Strategies for Nucleophilic C(sp^3)–(Radio)Fluorination

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ABSTRACT: This Perspective surveys the progress and current limitations of nucleophilic fluorination methodologies. Despite the long and rich history of C(sp^3)–F bond construction in chemical research, the inherent challenges associated with this transformation have largely constrained nucleophilic fluorination to a privileged reaction platform. In recent years, the Doyle group—along with many others—has pursued the study and development of this transformation with the intent of generating deeper mechanistic understanding, developing user-friendly fluorination reagents, and contributing to the invention of synthetic methods capable of enabling radiofluorination. Studies from our laboratory are discussed along with recent developments emanating from others in this field. Fluoride reagent development and the mechanistic implications of reagent identity are highlighted. We also outline the chemical space currently inaccessible under the purview of current synthetic technologies, and a series of future directions in the field that can potentially fill the existing dark spaces.

INTRODUCTION

The introduction of fluorine into molecular scaffolds, while rare in nature, is a valuable transformation in the field of synthetic organic chemistry.[1–15] The unique characteristics of fluorine—when installed at a specific position on a molecule—can markedly influence a compound's physiochemical properties.[16] It is, therefore, unsurprising that many industries have invested significant effort and resources into the development of synthetic methods to fluorinate organic molecules. In 2018 alone, approximately 50% of novel small-molecule drugs approved by the Food and Drug Administration (FDA) contained fluorine, and in 2019, 41% of the New Chemical Entities approved by the FDA contained at least one fluorine atom.[17–19] In addition, fluorinated molecules play a vital role in diagnostic medicine through the incorporation of fluorine-18 (^{18}F), which is the most frequently employed radioisotope for positron emission tomography (PET) imaging.[5]

Installing these strong bonds (C–F bond ~115 kcal/mol) is canonically accomplished by interfacing various functional groups with either electrophilic (F^+ or $F\bullet$) or nucleophilic (F^-) sources of fluorine.[7,20] With these two general reagent classes, there exist diverging reaction mechanisms, chemical spaces, and synthetic limitations. For example, while the electrophilic fluorinating reagents—such as fluorine (F_2) gas, hypofluorites, and fluoroxysulfates—have been used for their high reactivity, their corrosive nature, handling challenges, and functional group intolerance encouraged the development of alternative reagents.[7] This inspired the introduction of the bench-stable and user-friendly N–F reagents that have been critical to the progression of benchtop fluorination chemistry. Reagents—such as Selectfluor® and N-fluorobenzenesulfonimide (NFSI)—are key examples of how electrophilic fluorinating reagents have advanced from "first generation" fluorine sources to compounds with enhanced stability and high reactivity.[21–25]

Nucleophilic fluorination strategies are highly sought after, as they provide a strategic alternative for the installation of fluorine through polar mechanisms. This offers a complementary approach to the mechanisms of fluorine atom transfer accessed using electrophilic pathways. In the context of reagent profiles, sources of fluoride are practical in that they are often inexpensive, bench-stable, and readily accessible.[6,14,20] Furthermore, the development of these reagents has obviated the need for F_2 gas, which posed a significant safety and practicality challenge in fluorination chemistry.[20,26] Furthermore, fluoride reagents do not behave as oxidants, whereas electrophilic fluorinating reagents are generally oxidizing. Thus, nucleophilic fluorination strategies present orthogonal functional group compatibility by comparison to electrophilic strategies.[20,25] Finally, from a radiochemical perspective, [^{18}F]fluoride is the preferred reagent for PET tracer synthesis.[5,27–33]

Despite the synthetic utility and practicality of nucleophilic fluorination, the recalcitrant reactivity profile of fluoride remains a barrier to progress in this field. For example, fluoride sources often suffer from attenuated reactivity in substitution reactions, attributed primarily to the high charge density of fluoride and to the resulting impact upon solvation.[20] Despite important advances in the design of nucleophilic reagents, in the nearly 200 years since the very

first report of a nucleophilic fluorination reaction (in 1835), the available nucleophilic fluorinating reagents are largely limited to those presented in Figure 1.[34] Throughout the past decade, the Doyle laboratory has explored synthetic methodology development in the field of nucleophilic fluorination. With this Perspective, we aim to share our insights on the field by highlighting reagent designs and catalytic strategies that achieve mild and selective nucleophilic fluorination.

Special consideration is given to transformations of high interest in medicinal and process chemistry for which development has been limited. We note at the outset that this Perspective will focus solely on nucleophilic C(sp^3)–fluorination chemistry. The development of new synthetic methodologies for C(sp^2)–F bond formation is of broad importance and there have been many important contributions to this field over the past two decades. While we do not discuss this body of work specifically, we direct the interested reader to reports by experts in the field.[1,35–41] The four areas of nucleophilic C(sp^3)–fluorination this Perspective will cover are **1)** leveraging functional groups for fluorination, **2)** C(sp^3)–H fluorination, **3)** the synthesis of monofluorinated stereogenic centers, and **4)** radiofluorination. Finally, we will analyze the accessible chemical space provided by these nucleophilic fluorination methods and through this analysis, identify the remaining limitations and future directions of the field.

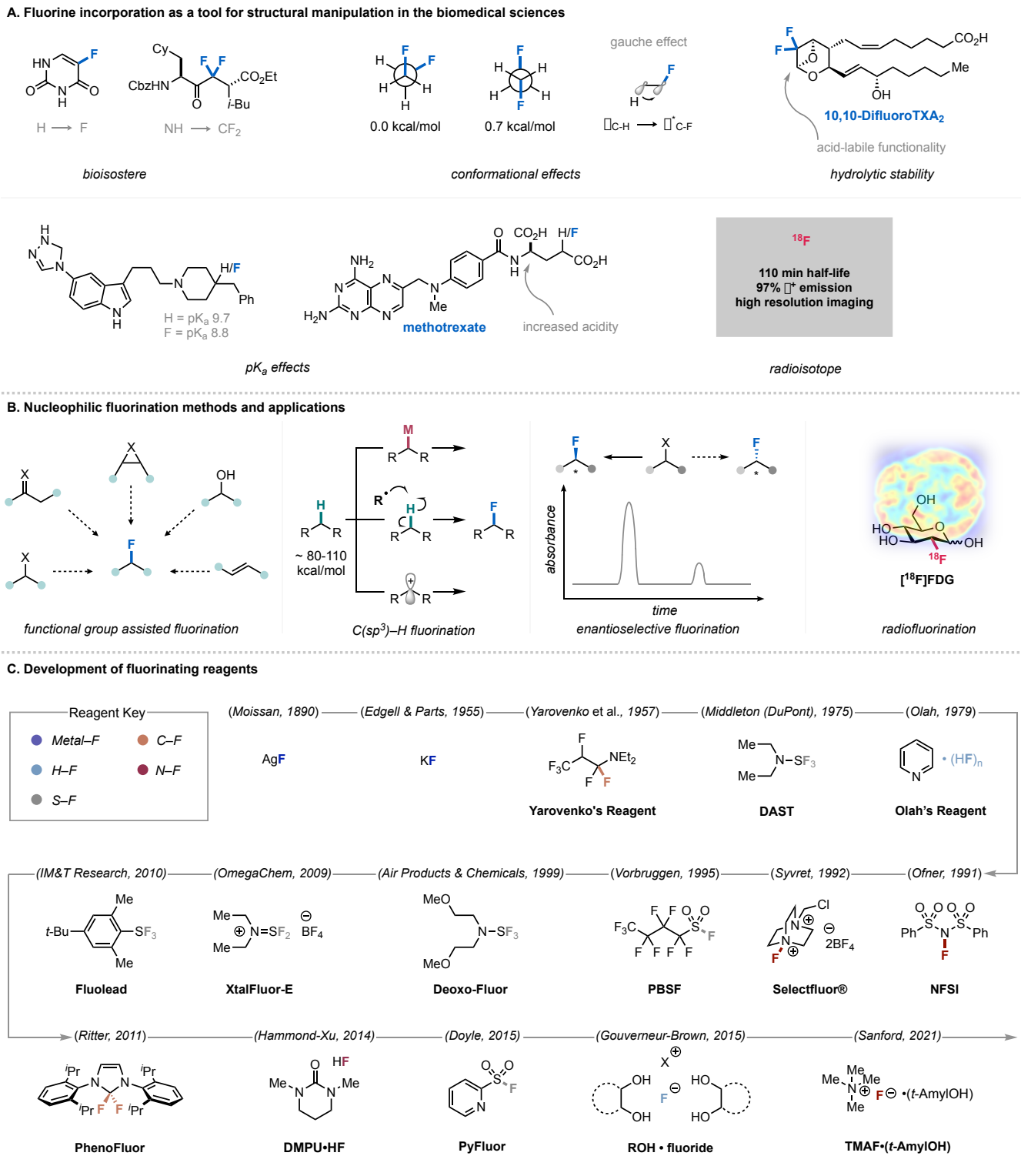

Figure 1. A) The effect of fluorine on the physiochemical properties of small molecules.[42,43] **B)** Methodologies and applications of nucleophilic fluorination in organic chemistry. **C)** Timeline of nucleophilic fluorination reagent development.[44–47]

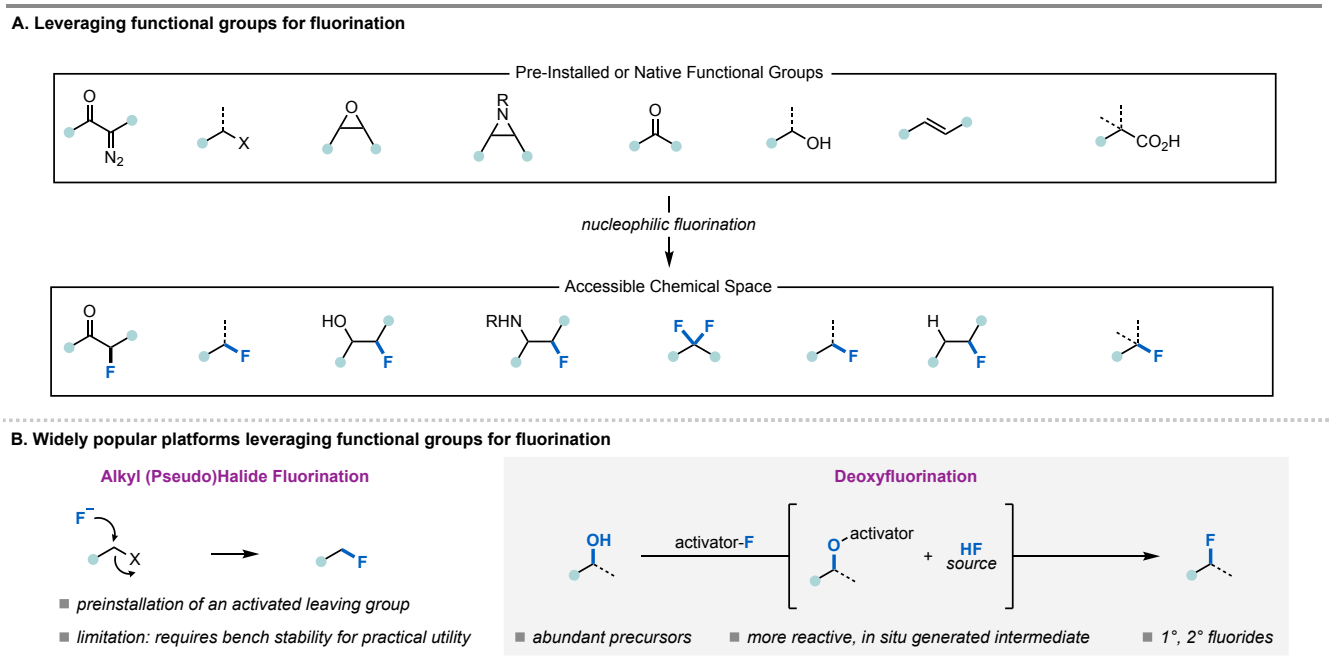

Figure 2. Overview of strategies to leverage functional groups for nucleophilic fluorination.

Chapter One: Leveraging Functional Groups for Fluorination

S_N1 and S_N2 reaction mechanisms are the touchstone of organic chemistry and have found widespread use in halogenation reactions. However, the poor nucleophilicity and high basicity of fluoride render nucleophilic fluorination via substitution a significant synthetic challenge.[7] Chemists have developed several strategies to overcome the reactivity challenges of fluoride, one being the manipulation of various substrate-bound functional groups for nucleophilic substitution (**Figure 2A**). While pre-functionalization is an empowering strategy for fluorination, the limitations imposed by the need to install these reactive handles have given rise to a complementary strategy of leveraging more abundant and stable functional groups as C–F bond precursors—such as alcohols, alkenes, ketones, and carboxylic acids—to expand the pool of possible starting materials (**Figure 2B**). In this chapter, we highlight key examples of functional groups that have been exploited for nucleophilic fluorination and discuss the opportunities for further reaction development.

Before a discussion of more modern methodologies, it is important to highlight the Finkelstein reaction, a classic reaction in organic chemistry that established the framework to leverage functional groups for fluorination.[48] The Finkelstein reaction enables the synthesis of alkyl fluorides and harnesses the inherent leaving group ability of electrophilic alkyl halides/pseudohalides in an S_N2 reaction with a metal halide nucleophile to accomplish a formal halide exchange. The extent of reaction success in this context depends on numerous factors, including nucleophile strength, leaving group identity, and anion stabilization/solvation. For example, weakly nucleophilic metal fluorides undergo swift reaction with strongly electrophilic alkyl halides/pseudohalides, due to both high stabilization of the leaving group and the strength of the resulting C–F bond. However, the high temperatures typically required for solvation (> 100 °C) often lead to competitive elimination, delivering the undesired alkene byproduct. Furthermore, only primary alkyl fluorides can be accessed via the Finkelstein reaction; secondary, vinyl, aryl, and tertiary alkyl halides are notably unreactive under the same conditions (**Figure 3**).

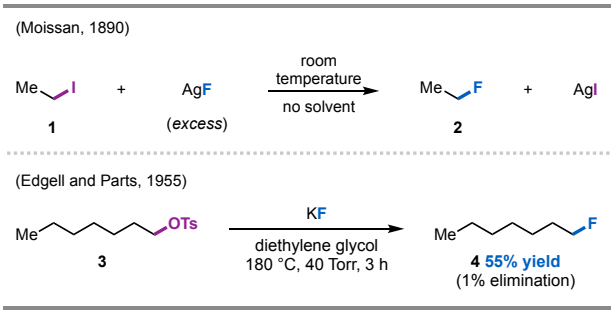

Figure 3. Early examples of fluorination via nucleophilic substitution.

