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Data Science-Guided Development of Deoxyfluorination Reagents with Enhanced Reactivity, Practicality, and Safety

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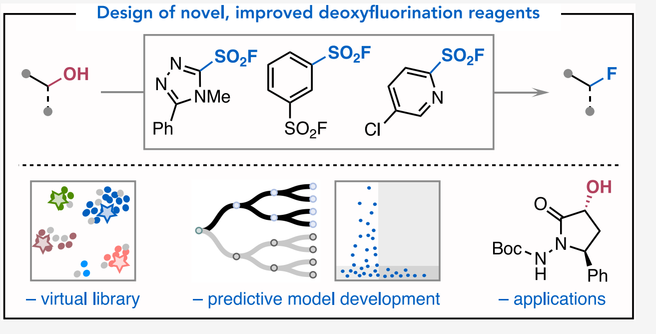
ABSTRACT: We report the discovery and development of several new (hetero)aryl sulfonyl fluoride reagents that have enhanced deoxyfluorination reactivity, improved physical properties, and excellent safety profiles compared to those of PyFluor and other fluorination reagents such as PBSF and DAST. To select structurally diverse reagents, we computed a virtual library of (hetero)aryl sulfonyl fluorides and leveraged training set design principles to broadly survey structure−activity relationships in a model deoxyfluorination reaction. We developed predictive models to optimize sulfonyl fluoride reagents for the deoxyfluorination of a key intermediate used in the synthesis of RIPK1 inhibitor GDC-8264. The top-performing reagents demonstrated broad applicability across diverse alcohol substrate classes, including complex natural products and active pharmaceutical ingredients, highlighting the power of data science-enabled approaches in reagent development.



■ INTRODUCTION

The development of synthetic methods for the installation of carbon−fluorine bonds is instrumental to the discovery of transformative molecules that can benefit society.[1−5] Fluorinated compounds are featured prominently in novel pharmaceuticals,[1,3,4,6] agrochemicals,[7] materials,[8] and polymers (Figure 1A).[9,10] Fluorine substitution often imparts unique conformational, physicochemical, and pharmacological properties on small molecules.[1,11] Among the many methods to form C−F bonds, deoxyfluorination of alcohols is the most widely utilized to install primary and secondary aliphatic fluorides, due in large part to the abundance and accessibility of alcohol-containing precursors.[12] Discovery of the first deoxyfluorination reagent, Yarovenko's reagent, in 1957 helped to popularize the field of aliphatic fluorination.[13,14] Since then, novel reagents such as diethylaminosulfur trifluoride (DAST), perfluorobutanesulfonyl fluoride (PBSF), PhenoFluor, Deoxo-Fluor and others have enabled access to a wide range of fluorinated products from alcohol starting materials (Figure 1B).[15−28] However, reactions employing these highly reactive reagents often lead to undesired elimination or rearrangement products. Established reagents for deoxyfluorination are often costly, highly reactive, or contain perfluoroalkyl groups, making them challenging to use in safe, sustainable, and environmentally responsible manufacturing.[5,26,29] For example, the persistent industrial waste produced from using perfluoroalkylated reagents such as PBSF, a highly reactive deoxyfluorination reagent, has led to regulatory restrictions on their use.[30−33]

As a consequence, the Doyle group previously developed 2-pyridinesulfonyl fluoride (PyFluor)[34] as a safe and low-cost reagent for deoxyfluorination of a wide range of alcohol substrates (Figure 1C). This first-generation reagent is typically selective for fluorination over elimination. However, PyFluor's relatively low reactivity, undesirable physical properties as a low-melting solid (mp = 29 °C), and poor performance in radiolabeling applications present challenges for its broad adoption−particularly on a manufacturing scale.

To address these challenges, our groups entered a research collaboration to harness the power of data science and data-rich experimentation[35,36] to design next-generation sulfonyl fluoride reagents. The central goal was to identify reagents that enhance reactivity and improve physical properties compared to those of PyFluor, while maintaining PyFluor's hallmark attributes of high safety and low cost. In this work, we assembled a virtual library of sulfonyl fluorides and used DFT featurization, unsupervised learning, and predictive modeling

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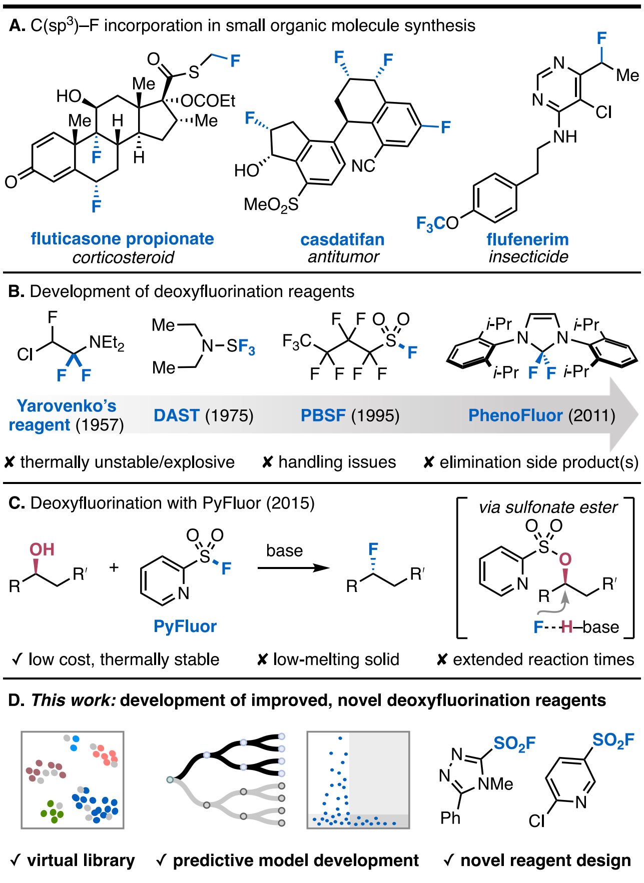

