each molecule of the metal catalyst takes part in multiple turnovers. Similarly, electrochemical fluorination can be carried out using the charge carrier (electrons) as the fluorination reagent, with a high atom economy, as the only side product at the counter-electrodes in aqueous electrolyte is usually H_2 gas (which is produced by reduction of protons); this approach generally avoids chemical oxidants or reductants.

3.2 Solvent Selection and the CHEM21 Solvent Guide

Given that solvent selection is arguably the most important of decisions for green process chemistry, solvents account for 80-90% of the total mass consumed (as opposed to energy) in a typical pharmaceutical synthetic process and are a significant source of environmental emissions and wastes. Many chemists in the pharmaceuticals sector are making use of pharmaceutical solvent selection guides developed by the industry to help them make greener choices. Solvents are listed as recommended or problemmatic or hazardous in the CHEM21 (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries) guide in accordance with health, safety and environmental (HSE) profiles. Traditional solvents in fluorination chemistry, such as DMF, NMP, DMSO, THF, and dichloromethane, are categorized as problematic or hazardous, and a preferential choice for a greener solvent has to be found.

As a consequence of these properties, water has become perhaps the most attractive “green” solvent used in fluorination chemistry, with its tremendous abundance, its non-toxicity, its non-flammability, its high specific heat, and some special solvation characteristics that can enhance both the rates and yields of certain reaction types via hydrophobic effects. The electron-rich aromatics can be successfully modified by aqueous-phase electrophilic fluorination with Selectfluor (or NFSI), when conditioned by carefully controlled pH. Aqueous fluorination has been expanded by the development of water-compatible transition metal catalysts for the formation of C–F bonds. Rhizom Registry reactions that are carried out in water commonly show different chemoselectivity than reactions carried out in organic solvents, and in some cases, a complementary product distribution is obtained that has experienced synthetic benefit.

2-methyltetrahydrofuran (2-MeTHF) is a bio-based alternative to PUFAs, THF, and dichloromethane and is produced from agriculture-derived feedstocks such as corn cobs and sugarcane bagasse. It has a higher boiling point (80°C vs. 66°C for THF) and better water immiscibility, which allows wet workup, and is renewable. Other bio-derived chemicals that have been proven to be compatible for nucleophilic and electrophilic fluorination reactions

are cyclopentyl methyl ether and diethyl carbonate. Other solvents that can be produced renewably, such as ethanol, ethyl acetate, and acetone, have also proven to be useful in some fluorination protocols.

4. Green Approaches to Electrophilic Fluorination

4.1 N-F Reagents under Mild and Aqueous Conditions

The chemistry of electrophilic fluorination with N-F reagents is among the most advanced of the fluorination chemistry. Both laboratory and industrial applications have gained widespread use of the three main commercial N-F reagents: Selectfluor (F-TEDA-BF4), n-fluorobenzenesulfonimide (NFSI) and 1-fluoropyridinium trifluoroacetate (NFTA). Innovations in these reactions have been related to conducting them in aqueous media, at room temperature, and, when feasible, under catalytic conditions, exemplary of "green chemistry." Gouverneur and co-workers have shown good atom economy and high regioselectivity in electrophilic fluorocyclization of alkynes using Selectfluor in water/acetonitrile at room temperature to give fluoroheterocycles.

Hypervalent iodine reagents have been investigated as precursors to electrophilic fluorine equivalents to be used with more favourable safety profiles. The reagents, ArI(F)X (e.g., Togni reagents, Umemoto reagents), provide electrophilic fluorine under mild conditions and possess improved chemoselectivity properties compared to strong electrophilic fluorinating reagents. In addition, the development of recyclable polymer-supported N-F reagents is a "green" innovation: the usage of fluorinating agents attached to polymethylhydrosiloxane (PMHS) in catalytic amounts with the use of electrochemical re-oxidation makes it possible to create a sustainable electrophilic fluorination cycle. Peng et al. have recently shown that reduced Selectfluor can be re-oxidized in situ to the ox state, which allows sub-stoichiometric consumption of Selectfluor in electrochemical cells with anodic oxidation as the terminal oxidation reaction.

4.2 Photocatalytic Electrophilic Fluorination

Photocatalysis is seen as a revolutionary platform for green organic synthesis, which holds the promise to perform difficult transformations under mild conditions with visible light as the energy input. In the case of electrophilic fluorination, photoredox catalysis has opened new avenues to C (SP^3)–H bond functionalization by radical pathways that are not feasible by classical ionic electrophilic pathways. Nicewicz and colleagues introduced a class of photocatalysts that are based on an acridinium conjugate, which was first used for electrophilic single-electron oxidation of an arene, then fluoride nucleophilic capture. The process is conducted under visible light irradiation at room temperature, without the need for transition metal catalysts and with excellent functional group tolerance.