Deoxyfluorination. Drawing inspiration from the Finkelstein reaction, chemists have developed methods to leverage native functionality for fluorination, with special interest paid to motifs commonly present in biologically active molecules. Owing to the abundance of alcohols as feedstock chemicals, deoxyfluorination—which conceptually proceeds via an oxygen activation/deoxygenation event while simultaneously providing a source of fluoride—is the most widely utilized methodology for the preparation of primary and secondary aliphatic fluorides (**Figure 2B**). Deoxyfluorination enables access to highly reactive leaving groups and/or nucleophiles *in situ*, thereby bypassing the synthetic steps required to either generate and store fluoride sources or convert alcohols into isolable, more reactive electrophiles.[49,50]

In 1957, discovery of the first deoxyfluorination reagent, Yarovenko's reagent (**5**), revolutionized the field of aliphatic fluorination (**Figure 4A**).[51] In solution, the reagent readily eliminates fluoride to form an iminium species, and the alcohol substrate attacks the iminium carbon to generate a highly reactive leaving group that is displaced by fluoride. Ultimately, cleavage of the strong alcohol C–O bond is driven thermodynamically by formation of the amide byproduct.

Deoxyfluorination became truly popularized, however, with the discovery and development of S–F reagents. Notably, the introduction of diethylaminosulfur trifluoride (DAST) (**7**) has enabled access to primary, secondary, and tertiary fluoride products from both alcohol and carbonyl starting materials (**Figure 4B**).[52,53] However, reactions facilitated by DAST can also give rise to either undesired elimination or rearrangement products. Additionally, DAST rapidly disproportionates to an explosive degradation product upon heating, leading to safety concerns for reagent storage and process applications.[54,55]

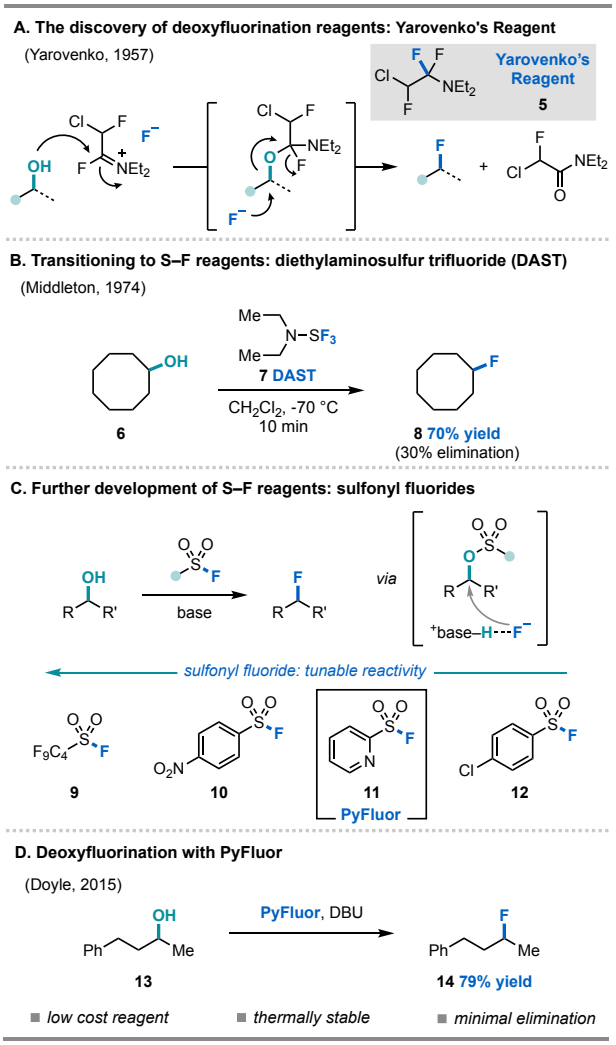

Figure 4. Deoxyfluorination reagents. **A)** Early discoveries from Yarovenko. **B)** Middleton's development of diethylaminosulfur trifluoride (DAST). **C)** Sulfonyl fluorides as stable reagents for nucleophilic fluorination. **D)** PyFluor as a deoxyfluorination reagent from Doyle and coworkers.

The potential of deoxyfluorination reactions as valuable transformations soon prompted the systematic design of safer, more thermally stable DAST derivatives, such as Deoxo-Fluor and the XtalFluor collection.[54,56] As interest in reagent development continued, sulfonyl fluorides soon became established for their utility in deoxyfluorination as well (**9**–**12**, **Figure 4C**). In a seminal report, Vorbrüggen and coworkers noted that *n*-perfluorobutanesulfonyl fluoride (PBSF) may react as a mixed anhydride of nonaflic acid and hydrogen fluoride (HF).[57] Conceptually, they postulated that alcohols may—upon reaction with PBSF in the presence of base—form the corresponding inverted fluorides via the *O*-nonaflate, with amidine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the non-nucleophilic base to prevent competitive side reactivity. Moreover, the authors considered that the resulting DBU•$(HF)_n$ complex formed *in situ* may enhance the nucleophilicity of fluoride in nonpolar solvents.

Broadly, sulfonyl fluorides are attractive deoxyfluorination reagents due to their stability toward reduction, hydrolysis, and thermolysis, in addition to their relative ease of synthesis.[58] Furthermore, sulfonate esters have been established as widely utilized precursors in both multistep fluorination and radiofluorination protocols.[59–61] For these reasons, the Doyle group was inspired to develop an inexpensive, operationally simple, and chemoselective sulfonyl fluoride deoxyfluorination reagent. To this end, the authors envisioned that a sufficiently electron-deficient aryl fluoride could react with an alcohol to effect deoxyfluorination from the corresponding ester. Based on this design principle, fine-tuning of electronics and structure led to the discovery of 2-pyridinesulfonyl fluoride, known commercially as PyFluor (**11**, **Figure 4C**).[62,63] In assessing the utility of this new reagent, the combination of DBU with several electron-deficient sulfonyl fluorides was explored for the deoxyfluorination of 4-phenyl-2-butanol (**13**, **Figure 4D**). Most electron-deficient aryl and heteroaryl sulfonyl fluorides outperformed PBSF, while PyFluor afforded 79% yield with >20:1 selectivity for fluorination over elimination (**14**, **Figure 4D**). Finally, in addition to its exceptional functional group tolerance, PyFluor is a readily accessible, inexpensive, and highly bench stable nucleophilic fluorination reagent by comparison to available alternatives.

While the Doyle group investigated sulfonyl fluoride reagent design in-depth, others explored the design of C–F reagents as a complementary approach. For example, Ritter and coworkers discovered that PhenoFluor[37], originally developed to facilitate the deoxyfluorination of phenols, could also effect deoxyfluorination from aliphatic alcohols, enabling access to fluorinated motifs previously inaccessible as a consequence of either functional group intolerance or competitive elimination.[49] For example, deoxyfluorination can be achieved with PhenoFluor (**15**) from an artemisinin derivative to deliver the fluorinated analog in 79% (**16**, **Figure 5A**). Additionally, PhenoFluor confers minimal deleterious side reactivity and offers predictable and selective incorporation of fluoride in

complex molecules bearing sensitive functionality, such as amino acids, sugars, steroids, alkaloids, and polyketides bearing multiple hydroxyl groups (**Figure 5A**).

Despite PhenoFluor's bench stability and highly selective reactivity, it is susceptible to rapid hydrolysis in the presence of water. In subsequent publications, Ritter and coworkers synthesized various PhenoFluor derivatives with the goal of developing a moisture-stable reagent.[38,39,64] Similarly, Hu and coworkers applied electronic and structural design principles to develop the 3,3-difluoro-1,2-diarylcyclopropene (CpFluor and variants) scaffold (**19**, **Figure 5B**) for efficient and selective deoxyfluorination of complex, electron-rich alcohols (**Figure 5B**).[65] It should be noted that despite the impressive scope of deoxyfluorination reagents developed, these transformations remain limited by the kinetics of the substitution mechanism through which they occur.

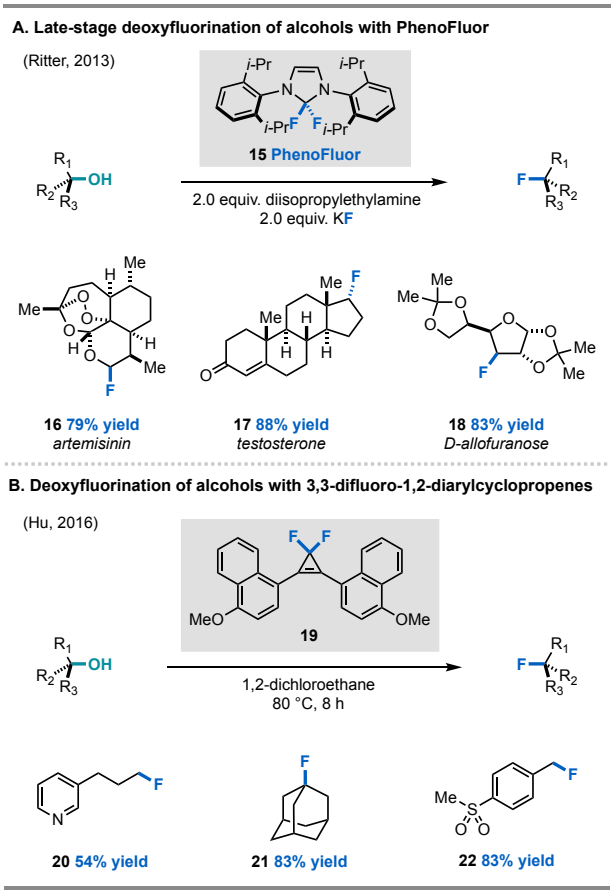

Figure 5. A) Deoxyfluorination with PhenoFluor from Ritter and coworkers. **B)** Deoxyfluorination with 3,3-difluoro-1,2-diarylcyclopropenes from Hu and coworkers.

Diazo Insertion. Chemists have leveraged a number of high-energy precursors—such as diazo compounds, epoxides, and aziridines—to facilitate fluorination chemistry.[66–68] Diazo species, which favorably react to release nitrogen gas and form carbene intermediates, are powerful tools for interfacing with poorly nucleophilic fluoride and have been leveraged for both direct and transition-metal catalyzed fluorination. For example, Moody and coworkers leveraged the Lewis acidity of HBF_4•Et_2O to enable room temperature nucleophilic fluorination of α-diazo-β-ketoesters (**Figure 6A**).[69] The reaction not only proceeded readily in a flow reactor, thereby reducing handling hazards of the diazo starting materials, but also provided access to valuable α-fluoro-β-ketoesters which can be readily converted to pharmaceutically relevant fluorinated heterocycles. Notably, despite large demand from pharmaceutical and agrochemical industries, very few methods exist for the synthesis of fluorinated heterocycles via nucleophilic fluorination; in fact, most strategies employ electrophilic fluorination of preformed heterocyclic scaffolds.

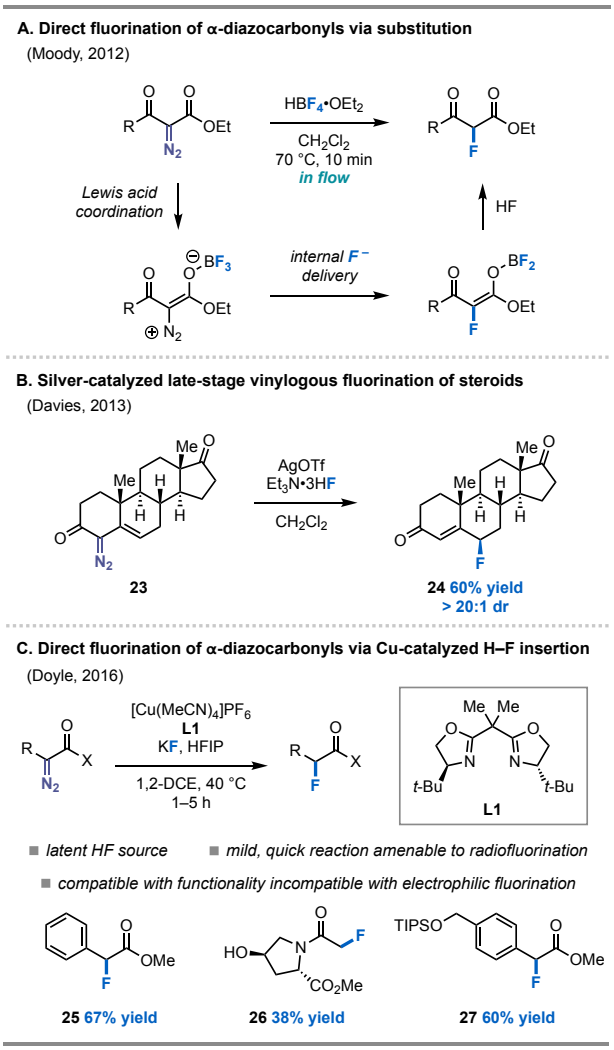

Figure 6. Examples of direct nucleophilic fluorination from diazocarbonyl compounds. **A)** Lewis acid-assisted diazocarbonyl fluorination from Moody and coworkers. **B)** Silver-catalyzed late-stage vinylogous diazocarbonyl fluorination of steroids. **C)** Copper-catalyzed HF insertion for the direct fluorination of diazocarbonyl compounds from Doyle and coworkers.

Transition-metal insertion into diazo compounds to form electrophilic metal carbenoids is another attractive route toward fluorination, and circumvents the limitations of classic substitution chemistry. In 2013, the Davies group took advantage of this concept to leverage potent carbenoid electrophiles for a variety of transformations, including the vinylogous fluorination of vinyl diazoacetates (**Figure 6B**).[70] Several years later, the Doyle

group explored electrophilic metal carbenoid intermediates for the direct fluorination of α-diazocarbonyl compounds (**Figure 6C**).[71] In this work, the authors discovered that the combination of [Cu(MeCN)$_4$PF$_6$] with a bis(oxazoline) ligand (**L1**) and KF/HFIP as a latent HF source allowed for mild reaction conditions (< 50 °C, 1–5 h) by comparison to direct fluorination, observing the fluorination of methyl phenyldiazoacetate (**25**) in 68% yield at 40 °C in one hour. Importantly, this feature allowed translation of the methodology to the radiochemical space (*vide infra*). The optimized reaction conditions furnished α-fluorocarbonyl products bearing numerous functional groups previously incompatible with electrophilic fluorination, allowing transformations from amino acid derivatives, peptides, and glycosides containing various unprotected protic amines and alcohols (**Figure 6C**).