Figure 1. (A)−(C) Prior art in deoxyfluorination reagent development and (D) overview of this work.

to identify highly reactive, crystalline solid, and safe reagents that would have been difficult to discover with chemical intuition alone. We evaluated the reactivity and scope of these sulfonyl fluoride reagents against a broad collection of representative alcohol substrates, as well as diverse, structurally complex alcohols that were previously resistant to deoxyfluorination with PyFluor (Figure 1D). Overall, our findings led to the discovery of several reagents with enhanced deoxyfluorination reactivity, favorable thermal process safety characteristics, and improved physicochemical properties.

RESULTS AND DISCUSSION

Virtual Library Construction. At the outset, we built a virtual library of sulfonyl fluorides to guide the selection of diverse reagents for synthesis, reactivity studies, and modeling (Figure 2A).[37−39] Given the limited commercial availability and affordability of sulfonyl fluorides, we performed a Reaxys structure search for (hetero)aryl thiols, a broadly available class of precursors that can be easily converted into sulfonyl fluorides through a one-pot, two-step oxidative procedure.[40] This search delivered >65,000 compounds that were subsequently filtered based on molecular weight (<600 g/mol), commercial availability, reported spectral data, and functional group compatibility (see Supporting Information (SI) for full details). This filtering provided us with a curated set of 3,517 thiols, which could initially serve as sulfonyl fluoride computational surrogates for analysis and training set selection. We then used SMARTS substructure manipulation to convert the SMILES string of each (hetero)aryl thiol to its corresponding sulfonyl fluoride.

Molecular descriptors for the library of sulfonyl fluorides were then computed for an ensemble of up to 5 representative conformers per sulfonyl fluoride, which were each subjected to DFT-level optimization and single point energy calculations

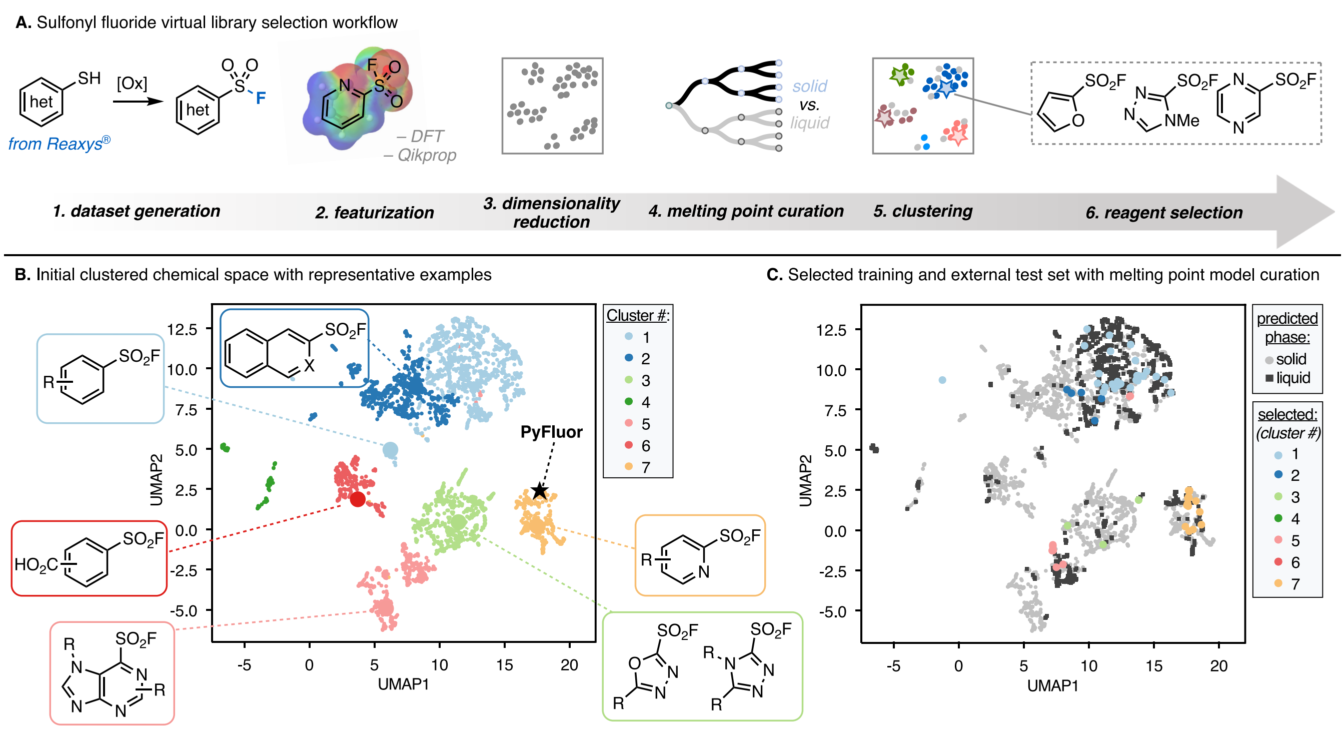

Figure 2. (A) Workflow used to construct sulfonyl fluoride virtual library. (B) Initial clustered chemical space with representative examples from each cluster. (C) Application of melting point prediction model and selected experimental data set.