An electrophilic C–H fluorination of arenes has been achieved by palladium catalysis and photoredox chemistry for the first time, without the need for pre-functionalization. Sanford and co. have created Pd(II)/Pd(IV)-catalyzed C–H fluorination with the aid of a photosensitizer and N-fluoropyridinium oxidant, giving a site-selective fluorination of arenes containing directing groups under conditions less severe than those of thermal Pd(IV)-mediated pathways. The photocatalytic method lowers the operating temperature from >100°C to ambient temperature, and sometimes it is even possible to use more environmentally friendly solvents. Copper-photoredox dual catalysis has also been found to be an effective approach to applying the fluorination of alkyl bromides with the assistance of radical intermediates, with CuII both as a photocatalyst and as a fluorine transfer agent.

4.3 Asymmetric Electrophilic Fluorination with Organocatalysis

Enantioselective electrophilic fluorination of prochiral substrates is an important challenge for the preparation of enantiomerically pure fluorinated bioactive molecules. Green methods without massive use of metal catalysts have appeared, such as the organocatalytic methods based on the use of chiral phase-transfer catalysts (PTCs) and chiral amine catalysts. Both groups have prepared PTCs based on cinchona alkaloids for the enantioselective fluorination of various β-ketoesters and oxindoles with NFSI or Selectfluor in aqueous biphasic systems with excellent enantioselectivities (up to 99% ee) under mild conditions. The aqueous phase allows for separation of the product and allows for simple catalyst recovery, while simultaneously improving atom economy and minimizing waste.

5. Green Strategies for Nucleophilic Fluorination

5.1 Late-Stage Fluorination via Metal Catalysis

Traditionally, nucleophilic fluorination has been carried out under anhydrous conditions and in polar aprotic solvents to enable the full exploitation of the nucleophilicity of fluoride ion, which is strongly solvated in protic solvents. The Sanford and Gouverneur groups independently showed the ability to perform nucleophilic fluorination of aryl boronic acids and aryl stannanes by a reaction sequence involving oxidative addition/transmetalation/reductive elimination using palladium catalysis. With anhydrous silver fluoride/cesium fluoride as the fluoride source, aryl fluorides are also prepared from the corresponding aryl boronic acid substrates under mild conditions (60/80° C) in DMF solvent, via the Pd(II)/Pd(IV)

catalytic cycle. Later enhancements led to the use of more eco-friendly solvents (ethanol/water mixtures) and decreased catalyst amounts.

Catalytic and catalytic-like nucleophilic fluorination by copper-mediated and copper-catalyzed routes has come under scrutiny because of the potential to make it green. Copper-based methodologies are intrinsically more sustainable in terms of metal sustainability due to the low toxicity of copper for the environment and the abundance of copper in the Earth's supply. Fier and Hartwig describe the fluorination of aryl iodides with silver fluoride, which results in the formation of aryl fluorides in good yields that are functional group tolerant. Follow-up mechanistic studies by Sanford found that Cu (III) species participate in the reductive elimination, and thus more efficient catalytic variants have been designed. Also, the Ni(0)/Ni(II)/Ni(IV) cycle is used for nucleophilic aryl fluorination reactions.

5.2 18F-Radiofluorination under Green Conditions

18F-labelled compounds are required for the positron emission tomography (PET) imaging technique, which is used for visualizing molecular targets in vivo without disrupting living systems. The short 18F half-life (109.8 minutes) poses the requirement of fast, high-yield and scalable radiolabeling methods, which is a specific challenge for the implementation of a green chemistry approach. Other traditional strategies involve nucleophilic 18F-radiofluorination of aryl diazonium salts or aryl boronic acids with 18F-fluoride, where high temperatures are required in DMF or DMSO, resulting in substantial radioactive waste streams. Green 18F-labeling methods have thus been a great priority for the PET community.

The Oxford hypervalent iodine (III) chemistry group, led by Gouverneur, has discovered a new class of 18F-labeling precursors that are very effective for the synthesis of [18F] aryl fluorides at room temperature and in aqueous media. They can be carried out in water/acetonitrile mixtures at ambient temperature with excellent radiochemical yields, without the need to use a lot of dangerous organic solvents and at a low temperature. A new green approach for 18F-labeling is based on silicon-fluoride acceptors (SiFAs), which undergo isotopic exchange reactions at room temperature in aqueous solution with considerably high specific activities. Chelation chemistry of the aluminum fluoride has permitted the rapid (5–10min) labelling of peptides with [18F] fluoride in aqueous solution at room temperature, which has been used for the clinical imaging of cancer biomarkers.