Alkene Fluorination. While high-energy and strained substrates have afforded access to α-fluorocarbonyls, β-fluoroalcohols, and β-fluoroamines, most substrates leveraged in this type of approach require at least one-step syntheses from abundant, commercial feedstocks. Therefore, there is significant interest in directly engaging the native alkene functionality—an abundant chemical feedstock—to access similar fluorinated products.[72,73]

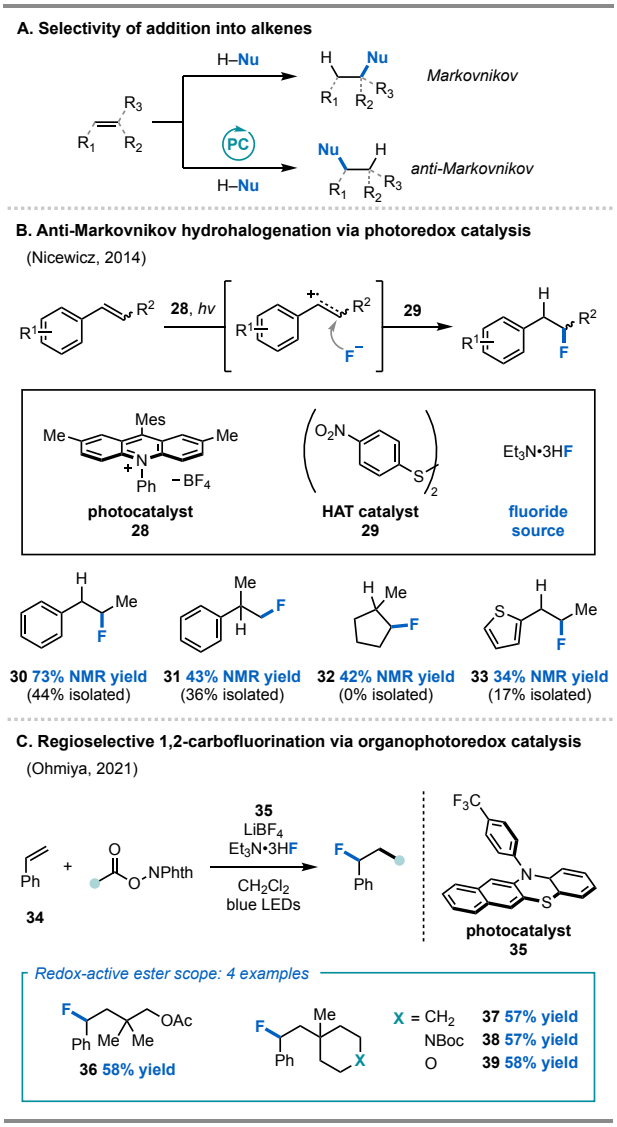

Figure 7. Nucleophilic fluorination of alkenes. **A)** Markovnikov and anti-Markovnikov selectivity for nucleophilic fluorination of alkenes. **B)** Photocatalytic anti-Markovnikov hydrohalogenation from Nicewicz and coworkers. **C)** Organophotocatalytic regioselective 1,2-carbofluorination from Ohmiya and coworkers.

However, without the thermodynamic driving forces associated with gaseous byproducts or ring strain release, the functionalization of alkenes requires alternate strategies, one being the generation of transient reactive intermediates *in situ*. For example, the addition of HF across an alkene generates a carbocation electrophile which undergoes nucleophilic attack to provide the Markovnikov functionalized product. Alternatively, new mechanistic platforms must be developed to generate other reactive species which can be interfaced with nucleophiles. One such platform is photoredox catalysis—offering either electron or energy transfer pathways to versatile radical intermediates from alkene starting materials—to enable complementary selectivity, enhanced functional group tolerance, and greater flexibility of accessible motifs by comparison to their heterolytic counterparts (**Figure 7A**).

Recently, Nicewicz and coworkers leveraged the mildness of photocatalysis and inherent reactivity of radicals to effect the anti-Markovnikov hydrofunctionalization of alkenes (**Figure 7B**).[74] This transformation proceeds via oxidative generation of the alkene radical cation, followed by nucleophilic attack and hydrogen atom transfer (HAT). The nucleophile scope is broad, encompassing not only fluorination, but also chlorination, phosphorylation, and sulfonylation. Specifically, hydrofluorination of styrene derivatives proceeded in good yield, and sterically hindered alkenes with more demanding oxidation potentials—such as trialkyl-substituted alkenes—were also amenable to fluorination, as determined by analysis of the crude reaction mixture. Similarly, Ohmiya and coworkers have harnessed alkenes in photocatalysis to achieve nucleophilic 1,2-carbofluorination (**Figure 7C**).[75] This work describes a vicinal difunctionalization protocol capable of rapidly constructing chemical complexity in a single step via three-component coupling between a vinylarene, an aliphatic redox-active ester (RAE), and a nucleophile.

Decarboxylative Fluorination. Photocatalytic decarboxylation is a widely employed mechanism in electrophilic fluorination given the practical advantages of using carboxylic acid precursors. Key work by Groves and coworkers represents one of the few examples of direct nucleophilic decarboxylative fluorination, wherein a manganese porphyrin catalyst, stoichiometric oxidant, and $Et_3N•3HF$ enabled the decarboxylative fluorination of a diverse set of benzylic, aliphatic, and α-heteroatomic carboxylic acids (**Figure 8A**).[76] The Doyle group envisioned a complementary photocatalytic approach to access similar products via a redox-neutral pathway (**Figure 8B**). In the proposed mechanism, a reductively generated radical intermediate can engage in oxidative radical-polar crossover (ORPC), paving the way for photocatalytic fluorination via a carbocation intermediate.[77] As an initial target substrate class, the authors selected redox-active phthalimide esters. While RAEs must be pre-formed from carboxylic acid precursors, these reactions are straightforward, quick, robust, and enable access to a wide variety of radical intermediates from readily available starting materials. The S_N1-type mechanism of this transformation, coupled with the mild reaction conditions permitted by photoredox catalysis, facilitates the fluorination of highly substituted aliphatic substrates, which are challenging to synthesize by other methods—nucleophilic and electrophilic alike. Furthermore, substrates bearing electron-rich functionality—often prone to deleterious side reactivity under the highly oxidizing conditions of electrophilic fluorination—were well-tolerated.

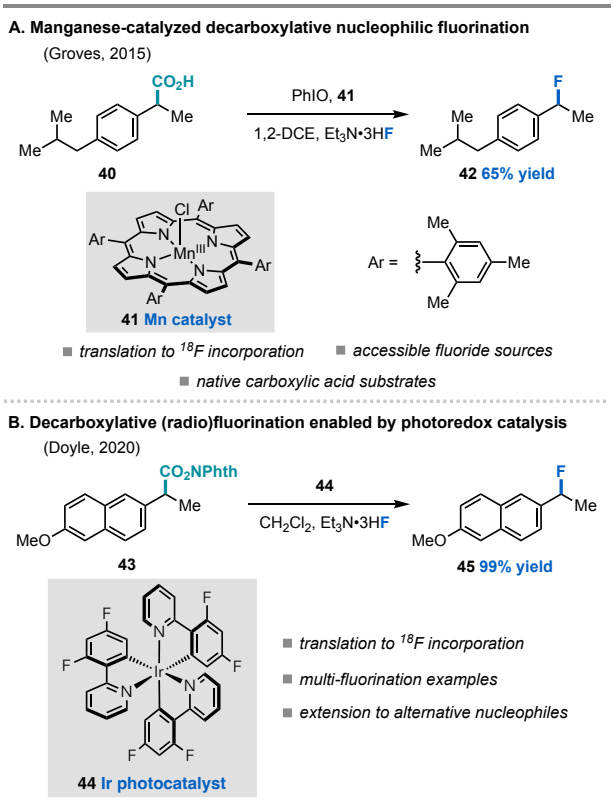

Figure 8. Examples of decarboxylative nucleophilic fluorination. **A)** Manganese-catalyzed decarboxylative nucleophilic fluorination from Groves and coworkers. **B)** Photocatalytic decarboxylative (radio)fluorination from Doyle and coworkers.

Chapter Two: C(sp^3)–H Fluorination

The ability to access fluorinated scaffolds directly from C(sp^3)–H bonds holds the potential to streamline synthetic routes and enable a wide variety of late-stage derivatization efforts. Despite the wealth of literature devoted to C(sp^3)–H functionalization, examples of C(sp^3)–H fluorination are predominantly restricted to the utilization of electrophilic fluorinating reagents, while few strategies for nucleophilic C(sp^3)–H fluorination have been disclosed. In assessing the current space of nucleophilic C(sp^3)–H fluorination chemistry, it becomes apparent that methodologies generally diverge at the specific mode of C(sp^3)–H bond activation, achieved through either transition-metal insertion into C(sp^3)–H bonds, the direct anodic oxidation of C(sp^3)–H bonds, or the generation of carbon-centered radical intermediates via HAT from C(sp^3)–H sites.[6] In the context of anodic oxidation, the interested reader is directed to original reports discussing electrochemical approaches to nucleophilic fluorination.[78–81]

C(sp^3)–H fluorination reactions that proceed via transition metal-catalyzed C(sp^3)–H insertion have undergone extensive research and development. However, strategies predicated on electrophilic fluorination have dominated this space. This is a result of limitations inherent to C(sp^3)–F reductive elimination from low-valent transition-metals such as Pd(II), as electrophilic fluorinating reagents not only perform

fluorine atom transfer, but also serve as stoichiometric oxidants to produce the high-valent Pd(IV) intermediates required for facile C(sp^3)–F reductive elimination.[6] In 2012, Sanford and coworkers devised a nucleophilic fluorination strategy for Pd-catalyzed C(sp^3)–H fluorination that decoupled the fluorine source from the stoichiometric oxidant (**Figure 9**).[82] In this work, hypervalent iodine (PhI(OPiv)$_2$) was employed as an exogenous oxidant, with silver fluoride (AgF) as the fluoride source, to accomplish the nucleophilic C(sp^3)–H fluorination of 8-methylquinoline derivatives. Specifically, Sanford and coworkers proposed that chelate-directed C(sp^3)–H activation of the 8-methylquinoline substrate generates a Pd(II) palladacycle intermediate, which is subsequently converted to the key Pd(IV) intermediate via oxidation by ArIF$_2$ generated *in situ.*

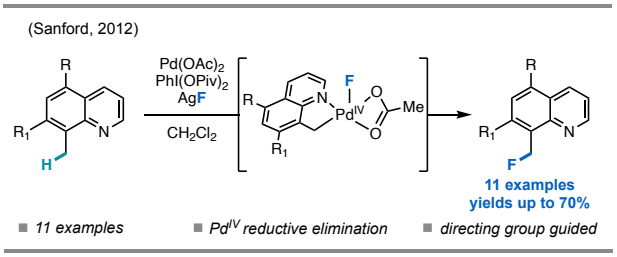

Figure 9. Sanford's Pd-catalyzed nucleophilic C(sp^3)–H fluorination.

Following this report, significant effort was directed toward expanding the types of C(sp^3)–H bonds amenable to nucleophilic C(sp^3)–H fluorination. Allylic fluorides are valuable motifs in medicinal chemistry, and the activation of allylic C(sp^3)–H bonds for nucleophilic fluorination has thus, become a highly desirable transformation. Reports detailing nucleophilic allylic fluorination have predominately required pre-functionalization of the allylic substrate, derivatizing from various building blocks, such as allylic halides, *p*-nitrobenzoates, trichloroacetimidates, and phosphorothioates (**Figure 10A**).[83–86] Furthermore, catalytic strategies effective for unactivated or benzylic C(sp^3)–H fluorination with electrophilic reagents have proven ineffective for allylic fluorination due to competing olefin oxidation.

With this knowledge, the Doyle group turned to a nucleophilic fluorination approach using Pd catalysis, and sought a mechanistic pathway that would circumvent the challenges associated with inner-sphere C(sp^3)–F reductive elimination from Pd(II). Accordingly, the authors explored the efficacy of a Pd(II)–sulfoxide catalyst system for C(sp^3)–H allylic fluorination, a catalyst system previously demonstrated by White and coworkers to promote allylic C(sp^3)–H acetoxylation (**Figure 10B**).[87] It was found that this catalyst, in combination with benzoquinone (BQ) as an oxidant and Et$_3$N•3HF as the fluoride source, successfully delivered the corresponding allylic fluorides. To improve reactivity, a series of metal–salen complexes were evaluated as Lewis acid cocatalysts, from which the combination of co-catalytic (salen)CrCl, Pd(TFA)$_2$ and a bis(benzyl sulfoxide) ligand (**L2**) was found to provide the desired allylic fluorides in excellent yields and with high branched: linear regioselectivity. Altogether, this approach to allylic C(sp^3)–H fluorination represents the first catalytic example of nucleophilic allylic C(sp^3)–H fluorination and was demonstrated across 15 allylic systems, including the late-stage allylic fluorination of a steroid scaffold in 59% yield with good regioselectivity (8:1 branched: linear) (**54**, **Figure 10C**).[88]

As an alternative to transition metal-mediated C(sp^3)–H insertion, radical chemistry has provided a highly enabling route to C(sp^3)–H fluorination. While HAT to access carbon-centered radicals is a common mechanistic feature in both electrophilic and nucleophilic C–H functionalization literature, only three examples of nucleophilic C(sp^3)–H fluorination via radical intermediacy have been disclosed, likely because electrophilic fluorine sources are polarity matched to react with nucleophilic carbon-centered radicals. Therefore, progress towards radical-based nucleophilic C(sp^3)–H fluorination lies in the discovery of key pathways that allow for carbon-centered radicals to productively interface with nucleophilic fluorinating reagents.