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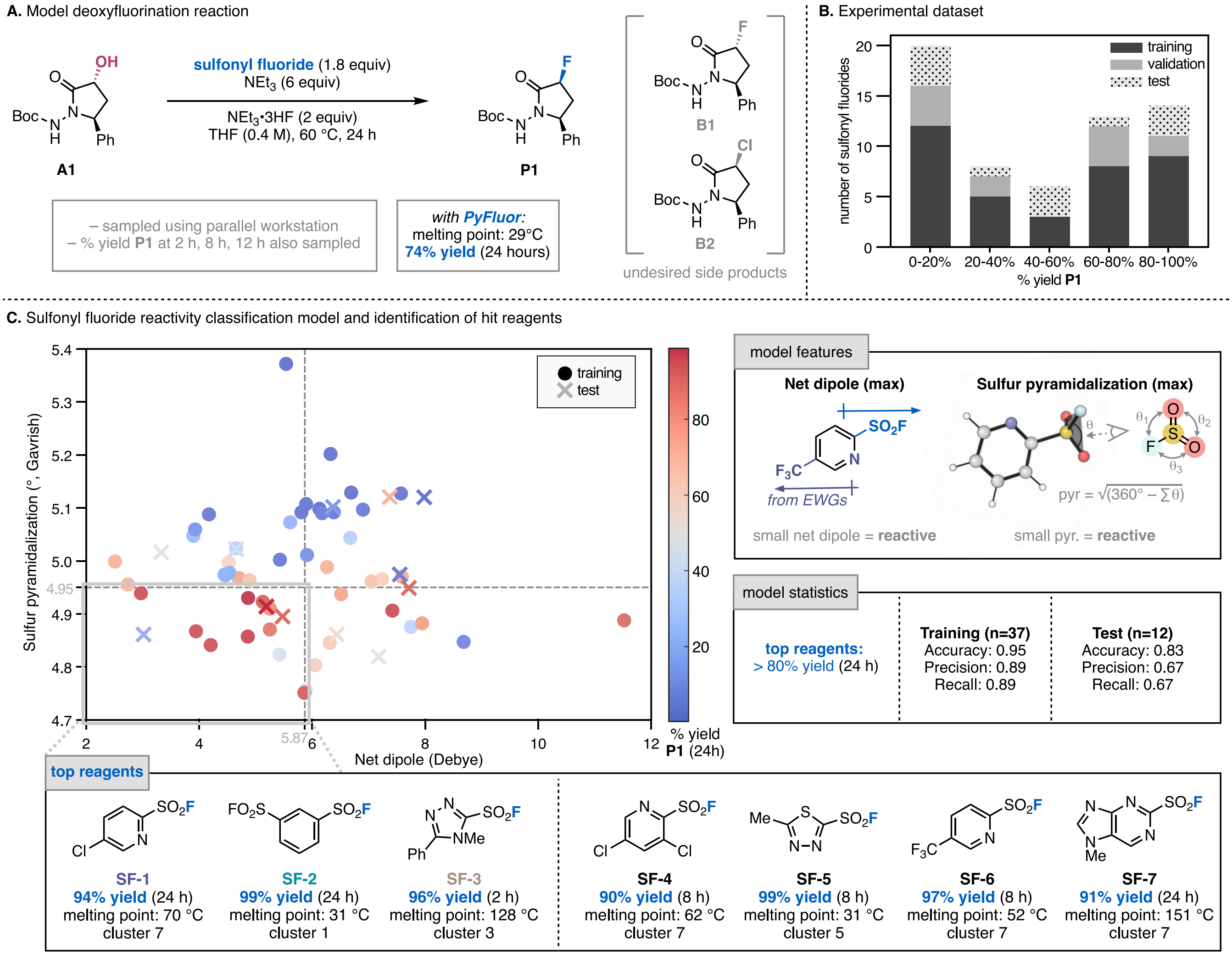

Figure 3. (A) Model deoxyfluorination reaction used to collect experimental data. (B) Experimental yield coverage and data set split. (C) Sulfonyl fluoride reactivity classification model and identification of hit reagents. Reactions run on 0.51 mmol scale using a parallel workstation (for exact setup, see the Supporting Information). Yields determined by HPLC assay.

(M062X/def2TSVP//B3LYP-D3(BJ)/def2SVP). Next, we extracted global (such as dipole and electronegativity) and atomic features (such as buried volume and NMR chemical shift) of the sulfonyl fluoride reagents. QikProp descriptors, which are commonly used to describe the pharmacokinetic properties of small organic molecules, were also calculated for physicochemical modeling efforts (*vide infra*).[41,42] To visualize the virtual library, we used Uniform Manifold Approximation and Projection (UMAP) to reduce the feature space to two dimensions.[43,44] Finally, we applied Ward's hierarchical clustering algorithm to divide the reagent space into seven distinct clusters, selected by optimizing the silhouette score (Figure 2B).[45] Notably, sulfonyl fluoride reagents that were evaluated in the original development of PyFluor, as part of the intuition-driven optimization campaign, covered a narrow region of chemical space, occupying only condensed areas of clusters 5 and 7.

