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# Sulfur fluoride exchange

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## Abstract

Sulfur Fluoride Exchange (SuFEx) is a click reaction par excellence that has revolutionized multiple research fields. In this Primer, we delve into the essential elements of SuFEx operation, catalysis, and SuFExable connective hubs. We also explore the cutting-edge applications of SuFEx in drug development, polymer science, and biochemistry. Additionally, we examine the potential limitations and promising prospects for this versatile click reaction.

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Author contributions

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Competing interests

Details of patents covering material related to the content of this Primer can be found in the supplementary information.

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## Introduction

Click chemistry[1], at its core, is a conceptual strategy aimed at rapidly synthesizing and discovering functional molecules. Inspired by Nature's efficient modular system for producing primary metabolites, click chemists use reliable, high-yielding reactions to connect readily available building blocks under mild conditions.

The first click reaction to make headlines was – the now well-known – copper-mediated azide-alkyne cycloaddition (CuAAC)[2,3]. This robust and uniquely reliable reaction ligates azides with terminal alkynes to afford 1,4-disubstituted triazoles with near-perfect precision. Nevertheless, absolute perfection is often just out of reach – the requirement for pre-functionalization of substrates (such as installing azide and/or alkyne groups), as well as copper's toxicity towards biological systems[4], are some shortcomings of CuAAC, driving click chemists to search for innovative new click-transformations.

Sulfur Fluoride Exchange (SuFEx)[5], builds upon the success of CuAAC while offering unique and complimentary connective power. SuFEx is characterized by selective activation of high oxidation state sulfur centers connected to fluoride, enabling exchange reactions with incoming nucleophiles. SuFEx reactions proceed under metal-free conditions, often accelerated by Lewis nitrogen bases, bifluoride salts, and biological nucleophiles, rendering this click transformation more favorable to biological conditions. Furthermore, amine and aryl alcohol groups are prevalent in many bioactive compounds; hence they can be directly employed for SuFEx, thereby eliminating synthetic steps associated with substrate pre-functionalization. Another feature of SuFEx is the availability of a diverse collection of SuFExable hubs that offer tremendous scope for exploring chemical space through click chemistry.

SuFEx owes its success to the unique reactivity profile of functional groups, specifically aryl fluorosulfates and aryl/alkyl sulfonyl fluorides. The high oxidation state sulfur-fluoride bonds (such as S(VI))[6] in these groups are incredibly resilient to oxidation[7], reduction[8], strong acids and thermolysis[5]. However, under specific reaction conditions, the electrophilicity of the S–F bond can be unleashed, allowing the click reaction to proceed rapidly. This latent reactivity results in exceptional levels of orthogonality, which is a critical objective of click chemistry. Consequently, SuFEx has played a pivotal role in various non-traditional approaches to function discovery, including inverse drug development[9] and the sleeping beauty approach[10].

The impact of SuFEx in the field of click chemistry cannot be understated. This Methods Primer provides comprehensive coverage of the concepts and requirements crucial for the success of SuFEx chemistry (Experimentation). It also highlights the versatile use of SuFEx in various fields, such as biochemistry, materials science and drug development (Applications). However, as with any cutting-edge technology, there are still limitations and challenges that need to be addressed (Limitations and Optimizations). The Primer concludes with an overview of the potential future directions for SuFEx click chemistry (Outlook).

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## Experimentation

This section provides a comprehensive guide to SuFEx experimentation, covering topics such as functional group compatibility, SuFEx catalysis, mechanisms and practical and safety considerations. This guide provides valuable insights and recommendations to help both new and experienced practitioners achieve reliable and robust results in SuFEx research.

### SuFExable Hubs

The wide range of SuFExable hubs for the creation of structurally diverse molecules offers a significant advantage over other click reactions[11]. Unlike CuAAC, which is restricted to coupling terminal alkynes with azides, SuFEx offers a rapidly expanding set of S–F-containing hubs, which is currently an area of innovative research (see Fig 1A for key SuFEx hub examples).

The most common SuFEx substrates are the sulfonyl fluorides (R–$SO_2F$) and aryl fluorosulfates (Ar–$OSO_2F$), both of which were fundamental to the development of the SuFEx reaction[5]. Sulfonyl fluorides[12] are accessible through various functional group interconversions starting from halides, thionyl chlorides, R–M, R–$SO_2M$, R–$SO_3M$, and R–SX[13–17].

Sulfuryl fluoride ($SO_2F_2$), a commodity fumigant gas, can be reacted with aromatic alcohols via a base-mediated SuFEx reaction to readily afford aryl fluorosulfates (Fig 1C)[18]. $SO_2F_2$ can be reacted with secondary amine nucleophiles to yield sulfamoyl fluorides ($R_2N$–$SO_2F$)[5]. Primary amines also react with $SO_2F_2$, although the sulfamoyl product is unstable and forms sulfamide byproducts via an elimination pathway[19].

Thionyl tetrafluoride ($SOF_4$) is perhaps one of the most versatile polyvalent S–F hubs, albeit a highly reactive and potentially dangerous gas. The reaction of $SOF_4$ with primary amines yields bench-stable iminosulfur oxydifluorides ($RN{=}SOF_2$) products (Fig 1D). These tetrahedral hubs allow multidimensional click projections to be made from the central sulfur atom; an important quality for biologically relevant applications. Finally, sulfonimidoyl fluorides (R–S(O)(NR′)–F) have been shown to be highly useful SuFEx hubs that uniquely allow for enantiospecific SuFEx reactions to occur[20,21].

SuFEx hubs with sulfonyl fluoride groups conjugated to π-systems provide opportunities for complementary click reactivity, such as conjugate addition and cycloaddition pathways. For example, ethenesulfonyl fluoride (ESF)[5,22–24], 1-bromoethene-1-sulfonyl fluoride (BESF)[25] and 2-substituted-alkynyl-1-sulfonyl fluorides (SASFs)[26] are Michael acceptors that work with various nucleophiles, including nitrogen-, oxygen-, and carbon-based nucleophiles, and also perform as dienophiles, without affecting the S–F functional group. Further, halogen-loaded alkenyl sulfonyl fluorides[27], such as β-chloroalkenylsulfonyl fluorides (BCASF)[28], offer the possibility of transition metal-mediated cross-coupling transformations.

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## SuFEx Catalysis

To consistently access the desired products, it is essential to select the appropriate catalyst and reagent combinations due to the distinct reactivity exhibited by both SuFExable hubs and nucleophilic partners. SuFEx catalysts are diverse and include nitrogenous Lewis bases, such as tertiary amines, amidines, phosphazenes, and guanidines (Fig 1B). Generally, the reactivity order of SuFEx catalysts follows their $pK_aH$ value, with amines being less reactive than amidines, guanidines, and phosphazines[11]. In addition to these Lewis bases, SuFEx reactions can also be facilitated by Lewis acids and bifluoride salts.

Tertiary amines, including triethylamine ($Et_3N$, $pK_aH$ = 18.8 in MeCN)[29,30], have been identified as catalysts that can accelerate the proton-mediated SuFEx reaction. For example, in the presence of $Et_3N$, $SO_2F_2$ reacts with aryl alcohols once and then stops – leaving the fluorosulfate S–F bond intact (Fig 1C). Similarly, primary amines react with $SOF_4$ in the presence of $Et_3N$ to form iminosulfur oxydifluorides (Fig 1D)[31]. However, the S–F bonds found in aryl fluorosulfates and iminosulfur oxydifluorides are less reactive than those in $SO_2F_2$ and $SOF_4$ owing to the decreased electrophilicity of the sulfur center. Therefore, stronger catalysts and reacting partners are required to facilitate further SuFEx transformations[31]. This desirable feature ensures that the sequential SuFEx decoration of S(VI) hubs with diverse modules is highly controllable.