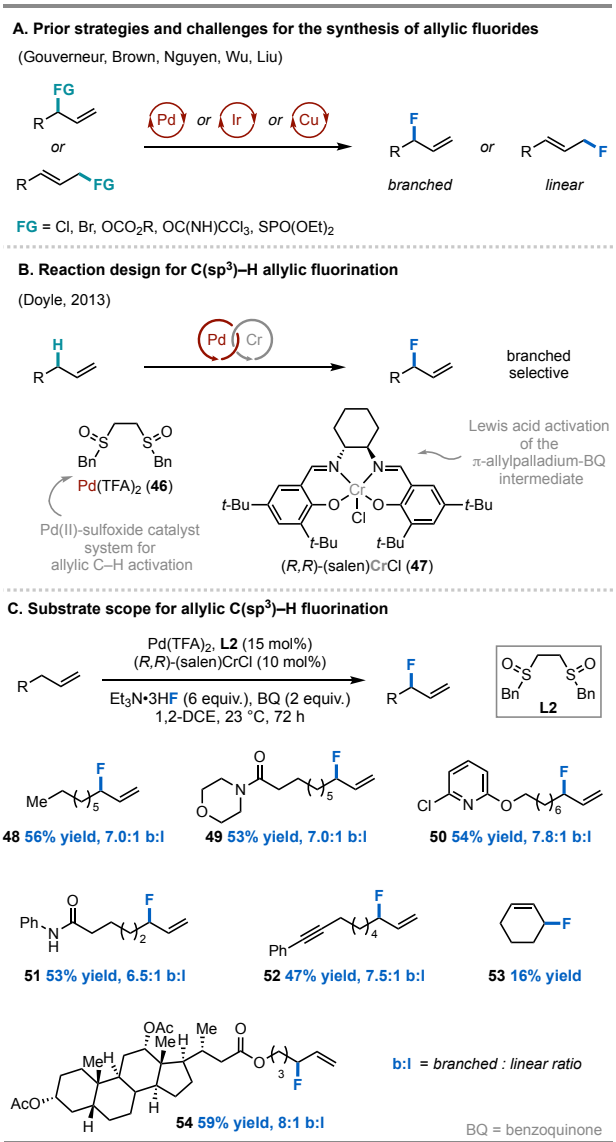

Figure 10. Nucleophilic allylic C(sp^3)–H fluorination in the Doyle group. **A)** Prior strategies and challenges in the synthesis of allylic fluorides. **B)** Reaction design for

palladium-catalyzed nucleophilic C(sp^3)–H allylic fluorination. **C)** Substrate scope for palladium-catalyzed nucleophilic C(sp^3)–H allylic fluorination.

In 2012, Groves and coworkers demonstrated that bioinspired Mn porphyrin catalysts can facilitate sequential HAT and fluorine atom transfer to a carbon-centered radical (**Figure 11A**).[89] This report represented a landmark achievement in the field of C(sp^3)–H fluorination, enabling the first—and at the time only—way to access unactivated alkyl fluoride motifs via direct C(sp^3)–H nucleophilic fluorination. This transformation uses AgF—an inexpensive and readily accessible metal fluoride salt—as the source of fluoride, and iodosobenzene (PhIO) as a stoichiometric oxo-transfer agent. In a subsequent report, the scope of this system was further extended to achieve fluorinated products from benzylic C(sp^3)–H bonds.[90] Impressively, this approach was readily translated to nucleophilic radiofluorination, wherein the incorporation of ^{18}F fluoride was demonstrated across 60 examples with excellent radiochemical conversions (*vide infra*). Zhang and coworkers later applied the conceptual framework laid by Groves through the development of a Cu-mediated HAT/fluorine atom transfer strategy to effect C(sp^3)–H fluorination from a formal Cu(III) fluoride complex (**Figure 11B**).[91] While various Cu(II) halides (such as Cu(II) chloride) are known to facilitate nucleophilic halogenation, Cu(II) fluorides do not possess such reactivity due to the strong anionic nature of the Cu(II)–F bond. However, it was posited that a Cu(III) fluoride species would exhibit more covalent Cu–F bond character, and therefore, enhanced reactivity as a nucleophilic fluorinating reagent. Overall, C(sp^3)–H fluorination from Cu(III) fluoride was demonstrated across seven C(sp^3)–H coupling partners, such as tetrahydrofuran, dioxane, and 18-crown-6.

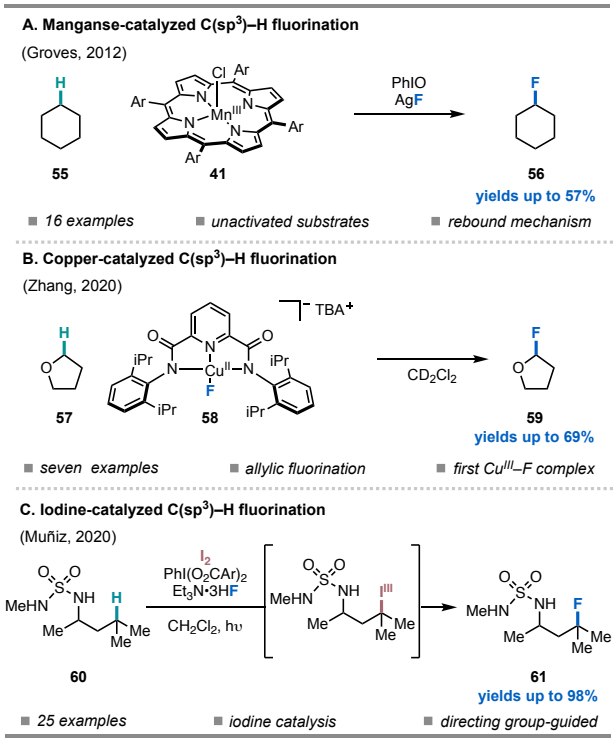

Figure 11. Radical-mediated strategies for nucleophilic C(sp^3)–H fluorination. **A)** Manganese-catalyzed nucleophilic C(sp^3)–H fluorination of alkanes from Groves and coworkers. **B)** Copper-catalyzed nucleophilic C(sp^3)–H fluorination from Zhang and coworkers. **C)** Iodine catalysis for nucleophilic C(sp^3)–H fluorination from Muñiz and coworkers.

More recently, Muñiz and coworkers disclosed an intramolecular methodology for the nucleophilic C(sp^3)–H fluorination of aliphatic sulfonamides and sulfamides (**Figure 11C**).[92] Specifically, this work achieves Hofmann–Löffler–Freytag-type reactivity by leveraging visible light irradiation and iodine catalysis. Important to this chemistry is the generation of a key amidyl radical intermediate from either a sulfonamide or sulfamide substrate, which facilitates intramolecular HAT to generate a carbon-centered radical. Notably, this work provides an example of the exquisite selectivity that may be achieved in HAT chemistry

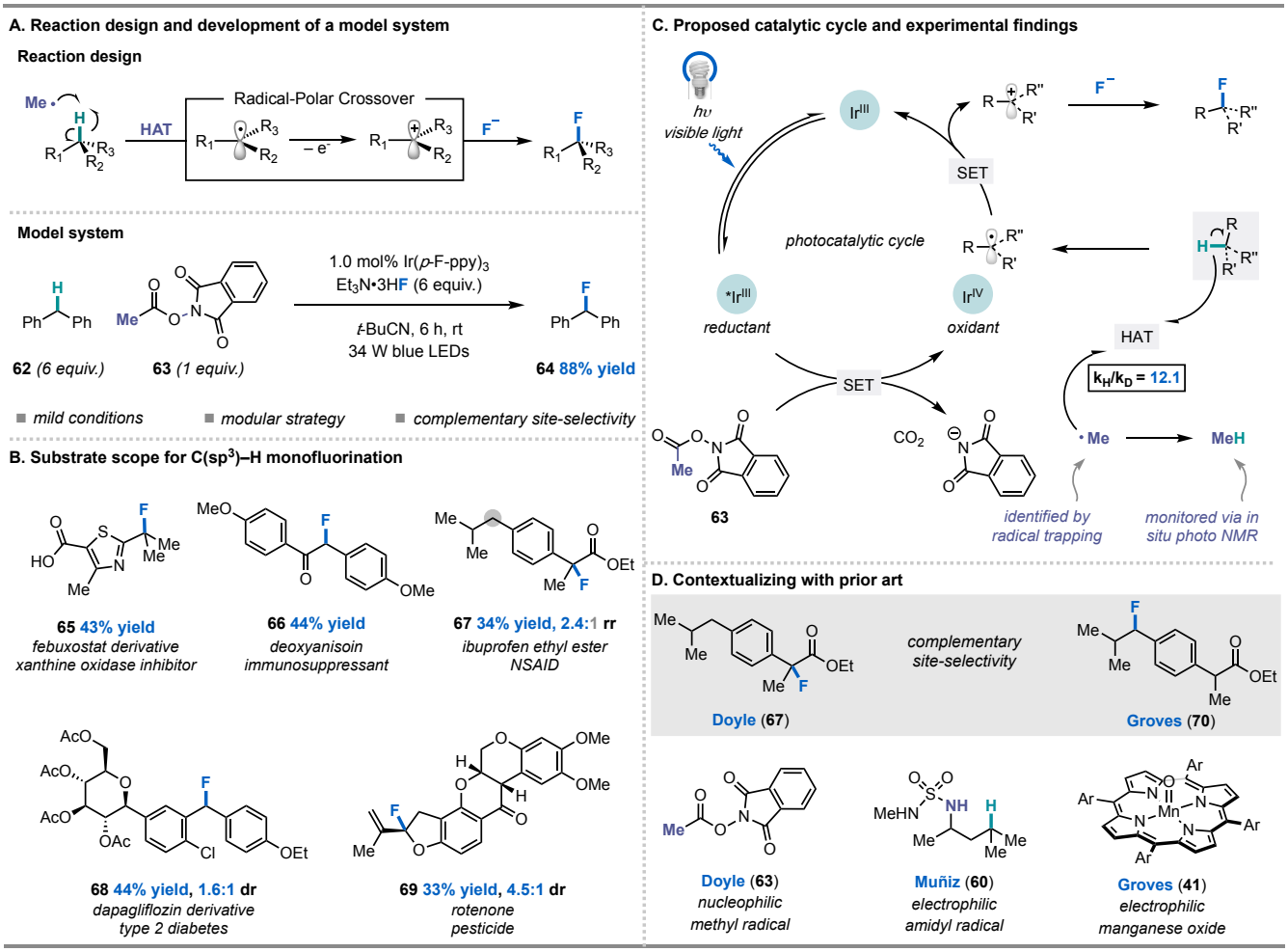

Figure 12. Photocatalytic nucleophilic C(sp³)–H fluorination using methyl radical as a hydrogen atom abstractor in the Doyle group. **A)** Reaction design and model system development. **B)** Select examples of substrate scope. **C)** Proposed catalytic cycle and experimental findings from mechanistic studies. **D)** Contextualizing this work with prior art in nucleophilic C(sp³)–H fluorination.

through the judicious implementation of directing groups. For example, for substrates bearing multiple accessible tertiary C(sp³)–H bonds, fluorination occured with complete selectivity for the C(sp³)–H bond accessible to the 1,6-HAT pathway. Furthermore, this work provides a highly effective solution to tertiary nucleophilic C(sp³)–H fluorination, typically very challenging to achieve through complementary nucleophilic methodologies.

Inspired by radical-mediated methodologies, the Doyle group sought to leverage the benefits of photocatalytic radical generation for the development of a nucleophilic C(sp³)–H fluorination approach.[93] As an alternative to direct interception of the carbon-centered radical intermediate with an electrophile or transition-metal species, the authors envisioned directing the carbon-centered radical through ORPC to deliver a carbocation, a strategy previously demonstrated by the Doyle group in the nucleophilic decarboxylative fluorination of redox-active phthalimide esters (*vide supra*). Most conveniently, this approach combines the benefits of photocatalytic radical generation and oxidation with the versatility of the carbocation as an electrophile.

In this work, mild generation of the carbocation was a priority for reaction design, and the proposed solution was to leverage the mildness of photocatalysis to generate a carbon-centered radical from the C(sp³)–H substrate via HAT, which could then proceed through ORPC to deliver a carbocation (**Figure 12A**). For C(sp³)–H fluorination, the Doyle group leveraged redox-active phthalimides as precursors to HAT mediators. Upon investigation of various HAT precursors, *N*-acetoxyphthalimide (**51**)—a precursor to the methyl radical—enabled C(sp³)–H fluorination in highest yield with broad scope and functional group tolerance, likely due to the strong thermodynamic and entropic driving force associated with the formation of methane (BDE = 105 kcal/mol), a byproduct that is also inert and non-nucleophilic (**Figure 12B**).[94] A mildly nucleophilic radical abstractor such as the methyl radical had yet to be evaluated in the context of C(sp³)–H functionalization, and this reaction platform lent itself to the exploration of new C(sp³)–H bond reactivity and site-selectivity (**Figure 12C**). Furthermore, through the intermediacy of a carbocation, this platform was also extended to broad nucleophile incorporation to construct C(sp³)–C, –N, –O, –S, and –Cl bonds.[93]

Prior to this work, the methyl radical had not been explored as a mediator of HAT in photocatalysis, and we envisioned that the concept of HAT between two C(sp³)

centers could enable access to new modes of reactivity and selectivity. Over the course of our studies, we became particularly interested in understanding whether site-selectivity for C(sp^3)–H fluorination could be modulated and controlled within a complex substrate, and whether the methyl radical could afford novel selectivity patterns in C–H functionalization. Using ibuprofen ethyl ester as a case study, we employed two different HAT mediators—a methoxy radical and a methyl radical—and found that on the basis of polarity matching, these radical species imparted orthogonal site-selectivity for C(sp^3)–H fluorination; while the more electrophilic methoxy radical favored HAT from the more electron-rich, secondary C(sp^3)–H site, the more nucleophilic methyl radical favored HAT from the more electron-poor, tertiary C(sp^3)–H site. This observation was intriguing, as it demonstrates the potential for modularity and predictable site-selectivity in this approach to nucleophilic C(sp^3)–H functionalization on the basis of simple reagent selection. Furthermore, prior examples of C(sp^3)–H functionalization with ibuprofen ethyl ester broadly demonstrate site-selectivity for the secondary C(sp^3)–H site, and therefore, highlight a unique selectivity profile offered by the methyl radical in HAT mechanisms (**Figure 12D**).[93]

We also note that concurrent with our work, Musacchio and coworkers disclosed a strategy for C(sp^3)–H fluorination leveraging an HAT-ORPC pathway. In this approach, HAT is mediated by an electrophilic *tert*-butoxy radical intermediate, liberated upon single-electron reduction and fragmentation of an organic peroxide reagent (**Figure 13A**). While broadly successful in the context of fluorination, this strategy was also amenable to a variety of nucleophilic functionalizations, including hydroxylation, etherification, and acetoxylation (**Figure 13B**).[95]

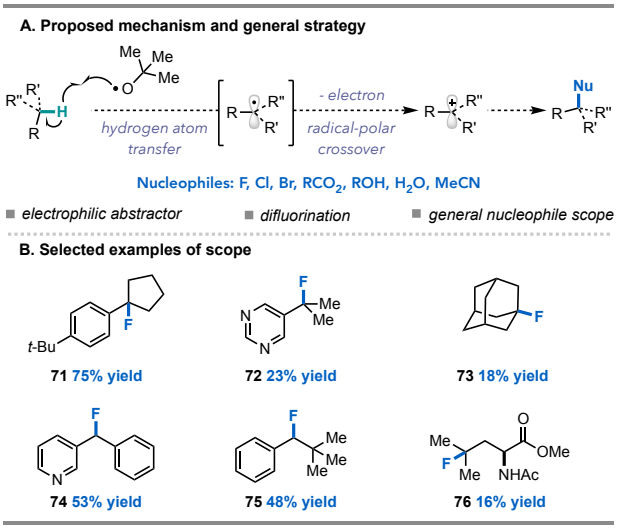

Figure 13. C(sp^3)–H fluorination from Musacchio and coworkers. **A.** Proposed mechanism and catalytic cycle. **B.** Selected examples of scope.