5.3 Deoxyfluorination under Green Conditions

One of the most relevant transformations in modern pharmaceutical synthesis is the replacement of an aliphatic hydroxyl moiety by fluorine – deoxyfluorination, which allows the direct conversion of the vast number of alcohol feedstocks into fluorinated derivatives. In classical deoxyfluorination, the use of DAST (diethylaminosulfur trifluoride), Deoxofluor or morpholinodifluorosulfinium tetrafluoroborate, all of which are moisture-sensitive, hazardous materials, must be used at cryogenic temperatures and cause highly toxic side products, HF. The use of bench-stable crystalline deoxyfluorinating agents such as PyFluor developed by the Ritter group and AlkylFluor that can be used at room temperature, stored for prolonged periods of time and can be used in the presence of ambient moisture are applications for green alternatives to deoxyfluorination.

PhenoFluor and PyFluor, developed by the Ritter group, are truly a first revolution in green chemistry for deoxyfluorination. PhenoFluor is a highly crystalline, bench-stable reagent that allows the reaction of phenols with high yields and very good functional group tolerance into the corresponding aryl fluorides under mild conditions. The piperidine derivative PyFluor, likewise, allows the deoxyfluorination of all aliphatic alcohols at ambient temperature. These are reagents that yield harmless byproducts of urea, which can be readily removed from the environment. Recently, electrochemical deoxyfluorination has been developed by several groups, which utilizes electricity as an external source to transfer the fluorine from an inorganic source, without requiring the use of a “reactive” fluorinating reagent.

6. Sustainable Trifluoromethylation Strategies

6.1 Photoredox and Copper-Catalyzed Trifluoromethylation

In the last decade, -CF3-functionalization reactions (trifluoromethylation) have experienced a breakthrough with photoredox and copper catalysis. The CF_3 radical, which can be photocatalytically generated from Togni's reagent, from Umemoto's reagent, with CF_3SO_2Na (Langlois reagent) or CF_3SO_2Cl, rapidly and under mild conditions reacts with olefins, arenes, and heteroarenes under the influence of visible light and organic or metal-based photocatalysts. MacMillan and coworkers first reported the Ir(III)-photocatalyzed radical trifluoromethylation of arenes and the Ir(III)-photocatalyzed radical trifluoromethylation of heteroarenes with the trifluoromethylating reagent CF_3I, which is formed in situ from the trifluoroacetate under oxidative conditions. This method is used without a transition metal catalyst in the coupling of substrates step at room temperature in acetonitrile, which is an advantage over the high-temperature thermal radical processes.

The catalytic trifluoromethylation approach with Cu(I)/Cu(III) cycles has proved to be a very efficient and sustainable method, in particular. The group of Buchwald has now developed a protocol for the Cu-catalyzed trifluoromethylation of aryl boronic acids that allows for the use of $TMSCF_3$ as the trifluoromethylating agent with the use of room-temperature oxygen as the terminal oxidant. Diao and colleagues subsequently switched to the more environmentally friendly CF_3 source sodium triflinate instead of the less sustainable $TMSCF_3$, which is too expensive and less accessible, and is also air- and moisture-stable, generating sodium sulfonate as the only byproduct. Trifluoromethylation under unusually mild conditions, using only inexpensive, readily available photocatalysts like acridinium salts, and avoiding the use of expensive iridium or ruthenium polypyridyl complexes.

6.2 Electrophilic Trifluoromethylation with Umemoto and Togni Reagents

The electrophilic trifluoromethylation of a variety of reagents, such as sulfonium and iodonium reagents, remains a fundamental synthetic method. The Togni reagents (hypervalent iodine-based) and the Umemoto reagents (sulfonium-based) are CF^{3+} equivalents that are used to react with nucleophilic substrates such as enolates, organometallics and electron-rich arenes. In the field of green chemistry, water-stable Togni reagents have been developed which allow trifluoromethylation of active methylene compounds in aqueous media or alcoholic solvents at room temperature, or in air atmosphere. The reduced iodine byproduct has been used and reused: Aryl iodide byproducts generated in Togni reagent reactions can be re-oxidized and re-charged with CF_3 to give a reusable Togni reagent for the next reaction - a circular reagent economy.

The ability of microflow chemistry (continuous flow reactors) to handle Umemoto reagents that are electrophilic and react violently has been powerfully applied to trifluoromethylation reactions, where reaction parameters are extremely well controlled at high temperatures and pressures without needing to use dangerous and reactive trifluoromethylating agents. Efficient heat transfer in microreactors is ensured by the large surface-area-to-volume ratio, thus preventing the occurrence of exotherms, which on a larger scale can be dangerous. Ley and coworkers showed that trifluoromethylation with Umemoto's reagent in continuous flow can occur twice as quickly in THF and only requires 40% of the solvent, highlighting the inherent green benefits of continuous flow chemistry for reagent-intensive fluorine chemistry.