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is a highly efficient organosuperbase ($pK_aH$ = 24.3 in MeCN)[30] and a versatile catalyst for numerous organic transformations, often performed under mild conditions. DBU can be successfully employed as a catalyst in silicon-mediated SuFEx reactions, owing to its exceptional basicity and ability to activate S–F bonds (Fig 1C). The catalytic loading of DBU depends on the SuFExability of the S(VI)–F bond in question. The order of reactivity of $SO_2F_2$- and $SOF_4$-derived S–F bonds toward SuFEx reactions with aryl silyl ethers has been tentatively suggested as follows[31]: RN=S($OF_2$ > R–$SO_2F$ > R–$OSO_2F$ > RN=S(O)(OAr)F. Therefore, the quantity of DBU required for SuFEx reactions involving R–$SO_2F$/R–$OSO_2F$ is significantly higher (10–30 mol%) than for RN=S(O)$F_2$ (3–10 mol%) substrates. This is a crucial factor in ensuring the effectiveness and control of sequential SuFEx reactions towards diverse and complex S(VI) hubs.

2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (BTMG), also known as Barton's base, is a strong guanidine base with a $pK_aH$ value of approximately 26 in MeCN[32]. When combined with the silicon reagent hexamethyldisilazane (HMDS), BTMG demonstrates remarkable efficiency as a SuFEx catalyst, facilitating the direct coupling of alkyl and aryl alcohols with SuFExable substrates (Fig 1C)[33,34]. These accelerated SuFEx reactions are complete within a matter of minutes, proceed in high yield, and require relatively low catalyst loadings (1–20 mol%) of BTMG[33]. Moreover, thanks to the volatility of the catalyst, silicon additive, and generated byproducts, these reactions can be easily purified by simple evaporation of the reaction mixtures, leading to analytically pure products in most cases.

2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), another organosuperbase ($pK_aH$ = 27.6 in MeCN)[35], can facilitate SuFEx reactions that involve challenging substrate combinations[11,31]. For example, BEMP has a remarkably

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lower catalytic loading (1–10 mol%) compared to DBU (10–30 mol%) in the SuFEx reaction between fluorosulfates and silyl ethers[36]. Furthermore, when dealing with sulfurofluoridoimidates (RN=S(O)(OAr)F), BEMP (5–10 mol%) is the catalyst of choice to activate the exchange with silylated nucleophiles[31]. By carefully selecting the catalyst (such as, $Et_3N$ → DBU → BEMP) and reaction conditions, multidimensional SuFEx ligations with diverse modules can be achieved in a stepwise manner, progressing from $SOF_4$ → $RN=S(O)F_2$ → $RN=S(O)(OAr^1)F$ → $(RN=S(O)(OAr^1)(OAr^2)$ (Fig 1D)[31].

Calcium(II) trifluoromethanesulfonimide ($CaNTf_2)_2$) is an efficient Lewis acidic catalyst that finds useful application in activating SuFExable substrates, particularly in the synthesis of nitrogenous S(VI) compounds such as sulfamides, sulfamates, sulfonimidates and sulfonamides that are commonly found in the drug landscape[37,38]. Sulfamoyl fluorides, particularly *N*-disubstituted examples, which possess increased electron density at the sulfur atom and, thus, exhibit decreased SuFExability, typically require harsh reaction conditions. However, $Ca(NTf_2)_2$, in conjunction with 1,4-diazabicyclo[2.2.2]octane (DABCO), can efficiently drive this exchange reaction at room temperature. The mechanism of this transformation is thought to involve $Ca(NTf_2)_2$ activation of the SuFExable group, with concomitant Lewis base activation of the amine nucleophile provided by DABCO[38]. This approach has the potential to overcome longstanding challenges in sulfamoyl fluoride synthesis, providing a more efficient, selective, and sustainable route to these compounds.

**Considerations for scaling up reactions—**Scaling up base-catalyzed SuFEx reactions can pose certain challenges. For instance, the relatively high catalyst loadings required with DBU can make the purification process more difficult on a larger scale. In the case of BEMP – despite its superiority as a SuFEx catalyst – air sensitivity, expense and lack of bulk accessibility limit its application in large-scale production. Furthermore, the strongly basic nature of organosuperbase SuFEx catalysts can limit substrate scope, especially when sensitive functional groups are present. For example, alkyl sulfonyl fluorides are incompatible with strong bases owing to the easy deprotonation of their α-H and subsequent elimination side reactions[39]. Therefore, careful consideration and optimization of the reaction conditions are necessary for successful scale-up and broad applicability of SuFEx reactions.

Using low-loadings of acidic SuFEx catalysts can address some of these issues[39]. For example, bifluoride ion salts comprising various organic and inorganic counterions ($Q^+[FHF]^-$) display superior catalytic activity in SuFEx-based polysulfate synthesis than either DBU or BEMP, requiring just 0.1 mol% loading in most cases; tris(dimethylamino)sulfonium bifluoride (Fig 1B) requires only 0.05 mol% loading to generate polysulfates with a molecular weight of up to 100 kDa[39]. These significantly lower catalyst loadings enable the efficient, cost-effective production of polysulfates and polysulfonates on an industrial scale. Moreover, bifluoride salt catalysts broaden the scope of SuFEx polymerization to encompass sensitive functional groups, like alkyl sulfonyl fluorides.

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## SuFEx Mechanism

Knowledge of reaction mechanisms can facilitate the design and synthesis of improved catalysts. Although SuFEx is a seemingly simple exchange reaction, the exact mechanism behind it is not yet fully understood, leaving several unanswered questions[33,40–42]. For instance, it is still unknown whether superbase SuFEx catalysts form precatalysts, whether the reaction occurs on the sulfur or silicon center, or whether the reaction proceeds through disassociation or an associative pathway with a concerted intermediary (given the capacity of both sulfur and silicon to accommodate hypervalent coordination via the 3d orbitals). Moreover, the rapid exchange of $^{18}F/^{19}F$ on the S(VI) center, suggests that the easy redistribution of ligands on the putative Si or S(VI) hypervalent intermediates might facilitate the SuFEx process[43].

The SuFEx reaction mechanism is primarily driven by the high charge of the central sulfur atom, making it attractive for nucleophiles to engage. Such exchange reactions are well-known for S(VI)–Cl bonds and are also relevant for SuFEx[5,11] and related chemistries such as sulfur(VI)-phenolate exchange (SuPhenEx)[42,44,45]. However, a unique feature of the SuFEx reaction is its ability to combine the significant stability of the S(VI)–F bond toward many nucleophiles, including water, with a high reactivity towards phenols (either silyl protected or unprotected), certain types of amines, and *O*-centered nucleophiles (alkoxy and phenolate anions). An illustrative example is the reaction of chiral sulfonimidoyl fluorides with phenolate nucleophiles[20]. Both experimental and theoretical studies have shown that phenolates react in an $S_N2$ fashion with inversion of configuration at the sulfur atom, as indicated in the potential energy surface shown in Fig 2, with low activation energies in line with smooth reactivity at room temperature.

While the mechanism described in Fig 2 likely operates for a variety of SuFEx and related exchange chemistries, several features still need to be explained. Firstly, the SuFEx reaction works highly efficiently with silyl-protected phenols or in the presence of silicon additives. One reason for this is likely the formation of the Si(VI)–F bond, the strongest covalent single bond in the periodic system (bond dissociation energy = 540 kJ/mol)[5,46]. While the formation of this bond is seemingly not essential to drive the reaction, it certainly contributes to it.