Chapter Three: Asymmetric Nucleophilic Fluorination

The need for enantiopure pharmaceuticals and agrochemicals is well-established, and a large variety of chiral fluorinated motifs have been introduced into several high-profile marketed drugs (**Figure 14A**).[13,96,97] For example, the discovery of fludrocortisone revealed that replacing hydrogen for fluorine at a strategic stereogenic center significantly improved biological efficacy and illustrated the power of fluorine as a bioisostere (**Figure 14C**).[98] Despite the significance of fluorine-containing stereocenters, the breadth of enantioselective nucleophilic fluorination methods remains limited in the context of the variety of asymmetric transformations otherwise at a chemist's disposal. To date, most successful approaches to enantioselective fluoride delivery leverage ring opening events from three-membered heterocycles (**Figure 14A**).[13] These platforms often lead to products of great value; for example, fluoride ring-opening of cyclic ethers yields a fluorohydrin scaffold, a critical architecture in several marketed therapeutics and readily derivatized to value-added substances (**Figure 14C**).[13]

More recently, developments in the field have favored 1,2-difunctionalization of olefins to introduce fluorinated stereocenters (**Figure 14A**).[99–101] However, the challenges inherent to asymmetric fluorination render these examples exceptional rather than common practice. In this chapter, we will highlight the various strategies that have built the field of asymmetric nucleophilic fluorination and address the challenges that remain. For recent reviews covering the extensive literature on asymmetric electrophilic fluorination, please see **refs. 13, 102,** and **103.**[13,102,103]

The development of chiral electrophilic fluorinating reagents has been critical to the progression of the asymmetric electrophilic fluorination field (**Figure 14B**). In particular, *N*-fluoroammonium salts have been widely used to impart enantiocontrol in electrophilic fluorination chemistry.[103] By comparison, asymmetric catalysis with nucleophilic fluoride remains limited, due in part to the poor nucleophilicity of fluoride and its basicity which can lead to either elimination or racemization of the resulting stereocenter. Furthermore, given the scarcity of chiral nucleophilic fluorinating reagents, few strategies exist that successfully abate racemic background reactivity. To date, only a select few reagents, including chiral ureas and chiral amine **81**/Co(salen), are known to impart high enantioselectivity (**Figure 15A**).[104,105] The first asymmetric nucleophilic fluorination was achieved by Hann and Sampson in 1989 via deoxyfluorination using an enantiopure DAST (*S*)-proline analog to afford up to 16% ee of fluorinated products.[106] However, the development of highly enantioselective deoxyfluorination reagents that boast the reactivity and functional group tolerance comparable to current state-of-the-art racemic reagents remains an outstanding challenge.

Asymmetric Ring-Opening Fluorination. In 2002, Haufe and co-workers reported the first studies toward enantioselective nucleophilic fluorination through the asymmetric ring opening of meso- and racemic-epoxides (**Figure 14D**).[107] Specifically, this transformation was achieved by employing an enantiopure (salen)chromium chloride mediator, allowing the conversion of various cyclic epoxides to the corresponding fluorohydrins in up to 66% ee. Due to catalyst poisoning by fluoride anion, this

approach required stoichiometric quantities of the chiral (salen)chromium reagent. Furthermore, high reaction temperatures and polar solvents were required to solubilize AgF, which conferred lower levels of asymmetric induction.

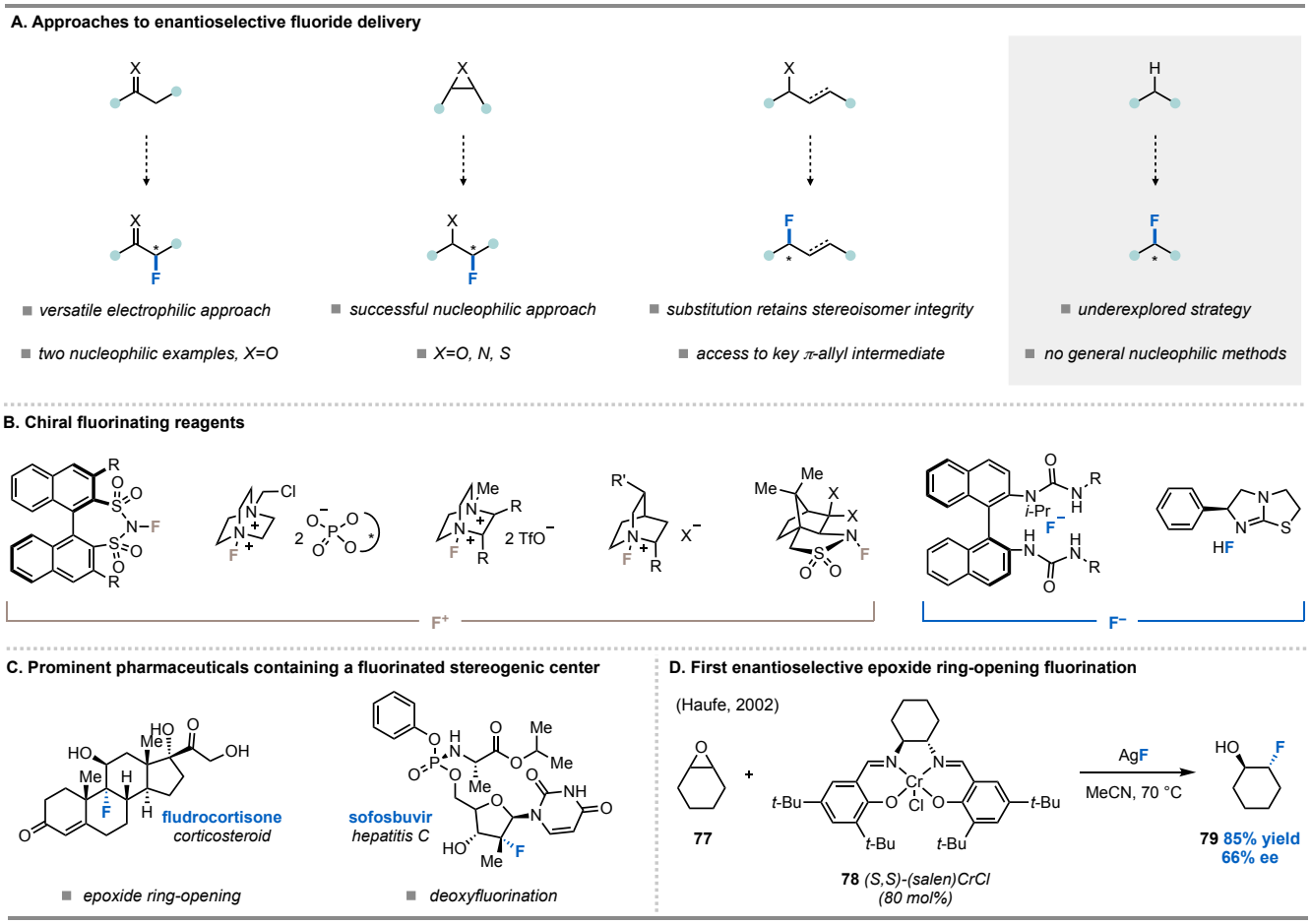

Figure 14. Overview of enantioselective nucleophilic fluorination. **A)** Examples of approaches to enantioselective fluoride delivery in nucleophilic fluorination. **B)** Select examples of chiral nucleophilic fluorinating reagents. **C)** Prominent pharmaceutical targets containing a fluorinated stereogenic center. **D)** The first example of enantioselective ring-opening nucleophilic fluorination of epoxides from Haufe and coworkers.

The Doyle laboratory's interest in asymmetric fluorination began with the development of a catalytic platform interfacing nucleophilic epoxide substitution with chiral fluorinating reagents.[104] To address the challenge of Lewis acid poisoning and undesired racemic background reactivity, the authors sought to generate a fluoride source *in situ* and in substoichiometric quantities. This concept led to utilization of benzoyl fluoride as a latent source of HF, which could be revealed in the presence of an alcohol and chiral (or achiral) amine catalyst (**Figure 15A**). Fluoride sources other than benzoyl fluoride (such as CsF, KF, NEt_3•3HF, and TBAF) resulted in either trace product formation or low asymmetric induction, thereby indicating that generation of the catalytic chiral amine-HF reagent *in situ* was of critical importance. Notably, this co-catalyst system led to a matched/mismatched effect on the enantioselectivity of the transformation (**Figure 15A**). The mechanism of this system was evaluated via kinetic, non-linear effect, kinetic isotope effect, Eyring, and Hammett studies. From these investigations, it was discovered that ring opening proceeds via a bimetallic mechanism, wherein (salen)Co activates the epoxide through a (salen)CoFHF intermediate (**Figure 15A**). Furthermore, the Lewis base co-catalyst serves as an axial ligand for Co, promoting dissociation of an inactive resting state Co-F-Co dimer and rendering the trans-ligated fluoride more nucleophilic. To further probe the cooperative bimetallic ring opening mechanism, linked dimeric catalyst **86** was subjected to the reaction conditions, upon which a ten-fold rate acceleration in ring opening was observed (**Figure 15B**). Not only did these studies lend further evidence to the proposed bimetallic ring-opening sequence, but also they revealed the synthetic utility of **86** itself in the desymmetrization of meso epoxides with fluoride. Indeed, improvements in both reaction rate and enantioselectivity were observed with **86** by comparison to (*R,R*)-(salen)Co catalyst **80** (**Figure 15B**).

The Doyle lab then applied a similar strategy to the catalytic hydrofluorination of aziridines for the synthesis of β-fluoroamines (**Figure 15C**).[108] The β-fluoroamine motif is of high medicinal value, as the β-fluoro group can influence the p*K*a of an amine through stereoelectronic and charge-dipole interactions.[15,109,110] Furthermore, the relative configurations of the two heteroatoms can impact both the physical and biochemical properties of a target. In this work, a number of enantioenriched β-fluoroamines were prepared via ring opening of enantioenriched

unsymmetrically substituted aziridines in excellent diastereoselectivity and ee (**Figure 15C).**

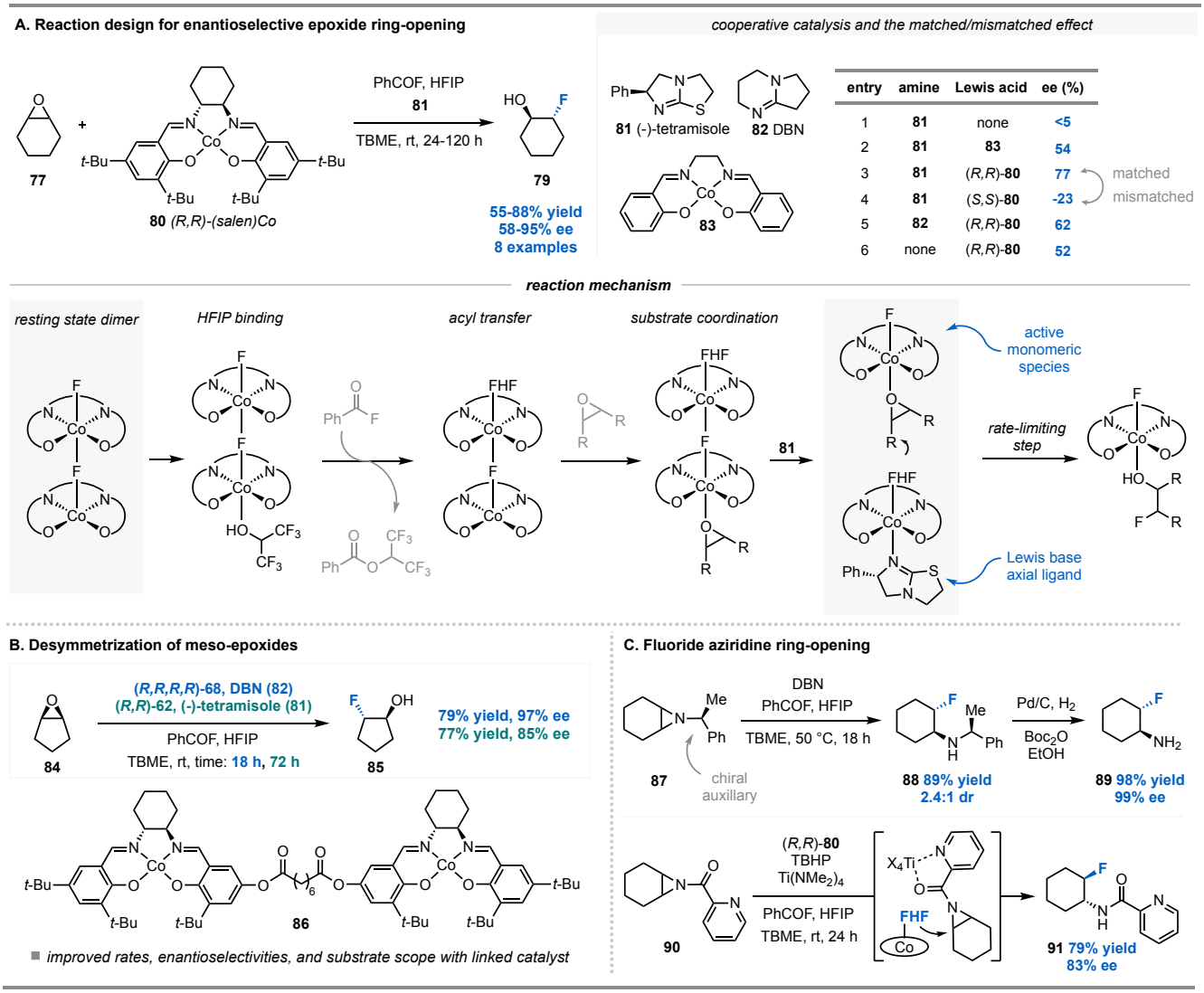

Figure 15. Enantioselective ring-opening of epoxides for nucleophilic fluorination in the Doyle group. **A)** Reaction design, optimization, results, and mechanistic rationale for enantioselective epoxide ring-opening fluorination. **B)** Desymmetrization of meso-epoxides. **C)** Enantioselective ring-opening fluorination of aziridines.