As noted above, PyFluor's low melting point leads to challenges with manufacturing, purifying, weighing, and transferring the semisolid reagent, especially on large scale. To identify solid reagents with higher melting points, we developed a machine learning (ML) model to predict the phase (liquid or solid) of each reagent in the virtual library at room temperature. A decision tree with a maximum depth of five and a binary melting point cutoff of 70 °C was trained on ~700 literature-reported melting points of (hetero)arylsulfonyl fluorides (see SI for details). With an external test accuracy of 0.81, this model was extrapolated to predict the melting point of all sulfonyl fluorides in our virtual library (Figure 2C, overlay on chemical space). The predicted melting points enabled us to curate our selected training set to favor high-melting sulfonyl fluorides with predicted improved crystallinity and chemical handling relative to PyFluor (Figure 2C).

After applying our melting point ML model as a filter to the chemical space, we next selected a diverse and representative training set of sulfonyl fluorides to experimentally investigate in a model deoxyfluorination reaction. We chose 49 sulfonyl fluorides that spanned five of the seven clusters, favoring those that were commercially available, easy to access, and inexpensive. We chose not to test sulfonyl fluorides from cluster 4 because of the relatively small size of this cluster (<20 compounds). Likewise, compounds from cluster 6 were not selected for testing because they contained a free carboxylic acid that could interfere with the deoxyfluorination reaction. Anticipating eventual validation of future modeling efforts, we also selected 12 additional sulfonyl fluorides to serve as out-of-

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sample tests (Figure 2C). This data science−driven approach ensured that we tested a broad range of reagents that are likely to have distinct structural and reactivity profiles compared to that of PyFluor. Additionally, many of the reagents selected for testing were solids with melting points >30 °C, indicating that the ML melting point curation step was successful. Out of the 61 total sulfonyl fluorides selected from our virtual library (comprising both training and external test sets), 71% were found to be solid at room temperature.

Reactivity Modeling. Our interest in identifying improved deoxyfluorination reagents stemmed from the unique challenges of fluorine installation in the stereoselective synthesis of receptor-interacting serine/threonine protein kinase 1 (RIPK1) inhibitor GDC-8264.[46] The early development route used PBSF to install the key fluorine moiety for multikilogram-scale deliveries,[47] but pending regulatory and environmental restrictions governing the use of PFAS prompted us to determine alternative approaches to secure a viable long-term manufacturing route.[32] From substrate **A1**, PyFluor in combination with $NEt_3 \cdot 3HF$, NEt_3, and THF at 60 °C for 24 h was identified as a suitable alternative and gave the desired product **P1** in 74% isolated yield (Figure 3A). However, its performance was unsatisfactory, and the slow kinetics of the reaction promoted numerous detrimental side reactions including diastereomer formation and chlorination (see SI for details).[48] Motivated by these challenges, we set out to construct statistical models that would predict improved reaction performance and allow us to identify safe reagents with desirable physical properties.

Our selected training set of sulfonyl fluorides was prepared and tested in the model deoxyfluorination reaction of substrate **A1** under the previously optimized conditions. In total, 61 sulfonyl fluorides were tested at multiple time points up to 48 h to capture the reactivity profile across each reaction (Figure 3B). In addition to recording the yield of **P1** at each time point, the remaining starting material and side product profiles were also quantified (fluorinated diastereomer **B1**, chlorinated side product **B2**, sulfonate ester intermediate) allowing for accurate monitoring of key reaction species. Once yield data collection was completed, the data set was divided into training, validation, and external test sets to begin model construction. We chose to initially evaluate the 24 h time point data as product conversion had plateaued for most reagents. At this time point, the average HPLC assay yield of **P1** across the data set was 46%, with a maximum assay yield of >99%.

An objective in modeling the experimental data was to identify the characteristics of high-yielding deoxyfluorination reagents and gain insight into the important molecular properties that lead to enhanced reactivity. We assessed different statistical modeling methods and identified that classification-based algorithms were best suited for our goal of a mechanistically interpretable model. First, the yield data was partitioned into binary outputs above and below 80% yield at 24 h and analyzed against each molecular descriptor. A threshold of 80% yield was selected to partition high-performing sulfonyl fluoride reagents that would represent an advance from PyFluor, while maintaining an even data distribution. Statistical metrics were employed to rank the fit of each classification model at different threshold values. A classification model was first identified with the pyramidalization of sulfur (Figure 3C, *y*-axis). Pyramidalization captures the deviation of the sulfonyl fluoride from its ideal tetrahedral geometry by summing the angles (θ) between the two carbonyl groups and fluorine, subtracting from 360° and taking the square root (Figure 3C, right).[49] Larger pyramidalization values indicate greater tetrahedral geometry, usually driven by steric repulsion of bulky substituents on the (hetero)aryl fragment. Smaller values, conversely, indicate increased trigonal planarity of the sulfonyl fluoride geometry (Figure 3C, right). The pyramidalization threshold indicates that sulfur centers with more planar geometries (pyramidalization values <4.95°) lead to faster depletion of the starting material and formation of the fluorinated product (see SI for details). Since sulfonyl fluorides with lower pyramidalization values correspond to those with less sterically hindered hetero(aryl) groups, this feature is likely indicating the importance of a sterically accessible sulfur center in the formation of the reactive sulfonate ester intermediate. Moreover, sulfonyl fluoride units with higher trigonal planarity may be able to adopt the required trigonal bipyramidal transition state geometry to generate the sulfonate ester intermediate more easily. Subsequently, a more planar orientation (i.e., lower pyramidalization) of the resulting sulfonate ester intermediate could also be correlated with faster fluoride displacement to generate product.