Another unresolved aspect of the SuFEx mechanism is the degree to which silyl groups play a role in the (nucleophile-driven) abstraction of $F^-$ from the sulfur atom. While Si-centered cations could theoretically be formed, this is unlikely to be relevant as SuFEx works well in solvents where any free $Si^+$-centered cation would rapidly react (such as water). However, strong Lewis acids (such as $Ca^{2+}$) can facilitate $F^-$ abstraction, as demonstrated both experimentally and theoretically[37,38,40,47]. In any case, the $F^-$ leaving group readily reacts with Si-centered protecting groups (a typical deprotection step for such moieties), thereby keeping the $F^-$ concentration to a minimum and freeing up new phenolate ions for the reaction.

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## On-water SuFEx

The reaction medium in which SuFEx occurs can considerably impact reaction rates and outcomes, as demonstrated by the on-water effect[48–51]. Water is an abundant source of protons ($H^+$), and the productive interplay between S(VI)–F and $H^+$ at the interface of aqueous-organic biphasic mixtures is beneficial for various SuFEx processes. The rate-accelerating effect of this interaction on SuFEx reactions has been demonstrated by the smooth coupling of aniline and phenylsulfonyl fluoride on-water at room temperature (Fig 3A)[5]. In contrast, the reaction completely stalls when the same substrates are refluxed together neat[5]. This on-water effect not only enables the efficient and convenient synthesis of highly SuFExable sulfonyl fluorides such as ESF[52] but also raises the possibility of further enhancement of the SuFEx reaction itself through analogous on-water effects.

On-water SuFEx catalysis can result in considerable impacts on reaction efficiency and outcome. For example, a new mode of SuFEx reactivity for the powerful diazotransfer reagent fluorosulfonyl azide ($FSO_2N_3$) was recently discovered on-water. S–F···H–OH interactions via the hydrogen bonding network at the phase boundary, likely facilitated by a microstructure similar to Fig 3A, cause amine nucleophiles ($R–NH_2$) to attack the azide nitrogen in preference to the sulfur center. This delivers azide products ($R–N_3$) and the byproduct $FSO_2NH_2$; the S–F bond of $FSO_2NH_2$ is more reactive than that in the parent reagent, and consequent hydrolysis in basic aqueous conditions drives the equilibrium toward a quantitative diazotransfer process[53].

## Practical Synthesis Considerations

The development of new S–F-containing substrates and reagents, many of which are unprecedented, is an ever-expanding area of chemistry, and considerations about handling new entities must be taken seriously. SuFEx reactions are generally conducted using standard organic chemistry equipment (such as round-bottomed flasks under an inert (if required) atmosphere). However, as with all true click reactions, SuFEx transformations tolerate water and oxygen well. Reactions are routinely monitored by thin-layer chromatography (TLC) on silica gel plates or liquid chromatography-mass spectrometry (LC-MS)[26,54]. Once the reaction is deemed complete, a workup is conducted, followed by purification as needed; often, evaporation of the reaction solvent is sufficient to yield analytically pure product.

Procedural enhancements are frequently the focal point of recent SuFEx advancements. One-pot protocols offer an increase in atom economy and a reduction in both the time and consumables required for a given chemical transformation. One example of this ideology in SuFEx is the development of the Accelerated SuFEx Click Chemistry (ASCC) procedure (Fig 1C)[33]. Under ASCC conditions, the requirement for prior synthesis of silyl ether substrates is eliminated by teaming BTMG with hexamethyldisilazane (HMDS) additive[33,34]. With the synergistic BTMG-HMDS reagent combination, a host of SuFEx products can be generated directly from phenols, with reaction rates vastly outperforming earlier SuFEx protocols.

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### Safety Considerations

SuFEx reactions should be conducted by individuals trained in standard synthetic organic chemistry operating procedures. Although every effort has been made to prioritize the inclusion of low-risk substrates, solvents, and reagents, SuFEx routinely employs flammable solvents, such as MeCN, and catalysts that are toxic and corrosive (for example DBU, $K[HF_2]$). SuFEx byproducts are generally considered benign. The hydrofluoric acid that is generated during the click reaction can be converted to a silyl fluoride ($R_3Si–F$) species by reacting with either the liberated silyl group (when silyl ethers are used) or with a silicon additive such as HMDS (in the case of the accelerated SuFEx protocol)[33]. In the presence of $Na^+$, the generated fluoride precipitates as NaF[20].

The generation of SuFExable hubs routinely involves the manipulation and handling of toxic gases, such as $SO_2F_2$ and $SOF_4$, creating additional logistical, accessibility, and safety considerations. Ex situ generation of $SO_2F_2$ circumvents the direct handling of the gaseous reagent; this can be achieved by employing reagents such as 1,1’-sulfonyldiimidazole (SDI) in combination with a fluoride source (such as KF) in a two-chamber setup[55,15].

Another workaround is the employment of solid, electrophilic $^+SO_2F$ donors that offer enhanced reactivity, substrate scope, and most importantly, practicality (Fig 3B). 1-(Fluorosulfonyl)-2,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (Fig 3B, **1**) is a bench-stable, non-toxic substitute for $SO_2F_2$ that exhibits accelerated and broader reactivity[56]; primary amines are readily converted to sulfamoyl fluorides with the fluorosulfuryl imidazolium salt without competing sulfamide formation, as often observed when using $SO_2F_2$. Phenol and amine substrates can also be converted to the corresponding fluorosulfates and sulfamoyl fluorides, respectively, by employing the solid reagent [4-(acetylamino)phenyl]imidodisulfuryl difluoride (AISF)[57,58]. Similarly, sulfuryl chloride fluoride gas ($ClSO_2F$) is a useful reagent for constructing sulfonyl fluorides. Replacing $ClSO_2F$ with crystalline 1-(fluorosulfonyl)-3-methyl-2-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazol-3-ium trifluoromethanesulfonate (Fig 3B, **2**) significantly simplifies the preparation of various alkenyl- and alkyl-sulfonyl fluorides[59].

In addition to enhancing user safety, using solid $^+SO_2F$ donors enables the precise stoichiometric delivery of the reagents, mitigating the potential release of excess $SO_2F_2$ gas (a potent greenhouse gas) into the atmosphere.

## Applications

SuFEx delivers functional molecules efficiently and reliably. As such, SuFEx has had a significant impact on drug discovery by bringing novel approaches for lead candidate identification to fruition while also having far-reaching impacts in materials science (specifically polymerization) and biochemical investigation[60,61].

### SuFEx-enabled Drug Discovery

Delivering affordable, effective drugs is one of the prime missions of click chemistry[1,62,63]. Through the rapid, irreversible connection of fragments or ligands, CuAAC has proven useful in creating diverse combinatorial libraries or new multifunctional modalities,

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exemplified by the discovery of drug candidates solithromycin (antibiotic)[64] and RapaLink-1 (third-generation mammalian target of rapamycin (mTOR) inhibitor)[65], and has been successfully applied in the synthesis of DNA-encoded libraries[66]. Likewise, combinatorial libraries with SuFEx-derived S–O or S–N linkers have yielded nucleoside mimics[67], anti-virals[68] and anti-insect[69] agents with improved potency.

Sulfamide or sulfuramidimidoyl fluoride linkers, which are resistant to enzymatic hydrolysis, can be made using the water-promoted SuFEx reaction[31,70] of iminosulfur oxydifluoride and primary or secondary amines, respectively, in microplates. Termed high-throughput medicinal chemistry, SuFEx enables the merger of high-throughput experimentation and direct assay read-out with high yield, water compatibility and benign byproducts (Fig 4A). In a proof-of-concept study, a miniaturizable workflow was developed[71] to synthesize 460 sulfamide or sulfuramidimidoyl fluoride compounds overnight, leading to the evolution of a 10-μM cysteine protease inhibitor down to 63 nM. This plug-and-play hit-to-lead optimization platform has been utilized to make bifunctional molecules that target two proteins, ENL/YEATS domain and E3 ligase, to induce ubiquitination and protein degradation in cells (Fig 4B)[72].