6.3 Difluoromethylation: Emerging Green Methods

The difluoromethyl group ($–CF_2$) is worthy of increasing interest as a CF_3 bioisostere with the added functionality of a hydrogen bond donor (pKa of the CF_2H group $\approx$ 25–28). The chemistry of difluoromethylation has proven to be more challenging than trifluoromethylation in the past because of the instability of the CHF_2 radical and the scarcity of bench-stable CHF_2 transfer reagents. Recent advances include the preparation of electrophilic CHF_2 sources such as S-(difluoromethyl)diarylsulfonium salts, and radical CHF_2 sources such as sodium difluoromethylsulfinate (CF_2HSO_2Na) and $TMSCHF_2$ as a nucleophilic CHF_2 source for addition to aldehydes and ketones. The CF_2HSO_2Na and the use of a light source, such as visible light, in water is a particularly green route that occurs at room temperature under visible light, employing earth-abundant organic photocatalysts.

7. Electrochemical Fluorination: A Green Energy Platform

7.1 Fundamentals of Electrochemical C–F Bond Formation

Electrochemical synthesis is one of the most atom-economical methods that does not require chemical oxidants/reductants to undergo organic fluorination with the basic reagent of electrons. However, in electrochemical fluorination (ECF), the substrate loses an electron, and the resulting intermediates (either carbocations or carbanions or radicals) are trapped by fluoride ion from the electrolyte (usually $Et_4NF•HF$, $Et_3N•5HF$, or HF/Et_3N). The process developed by Simons at 3M in the 1940s established the viability of electrochemical perfluorination of hydrocarbons using the source of fluorine, HF and nickel anodes. Modern academic ECF is based on this, uses less harsh conditions and only selectively fluorinates specific substrates, and uses a new "flow cell" design that has reduced risks relative to handling the HF.

Fuchigami and colleagues have contributed seminal work in the area of selective anodic fluorination of organosulfur and organophosphorus compounds, which involved the selective fluorination of the α-positions of these compounds. The selectivity of this electrochemical process is due to the presence of the sulphur or phosphorus lone pairs, which stabilize the cation radical intermediates involved, directing the attack on fluoride. Fluorination at positions based on the original sulphur functionality is performed by an innovative method named electrochemical fluorodesulfurization, in which a C–S bond is oxidized to a C–F bond while the byproduct thiol is easily removed.

7.2 Modern Electrochemical Flow Fluorination

Many practical problems of batch ECF have been overcome due to the combination of electrochemical fluorination and flow chemistry technology. In flow electrochemical reactors (flow cells), the substrate solution is continuously pumped through the space between the anode and cathode and the geometry of the cell is carefully designed to provide uniform substrate flow, current distribution and residence time. Flow cells have a small inter-electrode gap (usually 0.5–2 mm), which results in low ohmic resistance and thus in the ability to electrolyze them with low voltage. Yoshida's group first introduced the new term: 'electrochemical microreactor', and applied it for the generation and in situ use of reactive cationic intermediates (including α-silyl stabilized carbocations) for fluorination in the absence of over-reaction leading to selectively monofluorinated products.

The Novacentrix and Syrris flow cell platforms have been adapted for electrochemical trifluoromethylation with electrochemical oxidation of CF_3SO_2Na or CF_3SO_2Cl as CF_3 radical sources, demonstrating remarkable selectivity and yield in contrast to batch processes. The flow electrochemical method circumvents the use of photocatalysts completely (photons are replaced with electrons as sources of energy) and, as such, is potentially more scalable and energy efficient than the photoredox trifluoromethylation approach. Grouping various LCA studies to compare batch photoredox and flow electrochemical fluorination has shown that, with renewable electricity, the latter offers a lower carbon footprint, which has driven the inclusion of renewable electricity in electrochemical methods.

8. Biocatalytic Approaches to Fluorination

8.1 Fluorinase Enzymes: Nature's Fluorinating Machinery

The previously unknown ability of biological enzymes (catalysts) to undergo fluorination recently led to the discovery of enzymes that can form C–F bonds in a physiological environment at ambient temperature and pressure, which represents a new pathway to green fluorination chemistry. In 2002, the first and most well-characterized fluorinase, 5'-fluoro-5'-deoxyadenosine synthase (FlAsc) from Streptomyces cattleya, was discovered by O'Hagan and team, which converts S-adenosyl-L-methionine (SAM) and fluoride ion into 5'-fluoro-5'-deoxyadenosine (5'-FDA) and L-methionine. It can be noted as a kind of miracle: The enzyme is in aqueous solution, it functions at a neutral pH (between 7 and 8), at a physiological temperature (37°C), and with very good chemoselectivity, without producing any toxic products: this is a remarkable combination of all the green chemistry principles.