To further probe reactivity, a two-parameter classification model was developed to identify the characteristics of the best performing deoxyfluorination reagents. The molecular dipole, in addition to pyramidalization, most accurately partitioned the top-performing reagents (>80% yield **P1**, Figure 3C, *x*-axis). The dipole descriptor highlights that sulfonyl fluorides with electron-withdrawing groups (EWG) in the *para*- or *meta*-position leading to a low net molecular dipole were the best performers (Figure 3C, right). In the first step of the mechanism, sulfur serves as the electrophile for the alcohol nucleophile. Therefore, a less electron-rich sulfur center may facilitate the formation of the sulfonate ester intermediate. Second, the sulfonate ester is displaced in an S_N2-type attack from an incoming fluoride nucleophile. The presence of a second EWG could stabilize the conjugate base of the sulfonate ester anion during the fluorination step. The sulfur pyramidalization and net dipole descriptors provided insight into the most important characteristics for a successful deoxyfluorination reagent, namely an unhindered sulfur center that is electron-deficient from a distal EWG or heterocyclic ring. Moreover, good accuracy, precision, and recall metrics were observed for both the training and external test sets of sulfonyl fluorides, demonstrating this model's accuracy and predictive power (Figure 3C, right).

Reagent Selection. Through our modeling efforts, we were able to identify several sulfonyl fluoride reagents that exhibited both enhanced physical properties and improved deoxyfluorination reactivity with the model substrate **A1** (Figure 3C, bottom). Many of these optimal sulfonyl fluorides contain aryl cores that are structurally distinct from PyFluor, highlighting the opportunity for novel reagent discovery using this data science-guided workflow. Although we found many reactive sulfonyl fluorides, we down-selected three top-performing reagents (**SF-1**, **SF-2**, and **SF-3**) for further evaluation. Each of these three reagents originates from a distinct cluster, and as a result, possesses potentially unique reactivity and physicochemical properties.

Investigating the deoxyfluorination of **A1** with our top-performing reagents, we observed that, in addition to increased yield, all three reagents **SF-1**−**SF-3** reached maximum conversion to **P1** much earlier than the 24 h required for

PyFluor to converge (Figure 4). These reagents also compared favorably to PBSF, which reached incomplete conversion at 86% yield at 2 h, and then gradually eroded product formation over time. Notably, **SF-3** exhibited exceptionally fast conversion, achieving >80% assay yield of **P1** even at the first time point (~20 min from addition of base). The heteroatom-dense structure of this reagent, which would have been unlikely to be tested based on our chemical intuition, illustrates the benefits of leveraging unsupervised machine learning tools for reagent exploration.

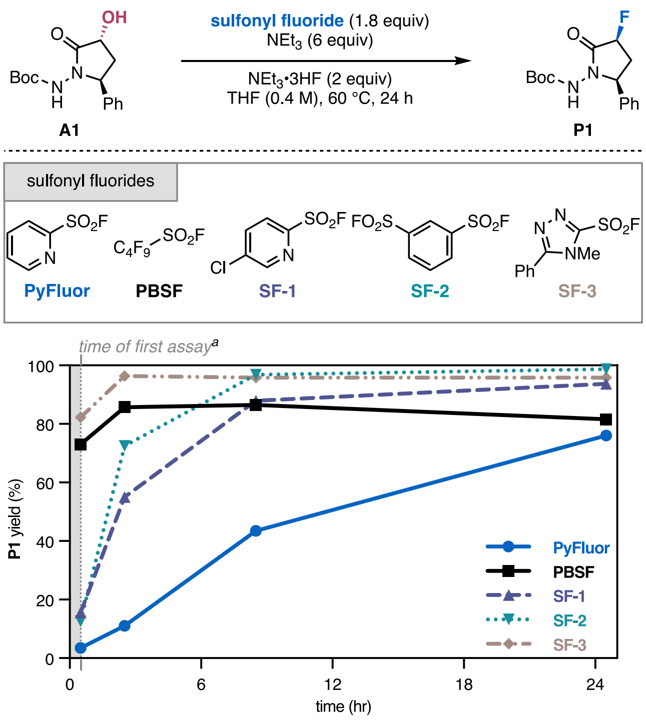

Figure 4. Further kinetic studies with **A1** and top-performing reagents. Reactions run on 0.51 mmol scale. Yields determined by HPLC assay. [a]NEt_3 was added at room temperature and then reactions were heated to 60 °C prior to first HPLC assay.

We also observed that these new reagents more effectively mitigate formation of undesired side products **B1** and **B2**. For the reaction with PyFluor, up to 1.3% of **B1** and 0.4% of **B2** were observed. Levels of these side products improved only marginally when using both **SF-1** and **SF-2** (1.5% **B1**, 0.2% **B2** and 1.2% **B1**, 0% **B2**, respectively). In contrast, with **SF-3**, neither **B1** nor **B2** was observed, highlighting the reagent's exquisite selectivity for the productive deoxyfluorination pathway.