The latent reactivity of SuFExable groups towards nucleophilic amino acid residues, such as tyrosine, lysine, serene, threonine and histidine, has sparked many applications in the era of mining the reactivity of the non-cysteine proteome[73–76] – making covalent connections with biomacromolecules. Sulfonyl fluorides have long been known as covalent inhibitors for various hydrolases, including proteases and esterases[77–80]. Phenylmethane sulfonyl fluoride is a promiscuous serine protease inhibitor and is commonly supplemented in lysis buffer for cell lysate preparation. In the 1960s, work on the structure-activity relationship of aromatic sulfonyl fluoride compounds[81–83] laid the foundation of the later exploration of selective hydrolase inhibition[84–87]. Further development requires not only protein structural insights but, more importantly, a toolbox for accessing diverse SuFExable compounds.

Agnostic screening of SuFEx fragment libraries against a chosen enzyme target has proven effective in developing selective, covalent inhibitors (Fig 5A). A SuFEx-focused library containing >1,500 electrophilic fragments[88], including aromatic, alkyl or alkenyl sulfonyl fluorides, and aryl fluorosulfates was screened for activity against human neutrophil elastase (hNE)[88]; 2-triflyl benzenesulfonyl fluoride emerged as a highly selective, sub-μM inhibitor of the enzyme by covalently modifying the catalytic residue, Ser195. The selectivity for hNE over its homologous serine protease cathepsin G indicated the strict dependence of the occurrence of such covalent SuFEx capture on the live enzyme (the local environment at binding sites and nucleophilicity perturbation from neighboring residues). This property of SuFExable head groups to only react covalently with nucleophilic groups when buried within a live protein structure while remaining chemically inert otherwise (such as when denatured proteins are used) is termed the "*sleeping beauty effect*"[10]. Parallel screenings of focused SuFExable fragment libraries[89] have also become a source of novel antibiotics[90], protease inhibtiros[91,92], and GTPase[93] inhibitors.

Although the prediction of a given SuFEx covalent capture is not yet possible, rational design of such inhibitors has made significant progress. With a known protein-compound

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pair, SuFExable groups are grafted onto the compound where a $pK_a$-perturbed nucleophilic amino acid residue sits juxtaposed. In an early example, a highly selective, covalent modification of Lys15 of transthyretin using either sulfonyl fluoride[94] or fluorosulfate[95] derivatives of a known 1,3,4-oxadiazole ligand at the thyroxin binding site was demonstrated. A known diaminoquinazoline ligand of decapping scavenger enzyme DcpS was SuFExed in an effort to target its Tyr113 or Tyr143 residue in an addressable way by changing the vector of the sulfonyl fluoride group[96]. Switching from sulfonyl fluoride to fluorosulfate, the molecule was re-addressed to an in-pocket serine[97], again affirming that the SuFEx reactivity is tightly controlled by geometry and conformation. More SuFEx-based molecules that covalently modify non-catalytic tyrosine[98–101], lysine[98,102–104], and histidine[98,105] have emerged in the past five years with a wide-spread target spectrum.

A complementary approach to target-oriented screening is compound-oriented drug discovery, where protein targets were characterized using alkynylated SuFEx compounds in cell lysates. Different from canonical activity-based protein profiling[58,106,107], this approach focuses on SuFExable compounds with intermediate complexity so that a lower background and higher validation rate could be expected. Biphenyl fluorosulfate was identified as a proteome-wide selective inhibitor of lipid binding protein CRABP2[108]. Later termed "*inverse drug discovery*"[9,109,110], this compound-centric chemoproteomic method characterized a handful of unprecedented protein-compound reaction pairs with human disease relevance.

The feasibility of inverse drug discovery is based on the fact that latent SuFEx groups, for example fluorosulfate and sulfuramidimidoyl fluoride, are generally unreactive to most proteins in the human proteome without a binding site and perfectly aligned reaction trajectory[108]. An often-overlooked feature of the fluorosulfate group is its potential as a non-covalent pharmacophore. Fluorosulfate is a bioisostere of the trifluoromethoxy group ($R–OCF_3$) — for example, a fluorosulfate analog recapitulated the activity of a potent soluble epoxide hydrolase (sEH) inhibitor that contains a trifluoromethoxy group[111]. Selected fluorosulfate derivatives of phenolic drugs (such as fulvestrant fluorosulfate) have demonstrated improved cytotoxicity against cancer cells and/or pharmacokinetics by inhibiting the metabolism of phenols[18]. More importantly, the SuFEx derivatization, fluorosulfonylation of phenols or amines, could be realized in a parallel microplate setting with direct screening potential[18,112].

## SuFEx-enabled $^{18}F$ Radiosynthesis

SuFExable compounds can also become potential diagnostic tools by substituting the natural-occurring fluorine-19 nuclide with a short-lived, positron-emitting fluorine-18 nuclide. Fluorine-18 is invaluable for positron-emission tomography (PET) imaging, a non-invasive technology widely used for early diagnosis of cancer and neuron-degenerative diseases[113,114]. Earlier works[115–117] using sulfonyl [$^{18}F$]fluoride were prevented from in vivo imaging, owing to hydrolysis liability and inevitable off-targets; byproduct fluoride anions enriched in skull and bones mitigated the imaging quality. SuFEx groups with phenoxy (aryl fluorosulfates) or amino (sulfamoyl fluorides) substitutions are at least 30-fold more stable than sulfonyl fluoride and are known to be stable in aqueous solution with

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a wide pH range (1–10)[43]. Their exchange reactions with alcohol or amine nucleophiles often require a strong base or bifluoride catalyst. However, experimental and computational analysis found fluoride substitution with another fluoride anion (fluoride exchange) involved a low barrier process [43]. This has led to the development of the first useful S–[$^{18}$F]F PET agent, based on a PARP inhibitor olaparib, for in vivo imaging of tumor xenografts in mice (Fig 5B). The same aryl [$^{18}$F]fluorosulfate could be synthesized via an alternative imidazole-to-[$^{18}$F]fluorine substitution process[118]. The even more inert sulfamoyl fluoride was radiolabeled via a [$^{18}$F]/[$^{19}$F] exchange[119].

## Diversity Oriented Clicking (DOC)

Developed as a means of fast-tracking the discovery of novel, functional scaffolds, Diversity Oriented Clicking (DOC)[26] merges modern SuFEx reactivity with the best classical click chemistries to generate compound libraries rapidly for direct evaluation in functional assays. To explore the concept of DOC, the SuFExable 2-substituted-alkynyl-1-sulfonyl fluoride (SASF) hub, comprising a reactive internal alkyne connected to a sulfonyl fluoride head group, was developed[26]. Access to these SuFExable hubs can be achieved using two complementary methods, depending on the electronic nature of the alkyne substrate. For electron-poor substrates, alkynide ions (generated via *n*-BuLi deprotonation of terminal alkynes) can be reacted with $SO_2F_2$ gas at –110 °C to directly afford SASFs. Replacing $SO_2F_2$ with fluorosulfonic acid anhydride ($FO_2S–O–SO_2F$) resulted in more reliable yields on a 10 mmol scale. For electron-rich alkynes, a one-pot process whereby an alkynide ion is reacted with sulfur dioxide gas followed by electrophilic fluorination with *N*-fluorobenzenesulfonimide is superior[26].