In the mechanism of the fluorinase action, fluoride is displaced by a highly activated methyl sulphonium group by a possible SN2 process, and its poor nucleophilicity in water is enhanced by strategic positioning of the substrate and fluoride in the active site of the enzyme, where the fluoride is partially desolvated and precisely positioned for back-side attack of the highly activated sulphonium group. Following these biochemical studies, other fluorinase enzymes were discovered in Nocardia brasiliensis and Streptomyces sp. These two enzymes, MA37 and FlAsc broader in their substrate scope and more thermostable than FlAsc suggest that expanding the substrate scope and thermostability of the enzyme will have a broader synthetic impact. Non-natural substrates, such as propargyl fluoride and fluorooleic acid precursors, were used for their application in one such example by applying directed evolution to engineer fluorinase variants with improved catalytic activity towards them, to extend the diversity of enzymatically promoted fluorination to pharmaceutically relevant targets.

8.2 Halogenase Enzymes and Engineered Fluorinating Biocatalysts

In addition to dedicated fluorinases, various flavin-dependent halogenases (FDHs), iron/α-ketoglutarate-dependent halogenases, and vanadium haloperoxidases have been investigated for biocatalytic fluorination with a natural tendency towards chlorination/bromination. The potential to direct these enzymes to incorporate fluorine is great, since the bond C–F is formed in different ways than C–Cl and C–Br and has a higher desolvation energy. But with the assistance of directed evolution and semi-rational protein engineering, Zhao, Arnold and co-workers have developed variants of cytochrome P450 that carry out enantioselective C–H fluorination of aliphatic substrates with fluorine-containing peroxides as the source of fluorine, which afford chiral fluorinated building blocks that are difficult to access using chemical means.

Biocatalytic fluorination in conjunction with chemoenzymatic synthesis cascades is one of the highly effective approaches to the green synthesis of fluorinated molecules. In these cascades, a fluorinase or synthetic fluorinase incorporates fluorine in early steps in aqueous, ambient conditions, and adds complexity via other chemical or enzymatic steps. Inverse electron demand transformations by the acyl carrier protein (ACP) dependent halogenases of natural products were recently demonstrated in vitro to incorporate fluorine into complex polyketide and non-ribosomal peptide scaffolds that highlight the potent structure-directing ability of these enzymes in developing novel biosynthetic pathways to fluorinated natural product analogs. Whole-cell biocatalysts with

all the required enzymes for a complete pathway to a fully fluorinated natural product would be the ideal green chemistry version of fermentation-derived production of fluorinated medicinals.

9. Flow Chemistry and Micro reactor Technology in Fluorination

9.1 Advantages of Continuous Flow for Hazardous Fluorination Reagents

Continuous flow chemistry has come to the fore as an enabling technology that tackles the key safety and efficiency issues needed for industrial and pharmaceutical chemistry involving reactive sources of fluorine, a fundamental element. Continuous flow chemistry has proven a game-changer in industry and pharmaceutical research for fluorination chemistry, where traditional batch processing of reactive sources of fluorine poses significant safety and efficiency issues. High reactor volume-to-surface area ratios, ambient temperature control, and enclosed, computer-controlled systems with the handling of hazardous reagents such as F_2, HF, DAST and reactive N-F species make flow chemistry an intrinsically safer platform for fluorination reactions. Process intensification in a microreactor, for example through reduced residence times, accelerated mixing, more efficient heat dissipation, and more efficient heat dissipation, can quickly lead to enhanced yields, selectivities, and waste reduction.

Now, the most atom-economical source of fluorine gas (F_2) is safely transformed by flow technology. It was Chambers and coworkers who proved that elemental HF can be metered safely into the channels of a microreactor, into which is dissolved an appropriate organic substrate, to the extent of obtaining selectively monofluorinated derivatives of activated aromatics in acetonitrile without the uncontrollable polyfluorination and exothermic reactions so typical of batch HF reactions. These are now developed and tested at pilot plant scale by Solvias and Bayer researchers to prove that such a process is industrially feasible – with full safety monitoring systems in place. In the flow F_2 approach, all the N-F electrophilic fluorination is eliminated, and the flow chemistry is significantly more atom-economic, eliminating the stoichiometric chemical waste from electrophilic N-F fluorination.

9.2 Integration with Analytical Tools and Process Analytical Technology (PAT)

PAT (Process Analytical Monitoring), combined with flow fluorination reactors, shows the green chemistry principle of real-time analysis for pollution prevention. Flow fluorination is also an ideal process for continuous monitoring of the reaction progress, consumption of reagents and product generation by inline NMR spectroscopy using benchtop $^{1}H/^{19}F$ NMR spectrometers, inline infrared spectroscopy (ReactIR) and inline mass spectrometry. The feedback can be automatically used to fine-tune flow rates, temperatures and reagent ratios to guarantee optimal environmental conditions, reducing the production of off-spec product and waste. The ^{19}F NMR chemical shift is especially sensitive to the fluorine environment and is a very informative indicator of the progress of reaction in fluorination chemistry that goes beyond the information contained in modern ^{1}H NMR.