As another key criterion, we also confirmed that these new reagents had acceptable thermal safety profiles based on differential scanning calorimetry (DSC). Specifically, **SF-1** and **SF-2** demonstrated low thermal safety risk based on the onset temperature and energy release of exothermic events, while **SF-3** showed higher risk based on DSC (T_{onset} (earliest exothermic event) = 220 °C, E_{exo} (earliest exothermic event) = 115 J/g) and with a higher exotherm (574 J/g) at 328 °C. Follow-up Phi-Tec adiabatic calorimetry testing using the Heat-Wait-Search (HWS) protocol on **SF-3** indicated the reagent could be used safely up to 77 °C (see SI for full details).[50]

General Alcohol Scope. Next, we aimed to assess if the reactivity trends that we had established on the model substrate **A1** could be extrapolated to deoxyfluorination on out-of-sample substrates. We selected an additional set of alcohols (**A2–A10**, Figure 5A) to evaluate with our top three reagents, with an emphasis on substrates for which deoxyfluorination with PyFluor is challenging.[34,39,51] This included a series of small, cyclic alcohols (**A2–A6**), representative aliphatic alcohols (**A7–A8**), and activated (hetero)benzylic alcohols with potentially problematic pendant functionality (**A9–A10**).[39,51] These substrates often required high temperatures, harsh conditions, or the use of hazardous reagents to achieve optimal deoxyfluorination yields.

We surveyed deoxyfluorination of each alcohol substrate under a standard set of literature-derived unoptimized reaction conditions without exogenous fluoride[39] with all three top reagents **SF-1–3** and compared their performance relative to PyFluor after 24 h (Figure 5B). Across all alcohol substrates **A2–A10**, at least one of the new reagents, **SF-1**, **2**, or **3**, significantly outperformed PyFluor, and in many cases, all three exhibited increased overall yields. In particular, **SF-3** demonstrated significant improvements in the deoxyfluorination of strained, cyclic alcohols. For example, we observed a 58% yield of deoxyfluorination product **P3** when using **SF-3**, compared to just 3% yield with PyFluor. To the best of our knowledge, effective deoxyfluorination of this substrate was only previously accessible with high-energy reagents PBSF or DAST,[39,52] illustrating the enhancement observed with this new triazole sulfonyl fluoride reagent. We observed similar reagent trends for deoxyfluorination of **A2** (26 to 71% yield), **A4** (0% to 39% yield), **A5** (1% to 50% yield), and **A6** (4% to 47% yield). For aliphatic and activated alcohols, **SF-2** emerged as the optimal reagent, offering improvements from PyFluor in all cases (**P7–P10**, Figure 5B). Deoxyfluorination via an S_N2-type substitution of the sulfonate ester intermediate led to exclusive inversion at the alcohol stereocenter, and only a single diastereomeric product was observed. Overall, our new reagents demonstrated broader applicability for the deoxyfluorination of a wide variety of alcohol substrates. Compared to PyFluor, we noted that **SF-1**, **2**, and **3** all exhibited higher average yields across **A2–A10** under these reaction conditions (Figure 5C). To explore additional substrate classes, a tertiary alcohol and a boronic ester-bearing alcohol were also tested (see Supporting Information).

Complex Alcohol Scope. As a final performance test of the new reagents, we were interested in determining whether they could be applied to the deoxyfluorination of structurally complex alcohol substrates. While late-stage fluorination is a promising avenue for rapid incorporation of fluorine into drug-like molecules, synthetic challenges arising from low reactivity and functional group intolerance limit the methods available for these transformations.[53−55] Notably, Ritter and co-workers have advanced protocols that are highly effective for the deoxyfluorination of structurally complex aliphatic alcohols using PhenoFluor[19] and AlkylFluor;[20] nevertheless, high temperatures, extended reaction times, and exogenous fluoride additives are often needed, making the protocols less attractive in an industrial setting. More recently developed reagents have sought to address these limitations but are often only employed in a single complex substrate example or are limited to a single class of alcohols (e.g., exclusively primary aliphatic or tertiary alcohols).[21−25,27,28,56−58] Thus, a reagent that can mediate deoxyfluorination of a broader variety of complex alcohols under milder conditions and shorter reaction times would be of great synthetic value.