SASF hubs readily undergo click-cycloaddition reactions with 1,3- and 1,5-dipoles and dienes to selectively forge heterocyclic ring systems (example structures are shown in Fig 5C). Nitrogen-containing dipoles like nitrile oxides, nitrones, azides, nitrile imines, sydnones, and münchnones can be reacted smoothly with SASFs, to afford isoxazoles, isoxazolines, triazoles, pyrazoles, and pyrroles respectively. When dienes and heterodienes are combined with SASFs, three-dimensional, densely-packed adducts as single diastereoisomers are isolated – highlighting the reliability and fidelity of click transformations. The pendant sulfonyl fluoride group can be readily modified through SuFEx chemistry with TBS-protected phenols to diversify the compound library rapidly.

SASFs can also react via Michael-type addition pathways[92]. Nucleophiles, including secondary amines, carboxylates, 1*H*-1,2,3-triazole, and halides, undergo facile conjugate addition to SASF hubs at room temperature to afford single products in both high yield and exceptional purity. In all cases, a single stereoisomer is produced with stereoselectivity determined by the nature of the employed nucleophile. For example, when secondary amines are reacted with SASFs, the *E*-isomer is solely formed, while the addition of halides and carboxylates favors the *Z*-isomer.

The compound libraries generated through DOC are primed for direct function screening. For example, 16 of the 151 screened heterocyclic compounds generated were found to inhibit the pathogenic methicillin-resistant strain *Staphylococcus aureus* USA 300[26].

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Evaluation of the Michael addition products against hNE revealed several 1,2,3-triazole-substituted ESFs and β-ester-substituted ESFs to be micromolar inhibitors of the enzyme[92].

## SuFEx-enabled Polymerizations

The first example of SuFEx-based polysulfate synthesis involved the DBU-catalyzed reaction of bis(aryl fluorosulfates) with bis(aryl silyl ethers), providing polymer with typical yields of >90%, molecular weights in the 20–140 kDa range, and dispersity values (Đ) from 1.4–1.8, as expected from step-growth polymerizations[36]. The next significant advancement was the development of improved catalysts, such as $(Me_2N)_3S^+[FHF]^-$ catalyst (Fig 6A)[39]. Bifluoride-catalyzed polymerization protocols have also been utilized in synthesizing high-performing polysulfate dielectrics, in which the combination of 2 mol% $KHF_2$ and 1 mol% 18-crown-6 was efficient in driving the SuFEx polymerization[120].

Further progress in the arena of SuFEx-enabled polymerizations has pursued three significant avenues. The first involves the addition of further functionality to the polymer backbone that is primed for additional derivatization. Polymers prepared from reacting $SOF_4$ and iminosulfur oxydifluorides contain two unaltered S–F bonds per repeating unit and meet this requirement, allowing for SuFEx-based post-polymerization modification (see Fig 6B)[121]. This development with $SOF_4$ yielded an entirely new family of helical polymers, each of which could function as a scaffold for a wide variety of SuFEx-addable moieties, ranging from aggregation-induced-emission-based fluorescent materials (AIEgens) via nucleobases to ferrocenes. The second feature, chirality, was realized by using chiral di-sulfonimidoyl fluorides[122] that react enantiospecifically and at lower temperatures (80 °C) with di-phenolates to yield chiral polymers ($M_n$ up to 300 kDa; typical Đ from 1.4–1.8; see Fig 6C)[21]. This addition of controllable chirality brings biomimetic functions closer for such polymers. In addition, these helical polymers combine high functionality with degradability under mild conditions (near-neutral water, 2 months)[42], offering an environmentally attractive feature to these functional materials.

The third significant advancement was the utilization of the chain-growth polymerization technique in SuFEx. All the polymerization events described above are step-growth in nature, resulting in relatively high dispersity values. Chain-growth polymerizations offer more promise for control, but this seemed difficult to obtain using SuFEx. Recently, a proof-of-principle for chain-growth SuFEx polymerization has been demonstrated by designing an initiator S–F-containing compound that reacts with a molecule containing both a silyl-protected phenol and a fluorosulfate moiety (Fig 6D)[123]. Reaction of the silyl ether with the initiator molecule results in an electron-withdrawing effect that activates the fluorosulfate group sufficiently to react with another protected phenol – a precise reactivity balance that yields a smooth chain-growth process while avoiding self-polymerization. This type of chain-growth process would be particularly intriguing if it could be combined with milder degradation processes, thereby bringing this aspect of SuFEx-clickable materials up to the environmental standards of the 21$^{st}$ century[124].

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### Bio-SuFEx

While SuFEx reactions can often occur under non-physiological conditions, SuFExable groups have an intrinsic selectivity for properly activated targets in biological systems. To this end, the SuFEx reaction has been polished to proceed under biocompatible conditions (for example, aqueous buffer conditions)[70]. To demonstrate the biological applicability of this click reaction, iminosulfur oxydifluorides have been bioconjugated via SuFEx to either an amine-modified single-strand DNA or a protein (bovine serum albumin or BSA). Sulfurofluoridoimidates (RN=S(O)(OAr)F), formed by reacting phenols with iminosulfur oxydifluorides under physiologically compatible conditions (pH = 8, 37 °C), could be further modified by an additional nucleophile, albeit under more forcing reaction conditions (pH = 10, 80 °C). This resulted in a 3-dimensional tripolar linkage composed of S–N and S–O bonds (Fig 7A). Libraries of iminosulfur oxydifluorides through reaction with both primary and secondary amines have been evaluated in a high-throughput screen, leading to the discovery of a potential inhibitor of bacterial cysteine protease SpeB (lead compound exhibited 480-fold higher potency compared with its non-SuFExed counterpart)[71].

Typically, sulfonyl fluorides and aryl fluorosulfates react with nucleophilic residues of biological targets only when proximally activated by their local chemical environment. Hence, the application of SuFEx as a general method for site-specific or residue-specific modification of natural peptides or proteins was long considered inaccessible. Recently this issue has been resolved by modifying the SuFEx reaction to selectively derivatize tyrosine residues[125]. Using tetramethylguanidine instead of the more classical SuFEx catalyst, DBU, led to the selective deprotonation of tyrosine over other nucleophilic amino acids (Fig 7B). The impressive chemoselectivity obviated the need for phenolic group silylation – an otherwise hindrance to the bio-applications of SuFEx – and allowed selective activation of tyrosine residues in general peptide or protein sequences, regardless of its chemical environment, expanding the scope of tyrosine-selective modification to include those residues present on protein surfaces. This Bio-SuFEx method is demonstrated by the derivatization of the cell-penetrating peptide TAT 47–57 with a fluorophore via its N-terminus tyrosine residue and subsequent imaging in HeLa cells (Fig 7B) and recombinant human erythropoietin.

### SuFEx-enabled Bioconjugation

An interesting subtype of rational design is SuFEx covalent capture between biomacromolecules. Compared to protein-small molecule binding, biomacromolecule-biomacromolecule binding, for example antigen-antibody or protein-aptamer recognition, is often with higher specificity and affinity. Sequence-defined peptides or aptamers with latent SuFExable groups, readily made by either solid-phase peptide synthesis[126–128] or late-stage bioconjugation[129–131], could improve the potency (*Cf.* non-covalent) by permanent crosslinking and degradation escape[132]. Genetic code expansion methods provide a powerful way to introduce non-canonical functionality into proteins in vivo. Both fluorosulfate-L-tyrosine (FSY) and fluorosulfonyloxybenzoyl-L-lysine (FSK) have been prepared and successfully encoded and expressed in *E. coli* and mammalian cells (Figure 7C)[133,134]. These SuFExable unnatural amino acids showcase proximity-based selectivity that can be utilized to either crosslink two interacting proteins or two proximal residues within

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a single protein, both providing critical information about the structure and biochemical activity of the target. As FSK has a longer and more flexible side chain than FSY, it can crosslink more distant sites. When FSY and FSK are used simultaneously, they can capture distinct positions of the same target, significantly increasing the resistance to mutation. Intermolecular crosslinking of important protein-protein interaction pairs has emerged as a new modality for anti-viral[135,136] or anti-cancer[137] drug discovery. Recently, the scope of nucleophilic partners for SuFExable proteins has also expanded to RNAs[138] and carbohydrates[139].