To achieve an asymmetric catalytic fluoride ring-opening of aziridines, the Doyle lab sought to leverage a catalyst system and strategy similar to that used in the enantioselective ring-opening fluorination of epoxides. By employing two catalysts—an achiral Ti(IV) cocatalyst along with (salen)Co—to separately affect aziridine activation and chiral fluoride delivery, several cyclic β-fluoroamines were afforded in up to 95% ee (**Figure 15C**).[111] From a mechanistic perspective, the success of ring-opening fluorination via chiral transition-metal complexes for asymmetric induction is largely due to the substrate activation pathway and the rigid chiral environment that is generated therein. As a result, this type of approach has received continued attention in the field, as demonstrated by Lautens and coworkers with a Rh-catalyzed enantioselective nucleophilic fluorination methodology for the ring opening of oxabicyclic alkenes (**Figure 16**).[112]

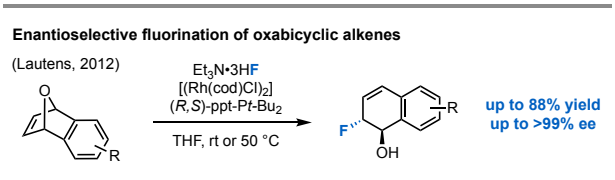

Figure 16. Enantioselective fluorination of oxabicyclic alkenes developed by Lautens and coworkers.

In a seminal report of enantioselective nucleophilic fluorination, Gouverneur and co-workers utilized a chiral phase-transfer approach for the asymmetric nucleophilic fluorination of episulfonium and aziridinium precursors with metal fluoride salts (**Figure 17**).[105,113] This work represents one of the few organocatalytic methods for enantioselective fluoride delivery capable of imparting high levels of enantioselectivity. Specifically, this biologically inspired strategy employed a chiral bis-urea

catalyst to act as a solid-liquid phase-transfer catalyst, thereby enabling enantioselective nucleophilic fluorination with a metal fluoride reagent. This approach was first demonstrated with racemic β-bromosulfides, accessed via the corresponding cis-epoxides, which act as substrate precursors to the reactive episulfonium intermediate (**Figure 17A**). Important to the success of this strategy was the use of an insoluble fluoride source to dissuade racemic background reactivity. Specifically, the catalytic process is initiated by ionization of the β-bromosulfide substrate and is followed by urea-anion coordination and transport, wherein urea-promoted anion-exchange favors fluoride binding over bromide binding due to the stronger hydrogen bonding interactions inherent to fluoride (**Figure 17A**). Notably, CsF was found to be optimal under these conditions due to the higher lattice energy of CsF relative to CsBr. Furthermore, the resulting product was not susceptible to racemization in the presence of catalyst, as the reverse reaction was found to be kinetically infeasible (computed energy barrier of 135 kJ/mol). In the context of scope, 12 β-bromosulfide derivatives were examined, with variations to aryl and sulfur protecting group substitution, and yield ranges of 53-98% with enantiomeric ratios of 91:9-97:3 (**Figure 17B**). Subsequently, Gouverneur and coworkers expanded upon this concept to achieve reactions with β-chloroamines as aziridinium precursors, using KF as a fluoride source and urea catalyst **100** (**Figure 17C**).[113] In this work, the authors achieved the synthesis of several medicinally valuable β-fluoroamines, including fluorinated analogs of MT-45 (opioid analgesic), lefetamine (stimulant), and diphenidine (dissociative anesthetic) (**Figure 17D**). We also note that in a more recent study, the Gouverneur group applied a similar approach to the synthesis of γ-fluoroamines, leveraging azetidinium triflates as the charged amine precursor.[114]

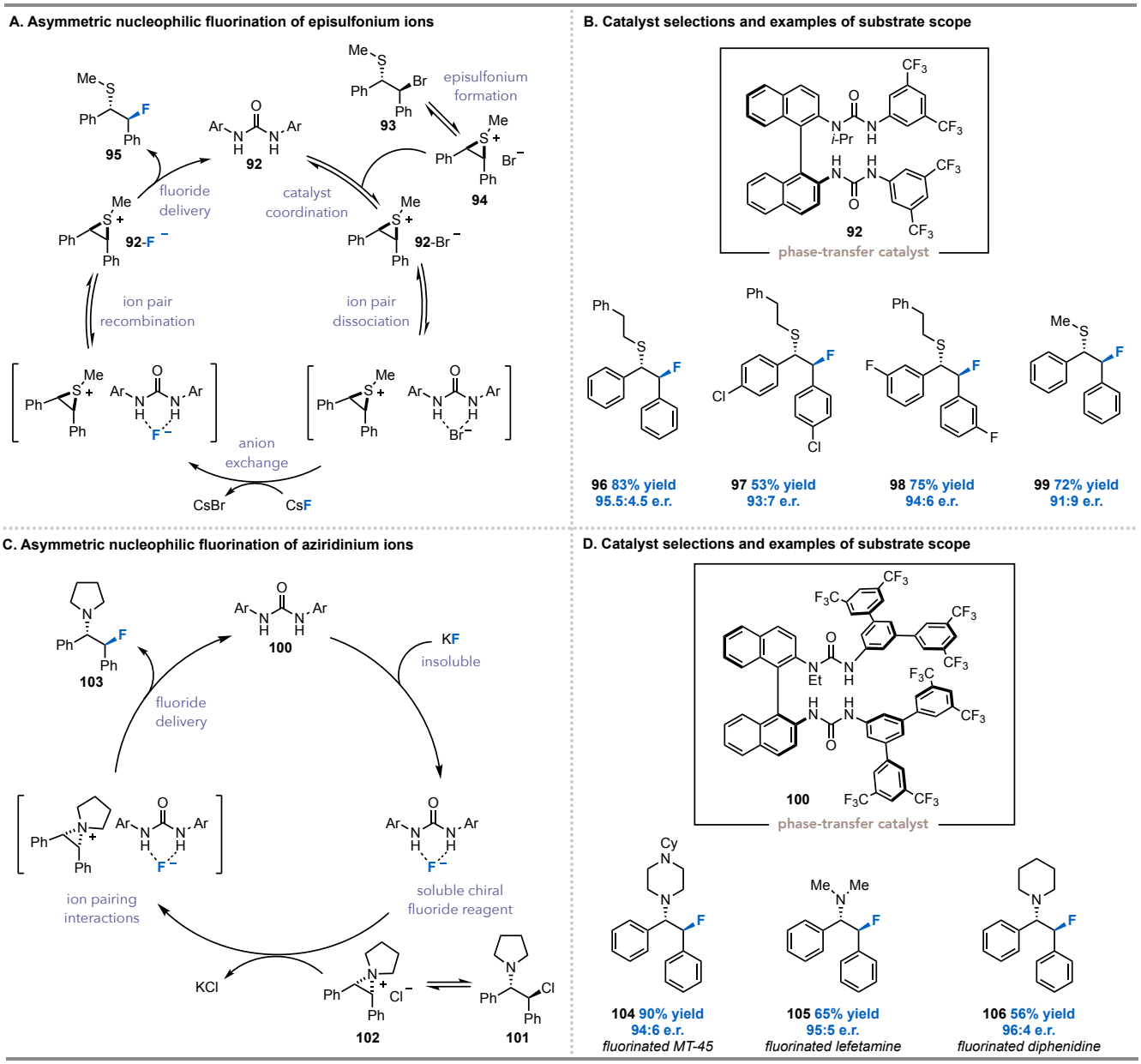

Figure 17. Enantioselective nucleophilic fluorination from Gouverneur and coworkers using phase-transfer catalysis. **A)** Proposed mechanism for the fluorination of episulfonium ions. **B)** Catalyst and examples of scope for the asymmetric

fluorination of episulfonium ions. **C)** Proposed mechanism for the asymmetric fluorination of aziridinium ions. **D)** Catalyst and examples of scope for the asymmetric fluorination of aziridinium ions.

1,2-fluorofunctionalizations. At present, fluorine-containing 1,2-difunctionalized architectures are highly represented in the pool of fluorinated chiral centers accessible via nucleophilic fluorination. Prominent examples in this area include oxidative dearomatization of substituted phenols,[115] enantioselective fluorination of β-dicarbonyls,[116] and enantio- and diasteroselective 1,2-difluorination of alkenes,[117,118] all of which are facilitated by hypervalent iodine chemistry. For example, the oxidative dearomatization by $PhI(OAc)_2$ demonstrated by Gaunt and coworkers proceeds through a fluorinated meso-cyclohexadienone intermediate, which subsequently undergoes enantioselective intramolecular Michael addition catalyzed by a chiral secondary amine catalyst.[115]

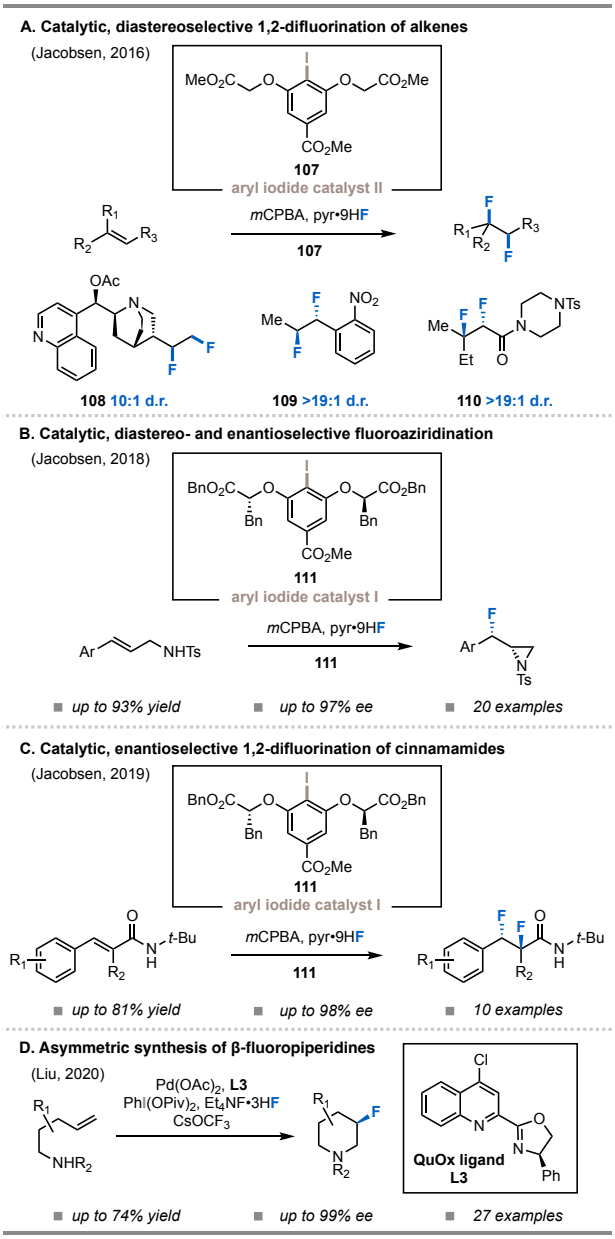

Figure 18. Asymmetric nucleophilic fluorination of alkenes. **A)** Enantioselective 1,2-difluorination of cinnamamides from Jacobsen and coworkers. **B)** Enantioselective 1,2-difluorination of alkenes from Jacobsen and coworkers. **C)** Enantioselective fluoroaziridination of alkenes from Jacobsen and coworkers. **D)** Enantioselective aminofluorination of unactivated alkenes from Liu and coworkers.

Furthermore, the Jacobsen group has recently leveraged Ar-I/HF/mCPBA systems for the fluorination of alkenes using (*R*)-binaphthyldiiodine as a chiral catalyst.[99,117–119] Specifically, Jacobsen and coworkers utilized this approach to achieve 1,2-difluorination, wherein the iodine catalyst was found to impart optimal enantioselectivity (**Figure 18A**).[117] Further development of this technique enabled the expansion of the 1,2-difluorination protocol to alkenes bearing *N*-*tert*-butyl amide substituents to achieve the fluorination of cinnamamides, where the *N*-*tert*-butyl amide substituent provides anchimeric assistance to enforce 1,2-difluorination versus a rearrangement pathway resulting in 1,1-difluorination (**Figure 18C**).[118] Excitingly, catalyst **111** could also be applied to a 1,2-aminofluorination strategy for the synthesis of high value fluoroaziridines (**Figure 18B**).[119] Finally, Liu and coworkers expanded this approach to the field of transition-metal catalysis to devise a complementary strategy for enantioselective aminofluorination. Notably, this report represents the first asymmetric Pd(II)-catalyzed aminofluorination of unactivated alkenes using chiral quinoline oxazolines (Quox) as ligands (**L3**).[120] Through this approach, β-fluoropiperidines can be accessed in high enantioselectivity using $Et_4NF{\cdot}3HF$ as the fluoride source (**Figure 18D**). We also note that Gilmour and coworkers have achieved enantioselective 1,2-difluorination of alkenes through an I^{I}/I^{III} catalysis approach.[121]

Asymmetric allylic fluorination. In the context of asymmetric nucleophilic fluorination, ring-opening and functional group substitution have served as dependable strategies. In particular, epoxides, aziridines, and alcohols are the most ubiquitous scaffolds from which structurally diverse stereogenic products may be obtained. Allylic halides, on the other hand, are less intuitive precursors to chiral $C(sp^3)$–F bonds, and as such, have received less attention.[122]

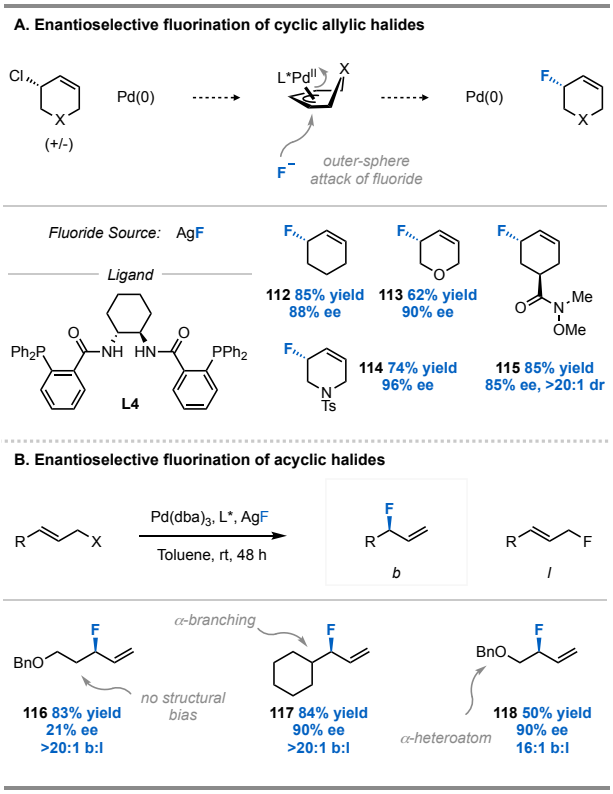

Figure 19. Asymmetric nucleophilic allylic fluorination in the Doyle group. **A)** Enantioselective fluorination of cyclic allylic halides. **B)** Enantioselective fluorination of acyclic allylic halides.