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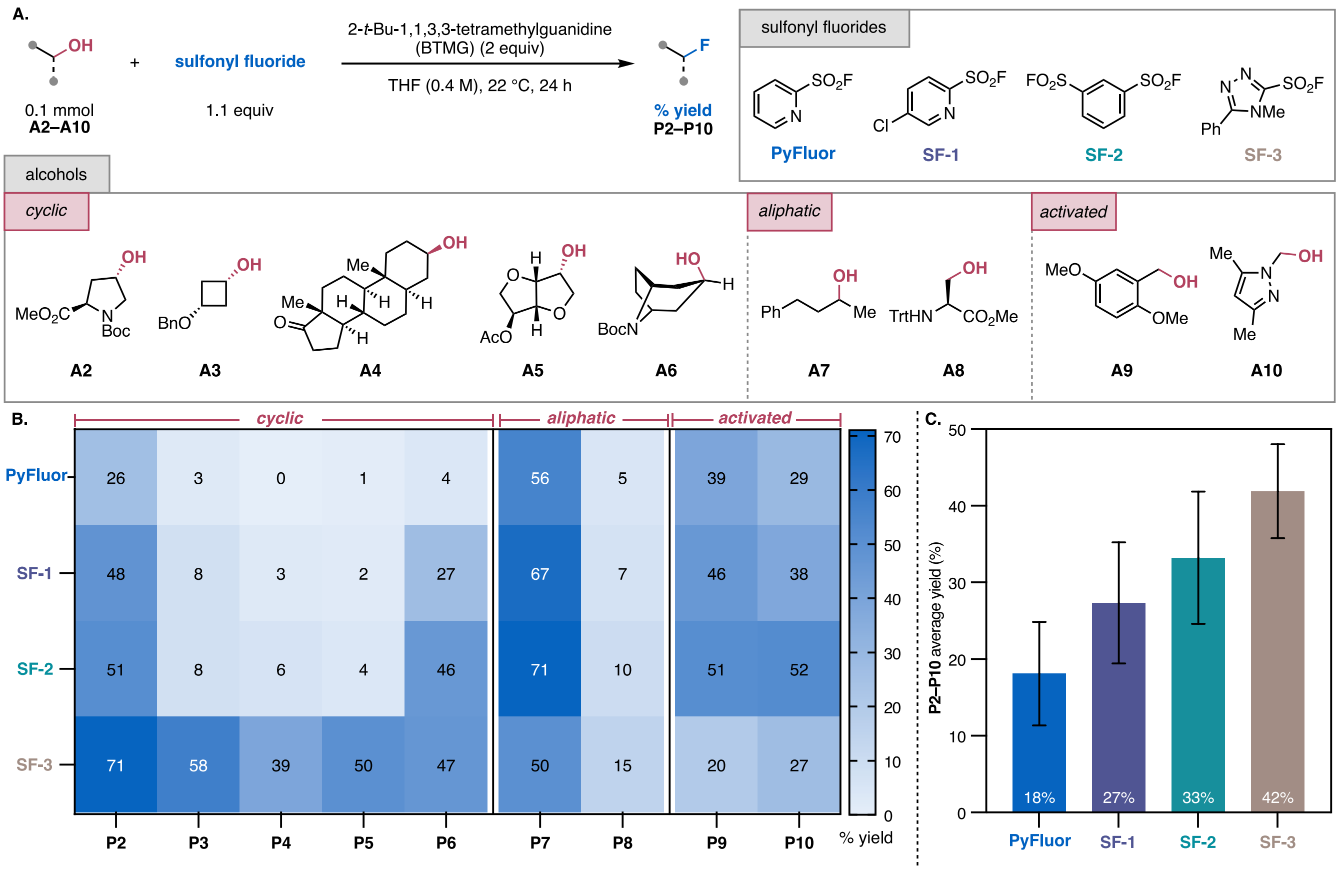

Figure 5. (A) Substrate scope of additional alcohol partners for deoxyfluorination with top reagents. (B) Yields of deoxyfluorination products for each alcohol and sulfonyl fluoride (yields are an average of two runs and were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as a standard). (C) Average yield with standard error bars of all alcohol substrates **A2**−**A10** by sulfonyl fluoride reagent.

We began by investigating the deoxyfluorination of ipatasertib intermediate **A11**. Ipatasertib is a selective pan-Akt inhibitor currently in clinical trials for the treatment of human cancers. **A11** contains a chiral cyclopentanol fragment linked to a highly substituted pyrimidine core.[59,60] Under standard conditions, we were pleased to observe rapid deoxyfluorination to form **P11** with **SF-2** in just 2 h at room temperature (64% yield, Figure 6). This reagent significantly outperformed both PyFluor and PBSF. Full comparisons of all sulfonyl fluorides for each complex alcohol substrate can be found in the Supporting Information. Reaction profiling also demonstrated the acute differences in the rate of deoxyfluorination of **A11** using **SF-2** versus PyFluor (Figure 6, right). While deoxyfluorination with **SF-2** was complete after just 2 h, PyFluor required almost 12 h to reach a modest 26% yield.

Inspired by our initial success with ipatasertib, we also tested several additional alcohols. Genentech Tau Probe 1 [^{18}F]-GTP1 ([^{18}F]-**P12**) is a small-molecule positron emission (PET) tracer developed for imaging tau aggregates in patients with Alzheimer's disease to facilitate disease progression monitoring.[61−63] For clinical manufacturing, [^{18}F]-GTP1 is synthesized via a nucleophilic substitution reaction with the corresponding *deutero*-tosylate precursor and K^{18}F.[64,65] As a proof of concept to demonstrate the possible compatibility of our newly developed reagents to radiofluorination, we reasoned that [^{19}F]-GTP1 could be alternatively prepared via deoxyfluorination of the free alcohol precursor **A12**. Previously reported deoxyfluorination of **A12** required 10 equiv of DAST to achieve just 21% yield.[66] Indeed, under our standard conditions we observed formation of deoxyfluorination product **P12** in 76% yield with **SF-2**, compared to just 28% yield with PyFluor, demonstrating the highly reactive nature of this new reagent. Additional experiments showed that unlike with PyFluor, deoxyfluorination with either **SF-2** or **SF-3** was complete within just 20 min at 70 °C, making this transformation ideal for radiolabeling given the short half-life of ^{18}F (110 min) (see SI for details).[67] With natural product derivative dihydroartemisinin (**A13**), we observed fluorinated product **P13** with **SF-2** in both greater yield and diastereoselectivity compared to those of PyFluor. Serendipitously, we discovered that upon substituting the reaction conditions to those developed for the model substrate (**A1**, Figure 3A), we observed a reversal in diastereoselectivity, with the yield of **P13** remaining significantly higher with our new reagents compared to PyFluor. Similarly, the alkaloid methyl reserpate showed a significant increase in the formation of deoxyfluorination product **P14** from 6 to 29% yield when comparing PyFluor to **SF-3**.