FSY incorporation also has additional latent functionality termed Genetically Encoded Chemical Conversion (GECCO; Fig 7D). When positioned proximal to serine or threonine residues, FSY converts them into dehydroalanine (Dha) or dehydrobutyrine (Dhb), respectively, via a SuFEx reaction and hydrolysis of the resulting sulfate linker[140]. The installed Dha in a protein can itself be chemically active and thus exploited to covalently attach thiol-saccharide to proteins as a glycoprotein mimic. The strategy of GECCO enables the insertion of chemically active unnatural functional groups to a protein, which would not be feasible using the conventional genetic code expansion approach because of the reactivity of the amino acid unit.

### SuFEx Activity-based Probes

SuFExable compounds are highly sought after for their hydrolytic stability and chemoselective reactivity, making them ideal for use as activity-based probes[141]. Motivated by a known sulfonyl fluoride-based adenosine triphosphate-analogue (ATP-analogue), a set of activity-based lysine-targeting probes for Src kinases was prepared (Fig 7E)[106]. One notable example is the development of XO44, an improved probe based on the promiscuous kinase inhibitor VX-680, which was used to compare the selectivity of conventional kinase inhibitors against a collection of kinases in cell lysate[107]. Similar approaches to develop activity-based probes suited to transthyretin[94] or serine proteases[142] are presented in the literature. SuFExable probes are also invaluable in chemical proteomic studies; it has been shown that incorporating a sulfonyl fluoride warhead into a previously known non-covalent inhibitor of the epidermal growth factor receptor, erlotinib, converted the inhibitor to a covalent inhibitor of the same target[143].

## Reproducibility and Data Deposition

In synthetic chemistry, the characterization of compounds is of utmost importance. Click chemistry is no exception, but it does provide a level of certainty in reaction outcomes that may not always be achievable with other chemical reactions.

Any new compounds produced using SuFEx click chemistry must be supported by sufficient experimental data to definitively determine their molecular structure and ensure uniformity. For new compounds, essential data must be obtained from NMR spectroscopy ($^{1}H$, $^{13}C$, 2-dimensional analysis, and, where appropriate, spectral data for heteroatoms such as $^{19}F$), high-resolution mass spectrometry, IR spectroscopy, boiling or melting point, and, for chiral molecules, optical rotation measurements. Additionally, X-ray crystallographic analysis can be utilized to verify the structure of a representative member of a compound class. Data

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obtained from X-ray diffraction must be stored in data repositories such as the Cambridge Crystallographic Data Centre (CCDC). For previously reported compounds, $^{1}H$ and $^{13}C$ NMR analyses, together with relevant citations, are usually sufficient. Supplementary documentation, including detailed experimental procedures and characterization data, should be made available alongside peer-reviewed publications, often free of charge. In cases where reagents and substrates are produced on a large scale or where a unique experimental setup is required, schematics and images can enhance reproducibility.

The beauty of click reactions lies in their robustness and reproducibility, which simplifies compound characterization, especially for high-throughput SuFEx processes performed in parallel. To determine the extent of reaction completion and quantify compound purity, a combination of TLC and LC-MS analysis can be employed. Once hit results are obtained from biological testing, lead compounds can be re-prepared and fully characterized to ensure accuracy.

Many peer-reviewed chemistry journals now encourage the sharing of raw data for compounds, particularly data associated with NMR spectroscopy. While NMR spectra are currently presented only as static images, providing primary data files in JCAMP format or .jdx files would significantly increase transparency in compound characterization. In line with this trend, funding agencies like the National Institutes of Health (NIH) in the US are now requiring the deposition of unsuccessful experimental results in accessible repositories to improve scientific reproducibility. These changes are likely to have a significant impact on the future of SuFEx method development.

## Limitations and Optimizations

### Catalyst Activity

Despite extensive research efforts to investigate the mechanism of SuFEx catalysis, many details remain elusive. While a complete understanding of the mechanism may not be necessary for utilizing the functional molecules that can be accessed through SuFEx, additional knowledge can facilitate the design and synthesis of more effective SuFEx catalysts. Currently, even the most promising SuFEx catalysts can require high loadings for challenging substrate combinations. For instance, 20 mol% of the active guanidine catalyst BTMG, along with HMDS and reaction temperatures of 60 °C, are necessary to catalyze reactions between aryl sulfonyl fluorides and secondary alcohols[33]. Enhanced understanding of the SuFEx mechanism can lead to the rational design of next-generation catalysts that can reduce catalyst loadings, temper harsh reaction conditions, and expand the range of substrates, such as enabling SuFEx reactions with tertiary alcohols.

### Reagent Safety and Accessibility

The synthesis of SuFEx hubs, both existing and novel, often involves the handling of toxic, gaseous reagents such as $SO_2F_2$ and $SOF_4$. This poses accessibility issues for the wider synthetic community, as well as additional considerations regarding safety, environmental impact and reaction scale for laboratories that handle these gases. One possible solution to these issues could be the transition to flow setups for SuFEx chemistries[144]; flow setups

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have the potential to enhance both the efficiency and safety of using gaseous reagents and could ultimately facilitate broader adoption of SuFEx chemistry by the synthetic community.

While $SO_2F_2$ is widely used in pest control settings, obtaining this reagent for research purposes can be challenging. A cursory SciFinder search reveals 9 suppliers in 4 countries (USA, China, Germany, and France) – for researchers outside of the associated shipping areas, acquiring the reagent can prove difficult. Although non-gaseous $^{+}SO_2F$ surrogates (Fig 3B) have gone some way to overcome this distribution inequity, they can be prohibitively expensive. Access to $SOF_4$ is even more problematic – the limited number of suppliers and significant cost creates bottlenecks in preparing the invaluable iminosulfur oxydifluoride functional group. Currently, no practical alternative exists for $SOF_4$, impeding further SuFEx development of the multidimensional hub, particularly in the fields of polymer science and medicinal chemistry (*vide supra*). Future research to address the limited supply of $SOF_4$ or generate novel means of accessing iminosulfur oxydifluorides will be highly valuable and represent a great opportunity within the click chemistry field.

## Enantioselective SuFEx Methods

The 3-dimensional space accessed via the iminosulfur oxydifluoride and (the recently utilized) sulfondiimidoyl fluoride[145] hubs brings the opportunity to exploit chirality – an intrinsic property of the biological targets of countless drugs (such as enzymes and receptors). However, the methods for generating chiral-at-S(VI) linkages currently rely on chiral pool strategies, and SuFEx has yet to address this limitation. While enantiospecific SuFEx[21,122,146] and SuPhenEx[42] protocols have been reported using enantiopure sulfonimidoyl fluoride starting materials, there is a notable lack of enantioselective SuFEx transformations. Therefore, the use of chiral catalysts or chiral organometallic complexes as nucleophiles in SuFEx reactions could bring this click reaction into the 3-dimensional world and be highly valuable in the enantioselective synthesis of SuFEx-based biological probes and drug candidates.

## Outlook

Over the past decade, SuFEx has emerged as a powerful click chemistry tool, particularly in the field of medicinal chemistry. Its success as a discovery platform has firmly established its position among other click reactions. However, predicting its future trajectory is challenging, given the rapid evolution of click reactions and the democratization of their applications, as demonstrated by the widespread use of CuAAC. Therefore, it is likely that SuFEx will continue to attract attention and play a critical role in drug discovery and other areas of chemical research, but the specific direction of its evolution, while no doubt will be exciting, remains uncertain.