Multi-step synthesis telescoping in flow systems, in which intermediates are not isolated but instead directly transferred to the subsequent reaction vessel, is an important development towards greener processes. The Jamison group at MIT showed the example of a 6-step continuous flow synthesis of the fluorinated antihistamine diphenhydramine hydrochloride with a minimum of 8, and an overall yield of >100 compared to the batch synthesis. Avoiding any intermediate separation operations saves solvent consumption, energy and time as well as enhances the overall yield. The same strategies are being used in the application to complex non-fluorinated pharmaceutical complexes, including sitagliptin and sorafenib, which are under intense investigation.

10. Computational Tools and Machine Learning in Green Fluorination Design

10.1 DFT-Guided Green Fluorination

In recent years, density functional theory (DFT) calculations have been essential and invaluable tools in understanding and rationalizing the mechanism of reactions to fluorinate molecules, as well as for searching for green reaction conditions, reagents and substrates in advance of experimental testing. The activation barriers of the fluorination steps, C–F bond dissociation energies and the relative stability of product isomer fluorinated molecules are computed well by DFT methods, with the prediction of the regioselectivity of electrophilic and nucleophilic fluorination. Using DFT calculations, the potential energy surfaces of C–H fluorination reactions of both the Jacobsen and the Gouverneur groups have been mapped, revealing that the key C–F reductive elimination step is both rate-determining and selectivity-determining, and that ligand design to stabilize the critical Pd(IV) intermediates has been judicious.

Developing Green Chemistry metrics calculators coupled with calculation programs such as quantum chemistry allows for evaluation of several paths of fluorination from a single point of view, based on both synthetic efficiency and environmental impact. With an approach like COSMO-RS (conductor-like screening model for real solvents), one can predict, among others, substrate solubility and

rates in green solvents. Such a picture lets one look into the immense chemical space of green solvents (including DES, ionic liquids and supercritical fluids) without having to perform time-consuming experimental testing. In the total synthesis of fluorinated drug candidates, maximum step economy together with minimum waste materials was achieved by guiding retro-synthetic analysis by quantum chemical computation and by appropriate calculation of "green" properties.

10.2 Machine Learning for Predicting Greener Fluorination Conditions

Recently, machine learning (ML) and artificial intelligence (AI) have been implemented successfully to predict and optimize the reaction conditions for fluorination. Large datasets of fluorination reactions (on Reaxys, SciFinder and USPTO patent databases) can be used to train graph neural networks which can accurately predict C–F bond-forming reaction yields, regioselectivity, and enantioselectivity for new substrates and which can perform virtual screening to rapidly screen millions of candidate substrates and conditions. The team at Jensen and their collaborators optimized a reaction space consisting of electrophilic C–H fluorinations using a Bayesian optimization algorithm that led to a number of combinations of catalyst/oxidants/solvents that performed better than predictions by human experts in just a small fraction of the experimental time.

Building on this, generative AI models are being used to design novel bioactive molecules that contain fluoro-atoms and have the desirable properties of low toxicity, easy-to-prepare, and environmentally friendly green synthesis pathways, by fine-tuning large language models (LLMs) trained on chemistry literature and variational autoencoders (VAEs) trained on data sets related to molecular properties. The idea of 'synthesizability scoring' has been introduced in molecular generation models to guide the generation of structures with computational scores that indicate how easily they can be synthesized using known green chemistry methods, thus biasing the output to synthesizable fluorinated molecules. Retrosynthesis tools using machine learning are in the spotlight, with examples like the RXN tool from IBM, which is commonly applied, and the Chemformer. One of the prominent examples of an ML-based retrosynthesis tool which is adapted to green fluorination pathways is IBM's RXN for Chemistry and Chemformer. The incorporation of these in the drug discovery process is expected to have a profound impact on the acceleration of building new synthetic taxonomy in affordable and environmentally friendly ways to eventually generate fluorinated drug candidates with high in vivo therapeutic activity.

11. Green Synthesis of Fluorinated Agrochemicals

11.1 The Growing Fluorine Content in Crop Protection Chemistry

Fluorine is now present in a majority of altered organic molecules (OFM) that are being registered as innovative agrochemicals, including pesticides, herbicides and fungicides, worldwide, and the agrochemical industry is one of the greatest consumers of OFM. In the same way as in pharmaceuticals, these driving forces are improved metabolic stability against microbial and enzymatic degradation in soil, better translocation in the plant vascular system, better efficacy in pest control at a lower application rate due to optimized target binding, and reduced photodegradation in the field. Fluorinated agrochemicals that are well known include the fungicide trifloxystrobin with several fluorine-containing aromatic rings, the insecticides imidacloprid and chlorfenapyr, and the herbicide flucarbazone-sodium.