Inspired by this challenge, the Doyle group investigated the enantioselective nucleophilic fluorination of allylic halides using a transition-metal catalysis approach (**Figure 19**).[123] Specifically, effective stereocontrol was achieved under a Pd-catalyzed platform with a chiral Trost bisphosphine ligand. Although the possibility exists for racemic background reactivity in the absence of Pd for this reaction, the authors proposed that the rate of reaction is accelerated by Pd-promoted ionization of the C–X bond. As in the (salen)Co chemistry, the reaction conditions are remarkably mild (under room temperature and atmospheric conditions) and feature an extensive scope (alcohols, amides, and silyl ethers are tolerated). While acyclic substrates containing non-branched alkyl chains gave moderate to low enantioselectivity, substrates possessing allylic substituents of greater steric or electronic bias afforded high asymmetric induction. Notably, at the time of publication, this methodology represented a very rare example of C(sp^3)–halogen bond formation mediated by a Pd(0)/Pd(II) couple, and demonstrated a unique mechanism for Pd(0)-catalyzed fluorination.

Chapter Four: Nucleophilic Radiofluorination

In recent years, fluorination chemistry has found widespread application in the fields of medical diagnosis and imaging.[2] Fluorinated molecules have acquired significant value for their service as radiotracers for PET imaging, a nuclear imaging technique widely utilized as a clinical tool in diagnostic medicine and analytical technique in both medical research and pharmaceutical development (**Figure 20A**). As a complement to both magnetic resonance imaging (MRI) and computed tomography (CT) imaging—techniques that reveal structural details of the human body—PET scans are unique in their elucidation of metabolic details, such as the biological function of a pharmaceutical target in the human body.[5,33] As a result, this imaging technique has provided the medical research community with not only a highly specific analytical tool for the *in vivo* assessment of pharmaceutical efficacy, but also—through the strategic administration of PET active compounds—an incredibly sensitive clinical tool for the diagnosis and treatment of cancer.

Recent decades have brought forth exciting advances in the field of nucleophilic radiofluorination. The Doyle group first examined radiochemical translation in the context of epoxide ring opening for the asymmetric synthesis of [^{18}F]fluorohydrins (**Figure 21A**).[124] Critical to the success of the ^{19}F variant of this chemistry was understanding the mechanism of fluoride delivery, wherein mechanistic studies revealed a homobimetallic mechanism with (salen)CoF(HF) as the key fluorinating reagent generated *in situ* from PhCOF (*vide supra).* Therefore, preparation of a [^{18}F](salen)CoF species was undertaken from a (*R,R,R,R*)-(salen)CoOTs precursor, without pivoting to less practical strategies such as the large-scale preparation of [^{18}F]PhCOF. To access this key ^{18}F reagent, the authors elected to prepare a [^{18}F]-enriched (salen)CoF species by performing counterion metathesis between a (*R,R,R,R*)-(salen)CoOTs precursor and [^{18}F]fluoride generated by elution of [^{18}F]fluoride from a quaternary ammonium cation (QMA) ion-exchange cartridge, a preparation technique that is directly analogues to the preparation of [^{18}F]KF. Notably, the preparation of this reagent is operationally simple, performed under air and without need for rigorously dried solvents and glassware. Overall, this radiosynthesis delivered a variety of [^{18}F]fluorohydrins in good RCY and excellent enantioselectivity. Furthermore, it was discovered that this strategy was capable of remote semi-automation, wherein a remote-controlled microwave cavity integrated into an automated liquid handler provided 12.3 mCi of [^{18}F]FMISO—a PET imaging probe for the detection of hypoxia—in 10.6% nondecay corrected RCY.

Following this work, Groves and Hooker demonstrated that a [^{18}F]-Mn(salen) reagent could also be prepared from a QMA cartridge, for the radiochemical translation of Groves' benzylic C(sp^3)–fluorination (*vide supra*) (**Figure 20B**).[125] Key to this approach was the Mn(salen)OTs catalyst; Groves and Hooker discovered that—in agreement with our own findings—Mn salen complexes substituted by more labile OTf and OTs ligands substantially outperformed complementary analogues such as Mn(salen)Cl, substituted by a strongly associated chloride ligand prohibiting efficient ligand exchange with ^{18}F[fluoride]. Overall, these conditions provided a highly enabling avenue for benzylic C(sp^3)–H radiofluorination, with radiochemical conversions (RCCs) up to 68%. Several years later, Groves and Hooker applied these techniques to the radiochemical translation of Groves' nucleophilic fluorination from unactivated C(sp^3)–H

bonds, here leveraging the Mn-porphyrin catalyst system to achieve optimal radiofluorination (**Figure 20B**).[126]

Gouverneur and coworkers have also demonstrated radiochemical translation of a nucleophilic ^{19}F fluorination methodology (**Figure 20B**).[83] Specifically, this radiofluorination example extends from their Pd-catalyzed nucleophilic allylic fluorination strategy, wherein the presence of *p*-nitrobenzoate leaving groups enabled fluorination across 12 examples of ^{19}F allylic fluorination. Working from no-carrier-added [^{18}F]TBAF as the source of [^{18}F]fluoride, a variety of cinnamyl derivatives were successfully subjected to radiofluorination. In a similar approach, Nguyen and coworkers accomplished radiochemical translation of their approach to allylic fluorination from trichloroacetimidate precursors, utilizing an Ir catalyst and [^{18}F]KF•Kryptofix$_{2.2.2}$ to accomplish this transformation (**Figure 20B**).[84] Sanford, Scott, and coworkers also accomplished radiochemical translation of a ^{19}F nucleophilic fluorination methodology, using Sanford's Pd-catalyzed nucleophilic C(sp^3)–H fluorination of 8-methylquinolines as a case study (*vide supra*)(**Figure 20B**).[127] One of the challenges inherent to radiofluorination chemistry is the identification of a suitable [^{18}F]fluoride source. Indeed, the key challenge in developing their radiochemical method was devising a strategy for the preparation and ready use of Ag[^{18}F]F , especially necessary given the importance of AgF in the original ^{19}F chemistry.

While attempts were made to conduct the chemistry with K[^{18}F]F•kryptofix$_{®2.2.2}$, this reagent did not promote ^{18}F incorporation, a result attributed to the significance of the Ag^+ counterion in this chemistry. Preparations of Ag[^{18}F]F, while known in the literature, are often limited by their complexity or need for specialized equipment, thereby rendering these strategies both impractical and difficult to automate. In the face of this limitation, the authors prepared Ag[^{18}F]F by eluting ^{18}F[fluoride] from a QMA ion exchange cartridge with an aqueous AgOTf eluent. The efficacy of this technique was demonstrated across 10 derivatives of 8-methylquinoline with radiochemical yields (RCYs) ranging from 0-21%. Furthermore, in a demonstration of practicality, the authors performed an automated radiosynthesis using a GE TRACERlab FX$_{FN}$ module.[127]

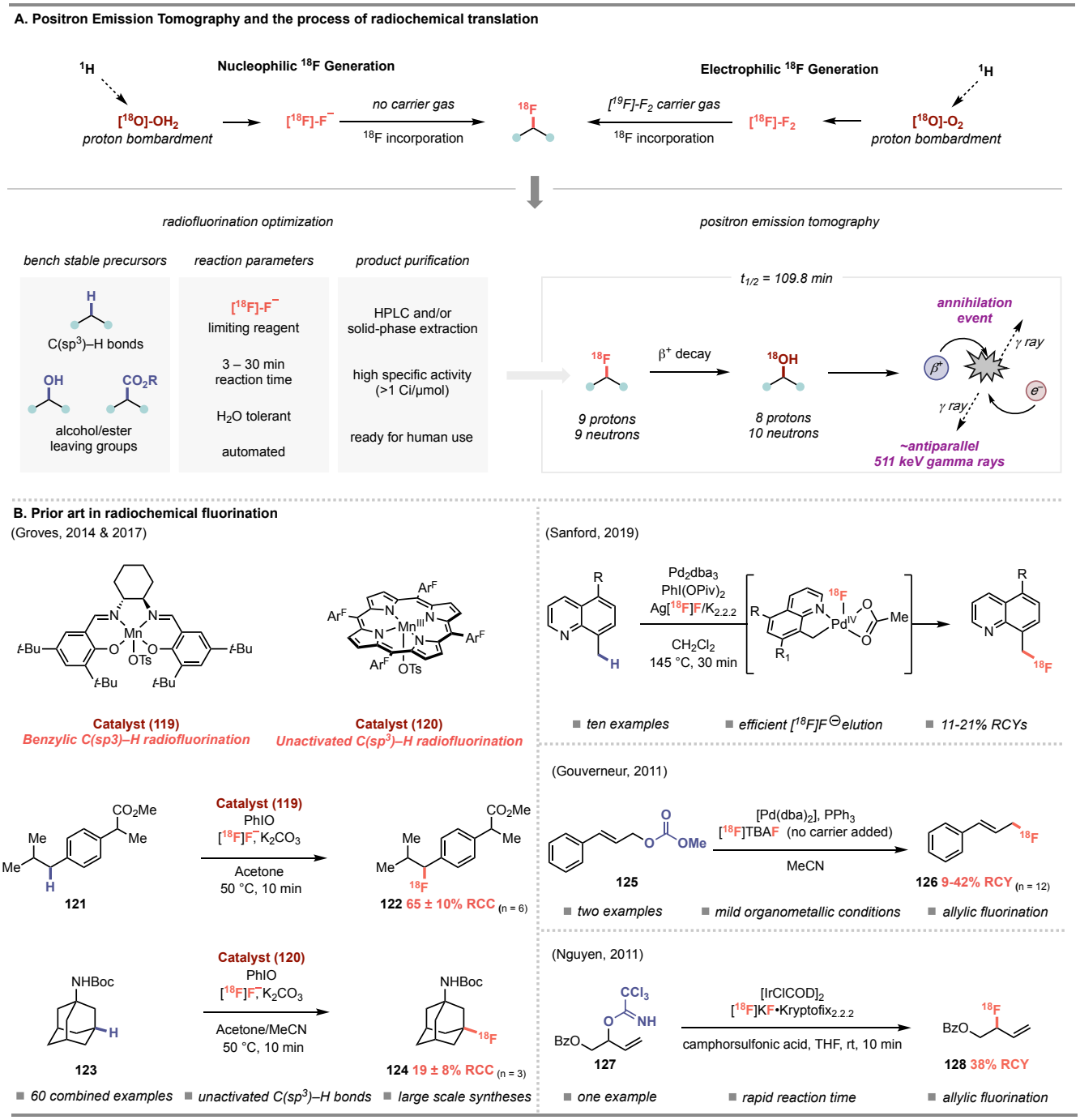

Figure 20. Overview of nucleophilic [^{18}F] fluorination for Positron Emission Tomography (PET). **A)** Background of Positron Emission Tomography and the radiochemical process. **B)** Prior art in nucleophilic [^{18}F] fluorination from the Groves, Sanford, Gouverneur, Nguyen, and Ritter groups.

The Doyle group was also able to accomplish the radiochemical translation of original ^{19}F methodologies, such as the PyFluor-mediated deoxyfluorination (**Figure 21B**).[62] To prepare the key [^{18}F]fluoride reagent, it was discovered that [^{18}F]PyFluor could be prepared in 88% RCC from 2-pyridinesulfonyl chloride and [^{18}F]KF/K_{222} after five minutes at 80 °C. Importantly, in the synthesis of [^{18}F]PyFluor, only a small fraction of [^{18}F]PyFluor is actually obtained, and an excess of sulfonyl chloride precursor remains unreacted. By telescoping the [^{18}F]PyFluor synthesis and subsequent deoxy-radiofluorination steps, unreacted sulfonyl chloride serves to activate the substate *in situ* by enabling stoichiometric formation of the key sulfonate intermediate. Overall, from [^{18}F]PyFluor, the authors achieved the synthesis of an ^{18}F labeled carbohydrate (**140**) in 15% RCC after 20 minutes at 80 °C, a notable advance from state-of-the-art radiosyntheses in the context of this ^{18}F product due to instability of the tosylate precursor widely utilized for its preparation. Excitingly, the synthesis of ^{18}F **140** represents the first report of a no-carrier-added deoxy-radiofluorination.

Furthermore, the Doyle group demonstrated radiochemical translation of the Cu-catalyzed α-diazocarbonyl nucleophilic fluorination technique (*vide*

supra) (**Figure 21C**).[71] This transformation was of particular interest in the context of ^{18}F derivatization given the medicinal relevance of α-[^{18}F]fluorocarbonyl compounds among PET radiotracers. Altogether, this protocol provided access to several ^{18}F-labeled substrates, and enabled the synthesis of widely utilized PET radiotracers in RCCs competitive with existing radiochemical preparations.