This Primer has highlighted how SuFEx has facilitated the discovery of numerous lead compounds against various diseases. SuFEx will continue to play a critical role in drug development programs in the future. By rapidly synthesizing accessible molecules and evaluating their functions in assays, the approach enables the exploration of chemical space accelerated by serendipity. Combining high-throughput SuFEx synthesis with more relevant disease models, such as patient-derived tumor organoids[147] (also in well plate settings),

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could significantly enhance this powerful workflow. This integration could even allow smaller research ventures to compete with larger pharmaceutical companies in terms of innovation.

As SuFEx continues to expand its versatility, the invention of novel SuFExable hubs will remain a key driver of progress. An important direction for future development is the generation of 3-dimensional motifs that can be prepared and reacted stereoselectively. This will enable the creation of molecules with unique physical and pharmacokinetic properties by combining the latent reactivity profiles of S–F-containing functional groups with other click chemistries, such as the recently developed Phosphorus Fluoride Exchange (PFEx)[148]. The bioisosteric properties of many SuFExable groups will enable the augmentation of the reactivity and pharmacokinetic profiles of lead candidates identified through other chemistries. For instance, the inclusion of fluorosulfate motifs can slow metabolism and enhance pharmacological properties. The expanding range of SuFEx-enabled functionalities may lead to the development of novel drug activation processes, such as SuFEx-activated drugs that selectively combine only at the site of therapeutic action. Additionally, SuFEx may find important applications in the design of linkage technologies used in higher-level therapies, such as antibody-drug conjugates and proteolysis targeting chimeras (PROTACs).

The resurgence of covalently targeted drugs is an exciting propsect[73]. Covalent drugs are sometimes viewed with skepticism, owing to concerns over off-target covalent bond formation and resulting toxicity. However, advances in the field have assuaged some of these concerns, and the potential benefits of covalent therapies, such as the ability to separate the pharmacodynamic and pharmacokinetic profiles of a molecule, are now being considered (for example, covalent $KRAS^{G12C}$ inhibitors). SuFExable warheads are poised to be at the forefront of covalent drug development, owing to the unique properties of S–F functional groups. These groups remain inert until activated by a specific protein environment, creating sacrificial electrophiles with unparalleled target specificity, known as the sleeping beauty effect.

The potential impact of artificial intelligence (AI) and machine learning on SuFEx technology is immense[149]. With the help of data-driven models, AI can facilitate the prediction of the physical properties of compounds and the optimization of reaction conditions, allowing for the rapid synthesis of complex and diverse molecules. By combining machine learning with protein structural information, researchers can design bespoke SuFEx-based covalent warheads with unprecedented specificity and efficacy, greatly accelerating the drug discovery process. In essence, the integration of AI and machine learning with SuFEx technology has the potential to revolutionize the way we explore chemical space and develop new drugs, enabling researchers to identify molecules with therapeutic potential more efficiently and effectively than ever before.

## Conclusions

This Primer provides a comprehensive overview of the Sulfur Fluoride Exchange (SuFEx) click reaction. The concepts important to the success of SuFEx have been outlined, along with descriptions of the most important SuFEx catalysts and hubs that make this reaction

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so versatile. A snapshot of some of the translational successes of SuFEx across the fields of drug development, polymer chemistry and biochemistry has been provided. While this innovative area of synthetic chemistry continues to face challenges and limitations, its potential for diverse and exciting applications is clear. To many, SuFEx is the second standard bearer of click chemistry (alongside CuAAC), and will no doubt move in new and unforeseen directions analogous to the story of its predecessor. As we look to the future, it is important to remember the underpinning philosophy of click chemistry and that the reactions are a means to an end, and that: “The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties”[150].

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Glossary

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| **SuFExable** | Functional groups containing sulfur-fluoride bonds that are compatible electrophiles in the SuFEx reaction (such as, sulfonyl fluorides, fluorosulfates, iminosulfur oxydifluorides) |
| **Orthogonality** | The selective reactivity of functional groups only when exposed to specific reaction conditions, while remaining untouched in all other instances |
| **Organosuperbases** | Strong organic bases with a basicity greater than that of proton sponge ($pK_BH^+$ = 18.6 in MeCN) |
| **SuFExability** | The propensity of an S–F-containing functional group to undergo catalyst-mediated exchange |
| **SuFExed** | The incorporation of a SuFExable group to the native structure of a molecule (such as, ligand, drug) |
| **Dispersity** | A measure of the heterogeneity of a polymer sample |

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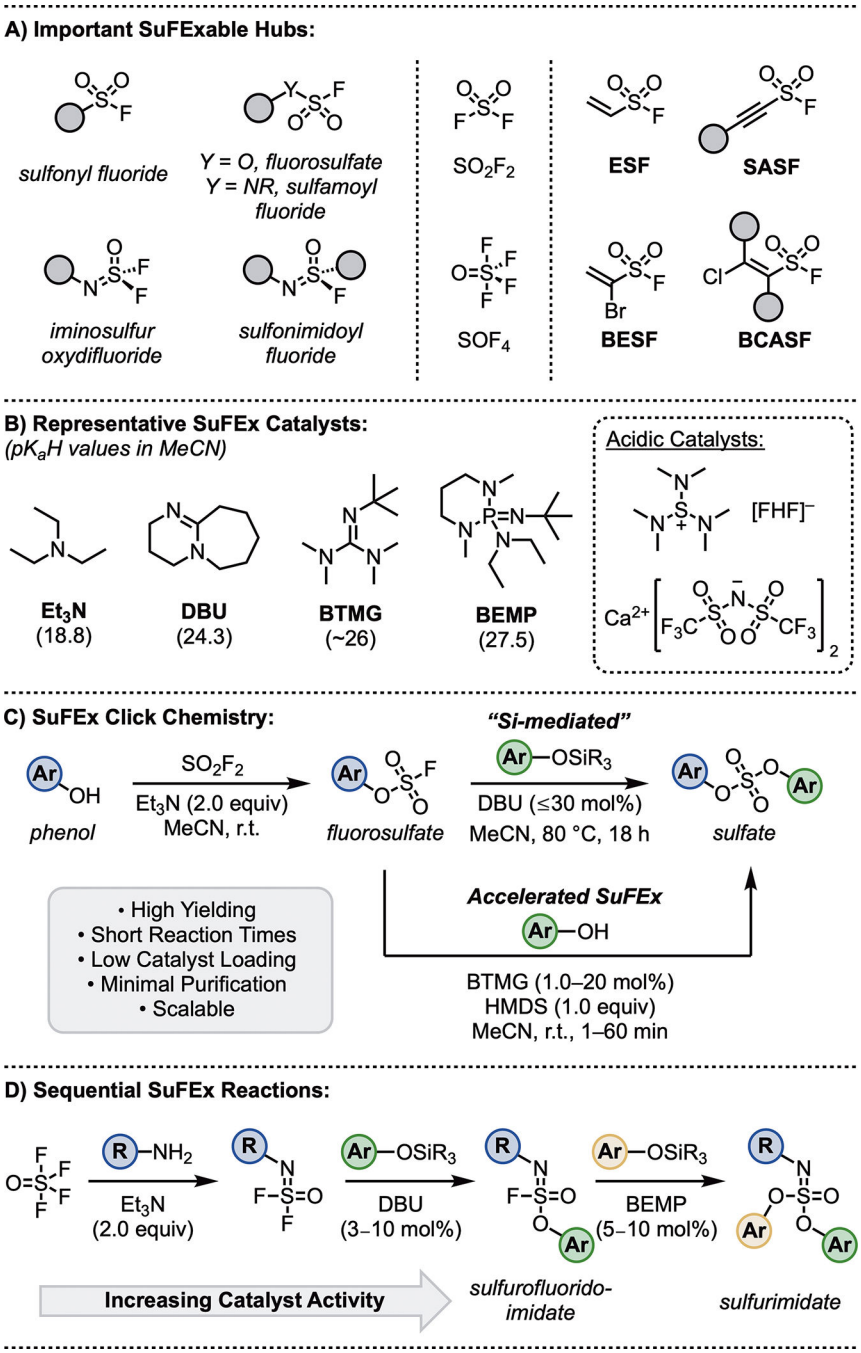


**Fig 1: Sulfur Fluoride Exchange (SuFEx).**

A) Important SuFEx hubs. B) SuFEx catalysts. Silicon-mediated and accelerated SuFEx click chemsitries. D) Sequential SuFEx reactions. Part C adapted with permission from ref 151, Elsevier.