The requirements for Agrochemical synthesis by green synthesis are also different from the synthesis of pharmaceuticals, as much larger amounts (thousands of tons of active substance per year) are to be produced, and there are additional stricter requirements concerning the cost per kilogram of active substances, as well as greater careful oversight by authorities concerning potential environmental persistence and ecotoxicology. Solvent savings and better heat management while solving scale-up problems enabled the continuous flow trifluoromethylation of pyridine and pyrimidine agrochemical intermediates has solved problems that enabled scaling up other similar processes in the 1980s. The problems of scaling up similar processes in the 1980s were solved by the development of continuous flow trifluoromethylation of pyridine and pyrimidine agrochemical intermediates, which has reduced solvent consumption and resulted in better heat management. The synthetic biocatalytic processes for some intermediates of fluorinated amino acid herbicides (Fluoro-Glyphosate) have been investigated by engineering aminomutases and transaminases; they may provide routes to biosynthetically derived fluorinated herbicide intermediates.

12. Non-Conventional Green Solvents for Fluorination

12.1 Deep Eutectic Solvents (DES)

Hydrogen Bond Donors (HBDs) and Hydrogen Bond Acceptors (HBAs) formulations are able to form Deep Eutectic Solvents (DES) with greatly reduced melting points when combined; this class of "green" reaction media are becoming an attractive choice in green chemistry for organic synthesis research. The DESs based on choline

chloride (choline chloride/urea, choline chloride/glycerol, and choline chloride/oxalic acid) have especially appealing properties because they can be biodegraded, are relatively nontoxic, consist of renewable components, and can be modified in PHG. In the field of fluorination chemistry, the DES comprised of choline chloride/urea is an efficient solvent for the electrophilic fluorination of activated arenes using Selectfluor, with results comparable to those obtained in DMF but with a significantly smaller environmental impact. The DES medium seems to behave similarly, perhaps always to a greater extent, than polar aprotic solvents do towards the fluoride anions, and thus increases the nucleophilic reactivity of fluoride, while retaining the practical handling benefits of a room temperature liquid.

12.2 Supercritical and Nearcritical Fluids

As a medium in which reaction may take place, supercritical carbon dioxide is investigated for application in fluorination chemistry for its properties of zero surface tension, tunable solvating power and complete recyclability. $ScCO_2$ is a poor solvent for ionic fluoride salts, but it has been used as a co-solvent with other solvents such as acetonitrile or as a transport medium in the supported ionic liquid phase (SILP) system for electrophilic fluorinations. As a result of its high diffusivity and low viscosity, $scCO_2$ can often provide better reaction rates than a system of organic solvents in heterogeneous fluorination reactions. Post-reaction depressurization allows for easy recovery of products without evaporation, whereas CO_2 is not flammable and will not pollute the atmosphere. The water near the critical point (270-370 ^{0}C, 250-300 bar) possesses dramatic increases in its ion product, and it has a much lower dielectric constant, making both acid- and base-mediated fluorinations impossible at ambient conditions.

13. Green Chemistry Metrics and Life Cycle Assessment in Fluorination

13.1 Applying Process Mass Intensity and E-Factor

Strong methods and indicators are needed for quantitative evaluation of the 'greenness' of fluorination processes in terms of both process efficiency and the impact on the environment. The pharmaceutical industry is the preferred measure used to represent the total mass of all materials used to produce a product, known as process mass intensity (PMI), as adopted by the ACS Green Chemistry Institute Pharmaceutical Roundtable. The PMI values typically used in fluorination steps are in the range of 50 to > 500, depending on the reagents' stoichiometry, solvent amount and purification needs. Classical chemical fluorination yields PMI values ranging from 100 to 500+, while electrochemical fluorination in flow, photocatalytic fluorination in water and biocatalytic fluorination in water are better: 15-40, 20-60 and 10-25, respectively.

Life cycle assessment (LCA) is a more comprehensive assessment of the environment that quantifies its impact on the environment over the entire life cycle of a chemical process, not just the manufacturing process. The following emissions and operational parameters must be taken into consideration for fluorination processes for which the LCA is to be done: global warming potential/ozone depletion potential of solvent F emissions, energy required to produce fluorine-containing solvents (especially HF from fluorspar) and aquatic toxicity of fluorine-containing process waste. The global warming potential (GWP) of the electrochemical process compared to the Pd-catalyzed nucleophilic fluorination of the corresponding aryl substrate is typically found to be 30–60% lower when using renewable electricity for powering the process, mainly because of the avoided use of a reagent and the lower consumption of solvents.