Taken together with our alcohol scope studies, the newly developed reagents exhibited superior deoxyfluorination reactivity with higher overall yields and faster kinetic profiles. Of note, we observe the most improvement in deoxyfluorination of cyclic alcohols with **SF-3**, whereas **SF-2** is most optimal for aliphatic and activated alcohols that were surveyed. The improved sulfonyl fluorides provide a complementary toolbox of reagents for deoxyfluorination of challenging substrates. Importantly, we defined improved reactivity trends with a diverse range of alcohol substrates, illustrating the general

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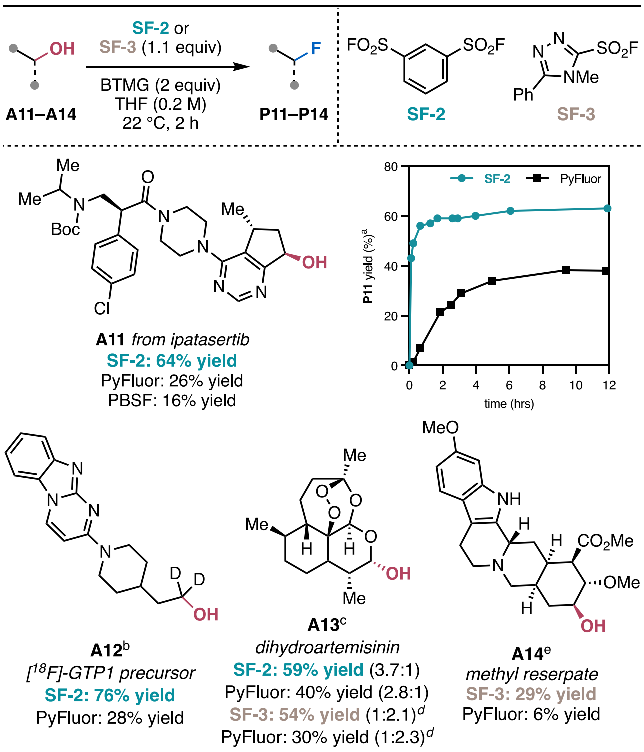

Figure 6. Complex alcohol scope (0.05 mmol scale). Yields are an average of two runs and were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as a standard. [a]Reaction was run in an NMR tube with 1-fluoronaphthalene as an internal standard. [b]Reaction was performed with BTPP (2 equiv) in 0.4 M MeCN (0.1 mmol scale). [c]Yields reported as a mixture of α:β product diastereomers. [d]Reaction was performed with sulfonyl fluoride (1.8 equiv), $NEt_3 \cdot 3HF$ (2 equiv), and NEt_3 (6 equiv). [e]Reaction was run at 60 °C for 48 h.

applicability of these new sulfonyl fluoride reagents for late-stage diversification and highlighting their broad synthetic value.

CONCLUSIONS

In summary, aided by data science and machine learning tools, we have developed several (hetero)aryl sulfonyl fluoride reagents that exhibit improved deoxyfluorination reactivity, attractive physical properties, and maintained high safety profiles compared to those of PyFluor. We constructed a virtual library of >3500 sulfonyl fluorides to guide the selection of structurally diverse reagents and to develop predictive models for both reagent melting point and reactivity of a key chiral intermediate in the synthesis of clinical candidate GDC-8264. After identifying several high-yielding sulfonyl fluorides, we applied these findings toward deoxyfluorination of a wide range of alcohol substrates, including complex natural products and small molecule therapeutics, to illustrate the generality of these reagents. We anticipate that these newly developed reagents will find broad synthetic use, especially as alternatives to thermally unstable or environmentally hazardous reagents like DAST and PBSF, which are becoming increasingly restricted. Moreover, we demonstrated how using a data science-guided workflow enabled the discovery of unique, nonintuitive reagents that possess desirable physical properties and high reactivity.

ASSOCIATED CONTENT

Data Availability Statement

All scripts are available on GitHub at https://github.com/doyle-lab-ucla/Genentech-deoxyfluorination. The sulfonyl fluoride virtual library is available at https://descriptor-libraries.molssi.org/sulfonyl-fluorides/ (MolSSI).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c07548.

Experimental procedures, experimental data, sulfonyl fluoride chemical space construction, melting point model construction, reactivity model construction, thermal safety studies, characterization and spectral data (PDF)

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Notes

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■ ABBREVIATIONS

DAST, diethylaminosulfur trifluoride; PBSF, perfluorobutane sulfonyl fluoride; m.p., melting point; DFT, density functional theory; SMILES, simplified molecular input line entry system; NMR, nuclear magnetic resonance; UMAP, Uniform Manifold Approximation Projection; ML, machine learning; RIPK1, receptor-interacting serine/threonine-protein kinase 1; PFAS, perfluoroalkylated substances; EWG, electron-withdrawing group; DSC, differential scanning calorimetry; FDA, Food and Drug Administration; BTMG, 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine; BTPP, *tert*-Butylimino-tri(pyrrolidino)-phosphorane

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