In a more recent report, the Doyle group described a photocatalytic, decarboxylative nucleophilic radiofluorination of redox-active *N*-hydroxyphthalimide esters (**Figure 21D**).[77] Broadly, the synthesis of aliphatic ^{18}F radiotracers is accomplished almost entirely via nucleophilic substitution with [^{18}F]KF and $K_{2.2.2}$ from the alkyl sulfonate precursor, and the general synthesis of secondary and tertiary ^{18}F targets remains a challenge. Therefore, the authors envisioned that an alternative route to the radiosynthesis of these scaffolds would be highly useful to the radiofluorination community. Through minor adjustments to the ^{19}F reaction conditions—notably with a switch to [^{18}F]KF/$K_{2.2.2}$ as the fluoride source—^{18}F incorporation was achieved for three pharmaceutical targets in low to good RCC within two minutes of irradiation. Notably, the translation of this chemistry from ^{19}F to ^{18}F fluorination involved the development and engineering of an automated, radiosynthetic photoreactor, enabling one of the few photocatalytic radiosynthesis known to date.

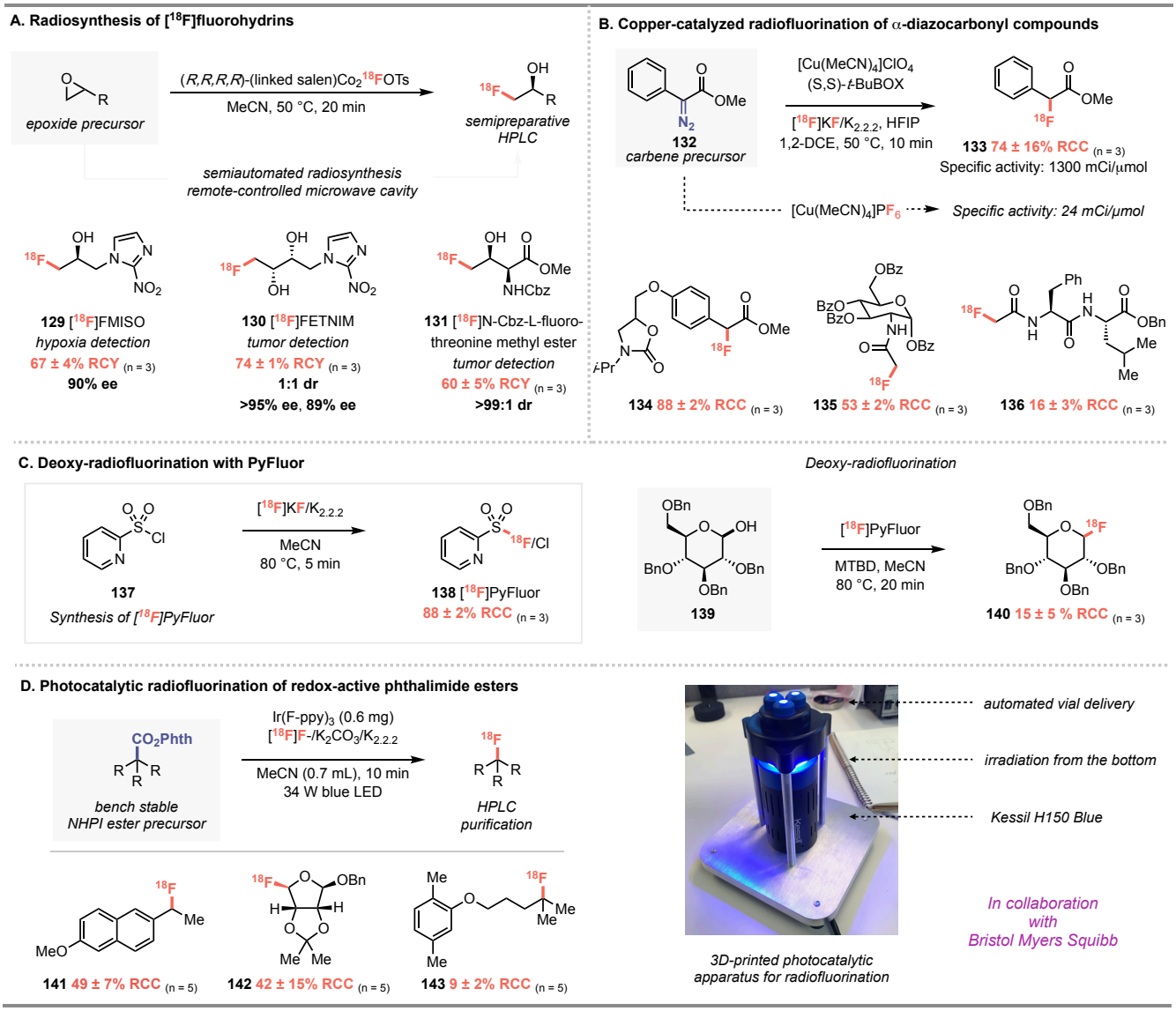

Figure 21. Examples of nucleophilic [^{18}F] fluorination in the Doyle group. **A)** Radiosynthesis of [^{18}F]fluorohydrins. **B)** Copper-catalyzed radiofluorination of α-diazocarbonyl compounds. **C)** Deoxy-radiofluorination with PyFluor. **D)** Photocatalytic radiofluorination of redox-active phthalimide esters.

CONCLUSION AND OUTLOOK

Nucleophilic fluorination has experienced significant growth throughout modern chemistry. Nevertheless, the challenges of this chemistry continue to inspire the development of new reagents, the design of more generalizable synthetic reactions, and mechanistic studies that elucidate fundamental principles of reactivity. In this

Perspective, we discussed the evolution of the reactivity space of nucleophilic fluorination, as well as its translation to enantioselective and radiofluorination platforms. Throughout each chapter of this Perspective, we highlighted how reagent development has expanded the pool of accessible mechanisms and substrate classes through advances in reactivity or selectivity. Nevertheless, achieving efficient reactivity, high selectivity, low cost, and atom economy remain outstanding challenges in the field. To evaluate the current scope of existing nucleophilic fluorination methods, as well as guide further methodological expansion, we apply a data science approach to visualize and analyze the chemical space of fluorinated products. This data science workflow, previously developed by the Doyle group for the generation of diverse substrate scopes, involves visualization of chemical space through molecular featurization and dimensionality reduction, followed by application of a clustering algorithm.[128] Here, we adapted this approach to enhance our perspective on the current state of nucleophilic fluorination methodologies.

By generating a scope of desired fluorinated products, we evaluated the generality of existing fluorination methods. As the focus of this perspective is on C(sp^3)-fluorinated compounds, this product class was selected from which to generate a maximally diverse subset. Using the Reaxys database, we searched for all known C(sp^3)-fluorinated compounds, excluding perfluoroalkyl substances. The resulting list of over 35,000 compounds composes the total chemical space for fluorination reactions. To visualize the chemical space in two dimensions, we first used Mordred,[129] an open-source and computationally inexpensive molecular descriptor calculator, to featurize the 35,000 fluorinated compounds; the ~1,800 generated features, which include molecular weight, fraction of C(sp^3) carbons, and bond polarizability, were then subjected to dimensionality reduction using Principal Component Analysis (PCA). The first two principal components, PC1 and PC2, can be plotted in two dimensions to visualize the chemical space (**Figure 22, gray dots**). Curious as to how much of the total chemical space is covered by the products from the Doyle group's previously published nucleophilic fluorination methods,[62,63,71,77,88,93,104,108,111,123,130,131] we plotted these molecules on top of the two-dimensional chemical space projection (**Figure 22, navy dots).** This analysis clearly shows that the structural diversity in accessible products is significantly limited compared to the potential chemical space of fluorinated products. As a consequence of limitations in current fluorination methodologies, substrate scopes tend to be limited to the lower left region of chemical space. Application of a hierarchical clustering algorithm groups the fluorinated products based on similarities in their Mordred descriptors, such that products within the same cluster are structurally similar to one another and structurally different from products within other clusters (**Figure 22**). In general, we can make sense of the clusters as follows: Cluster 1 contains structures typically considered to be small molecules; Cluster 2 contains steroidal scaffolds; Cluster 3 contains what we may consider more "complex" or "drug-like" targets in our substrate scopes; Cluster 4 contains densely functionalized late-stage targets; and Cluster 5 contains high molecular weight poly- and macrocyclic molecules. Interestingly, of the 213 products from our previous fluorination methods, the distribution within clusters can be seen in Figure 22C, wherein Clusters 2, 4, and 5 are grossly underrepresented as compared to Clusters 1 and 3.

In the original report of this workflow, the chosen substrate scope comprised the centermost molecule from each cluster. However, with a chemical space of over 35,000 molecules in this case, we applied a hybrid approach: the centermost molecule from each cluster, plus 4 additional substrates from each cluster that were selected through a combination of data science techniques and human chemical expertise. A selection algorithm identified 10 maximally spread molecules within each cluster, out of which we ultimately chose 4 chemically relevant and representative products. The resulting "product scope" of 25 molecules can be seen in Figure 22. While some of these products could certainly be directly accessed via existing fluorination technologies, this analysis also highlights the outstanding limitations in the field, specifically with respect to late-stage selective fluorination of complex substrates. It is our hope that this type of analysis could be used to inspire new methods and reagents for the selective fluorination of new substrate classes.

We believe that the field of nucleophilic fluorination remains relatively "untapped" compared to other transformations in organic chemistry. Recent synthetic advances have been driven forward by employing various catalytic strategies—including electrochemistry, biocatalysis, mechanochemistry, photocatalysis, and base-metal catalysis. In looking towards next generation fluorination methods, we believe that additional progress in the field could be reached by working beyond precious-metal catalysis and discovering new strategies through organocatalysis or biocatalytic fluorination.[132] Future pursuits aside, we acknowledge the significant progress that has been made in this field of research, despite the inherent limitations of fluoride reagents and the limited examples of biological fluorination mechanisms. Looking ahead, it is our hope that nucleophilic fluorination continues to drive invention, creativity, and inspiration, pushing chemists to new heights of synthetic prowess.

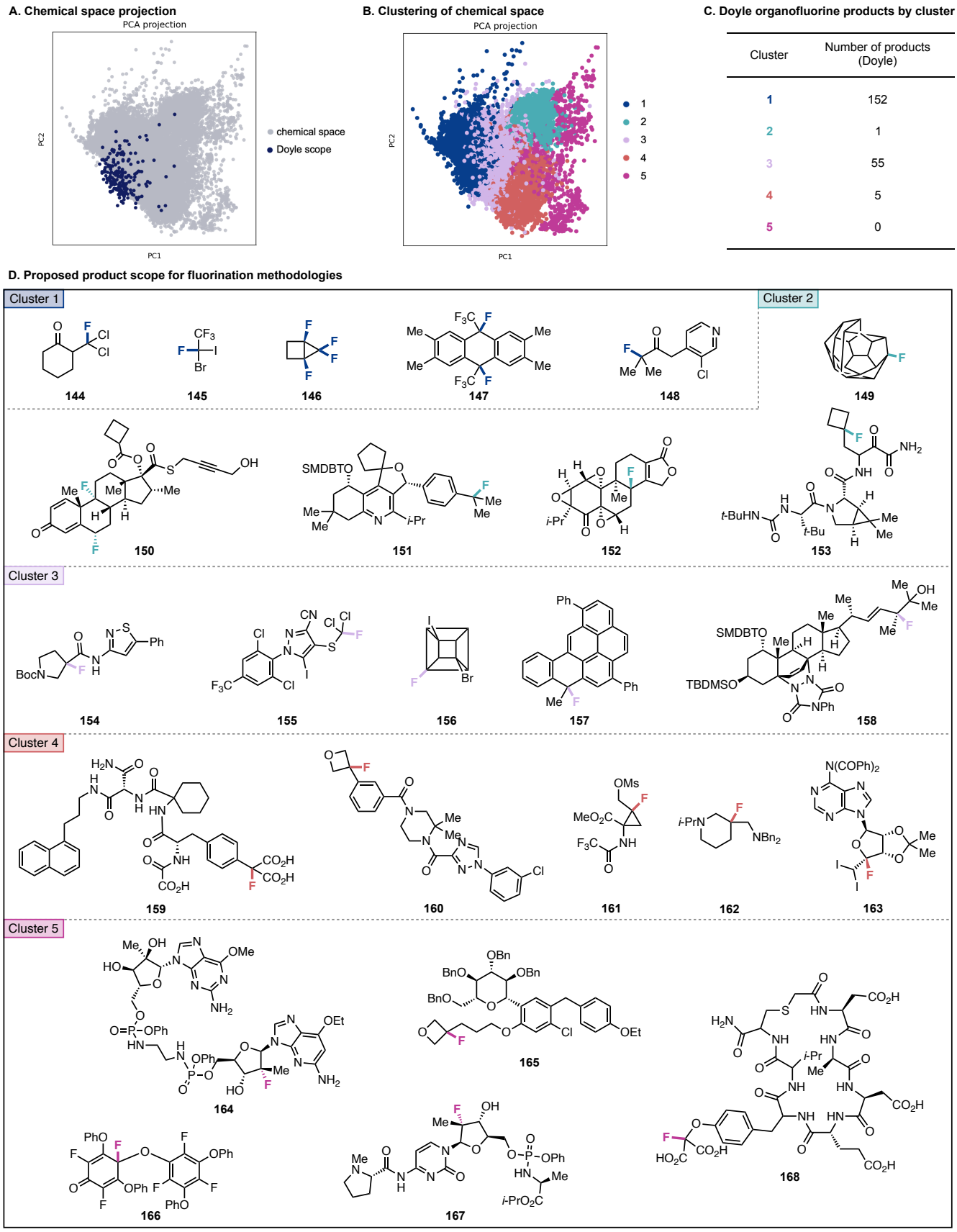

Figure 22. Data science approach for the evaluation of existing chemical space for organofluorine products. **A)** PCA projection of chemical space with organofluorine products from our lab's previously published methodologies. **B)** PCA projection of chemical space colored by cluster. **C)** Distribution of our previously published organofluorine products by cluster. **D)** Proposed algorithmically selected product scope.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Python scripts and list of molecules used for chemical space analysis (PDF).

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Notes

The authors declare no competing financial interest.

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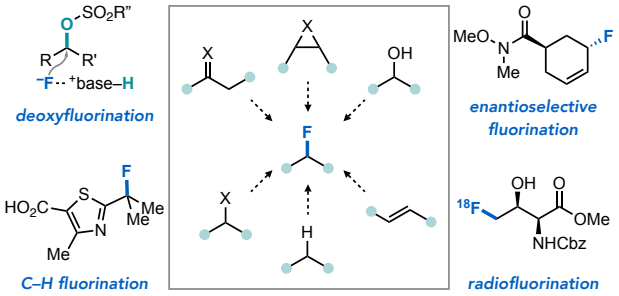

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