14. Challenges and Future Perspectives

14.1 Current Limitations and Knowledge Gaps

However, the implementation of 'green' fluorination chemistry in the synthesis of a wide range of bioactive molecules still has a wealth of challenges to be overcome. Many green pathways have been known and successfully applied for simple model-based substrates under the idealized conditions on which they have been developed, and most of these methodologies are not easily applicable to complex and multifunctional substrates like drug molecules with several potentially reactive sites and acid/base sensitive functionalities. The creation of chemoselective tools and protecting group strategies that are consistent with green fluorination situations is a vital unmet need. Second, from a green chemistry point of view, it is ideal, but, as mentioned, biocatalytic fluorination currently has a relatively narrow substrate scope and can be performed mostly on molar substrates close to the catalytic site, such as adenosyl or amino acid-derived substrates. To expand enzymatic fluorination to widely diverging scaffolds in medicinal products calls for significant scaffold design efforts.

Third, the economic competitiveness of green fluorination methods compared to the existing industrial methods is not realized at the production scale for most of the methodologies. A detailed techno-economic analysis taking into account capital cost, reagent recycling, energy consumption and regulatory compliance is required to guide industrial adoption. Fourth, the disposal and fate of byproducts of fluorinated chemical synthesis with recalcitrant molecules containing fluorine, which can give rise to environmental fluorine loadings, are still an issue.

Future research is important in the development of strategies for the recovery and recycling of fluorine from synthesis waste streams, as is the case for the platinum group metals in the pharmaceutical industry.

14.2 Emerging Opportunities and Future Directions

There are also several promising new methods poised to bring greater advancement to green fluorination chemistry in the future. Enantioselective C–F bond formation using earth-abundant transition metal catalysts (Iron, Cobalt, Nickel, or Manganese catalysts) is still an unsolved challenge, intending to replace the more expensive and less sustainable precious metal catalysts. Iron-catalyzed radical fluorination in particular is a highly attractive and underutilized area of chemistry where the ability of Fe (II)/Fe (III) cycles for generation and transfer of radical intermediates comes into play. Mechanotechnology (ball milling) was applied to fluorination reactions to show that these reactions can proceed without any employment of solvents, and the application to deoxyfluorination and electrophilic fluorination of activated molecules held great promise.

By the combination of photocatalysis with biocatalysis, using light-harvesting organic chromophores and enzymes as the catalytic component, it may be possible to perform new classes of C–H fluorination reactions with unparalleled chemoselectivity and 100% stereochemical control with excellent oxidation selectivity under aqueous conditions. The ultimate goal of green synthesis is that synthetic biology technologies can be used to transform organic molecules and install a heterologous fluorinase pathway in high cell density fermentation organisms (E. coli, S. cerevisiae) to enable scale-up production of required small molecules, such as building blocks, using fermentation processes. Lastly, the development and evolution of AI-powered retrosynthesis platforms that incorporate greenness scores will be a major force shaping drug discovery programmes' choice of sustainable fluorination methods at an increasingly early stage in the process.

15. Conclusion

Over the last decade, there has been a remarkable "fusion" of the general principles of green chemistry with the ever-increasing interest in the synthesis of fluorinated molecules, which are widely used in pharmaceutical, agrochemical and materials applications. The resultant data from the surveyed literature conclusively indicated green fluorination chemistry is far more than a theoretical possibility; it is becoming more of a reality and more economically competitive with conventional methods. In these methods that provide clean energy inputs, C–F bond formation is achieved at ambient temperature with photocatalytic and electrochemical methods; flow chemistry handles reactive fluorinating agents with safety and efficiency; biocatalytic fluorinases are operated under extremely mild conditions (water, physiological temperature); and machine learning speeds the discovery of optimal green synthesis routes. The use of strong green chemistry metrics such as PMI, E-factor, and LCA gives a quantitative basis for the comparison of the methods using an objective criterion to select processes.

However, there are still challenges, including achieving wider substrate scope and scalability of biocatalytic approaches, designing “green processes” of earth-abundant metal catalysts for enantioselective fluorination at an industrial scale, and demonstrating the techno-economic competitiveness of the process. The future of the field, however, looks bright for sustainability as if the regulatory push, corporate sustainability agenda and the inherent scientific attractiveness of high-impact biological functions attained by a relatively benign chemistry were more than enough to secure it. We expect the industrial application of electrochemical flow fluorination, the first commercial utilization of biocatalytic C–F bond formation, as well as the routine use of the AI-driven green fluorination paradigm for pharmaceutical discovery, to take place in the coming decade. The green chemistry fluorination revolution is not far in the future; it is happening here, now.

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Kande Madhavi: Contributed to data curation, organization of the literature.

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