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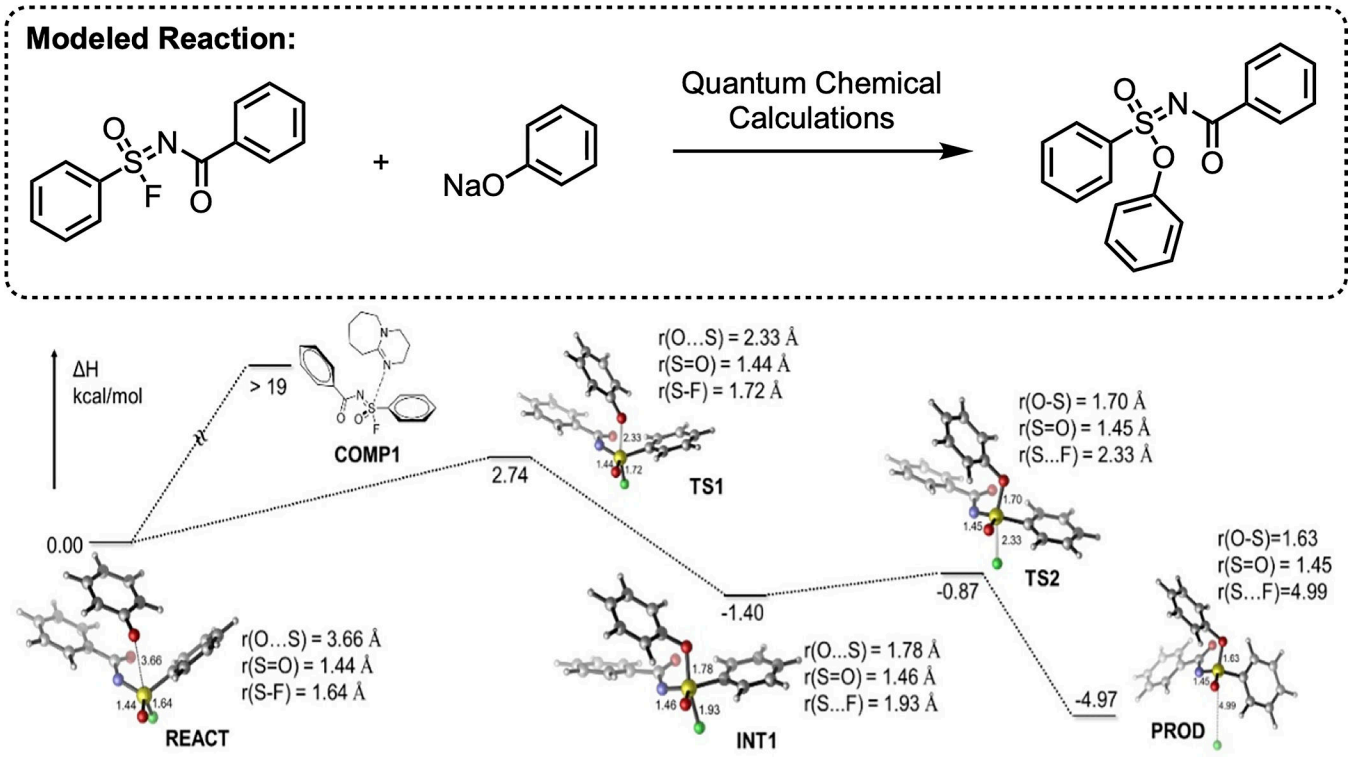


**Fig 2. Investigation into the SuFEx mechanism.**

Potential energy surface (PES) of the reaction of sodium phenolate with sulfonimidoyl fluorides. Part B reprinted with permission from ref 20, Wiley.

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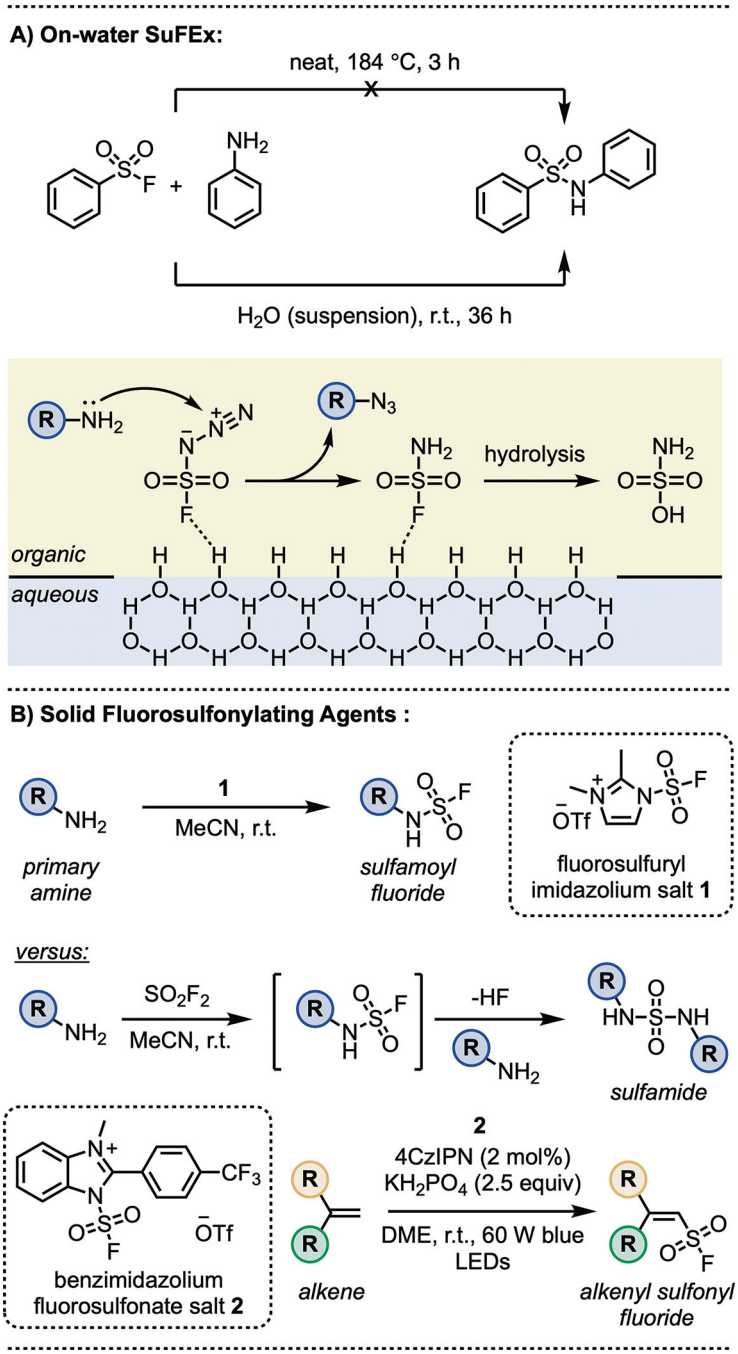


**Fig 3. Enhancing SuFEx reactivity and practicability.**

A) On-water SuFEx. B) Structures and applications of solid fluorosulfonylating agents.

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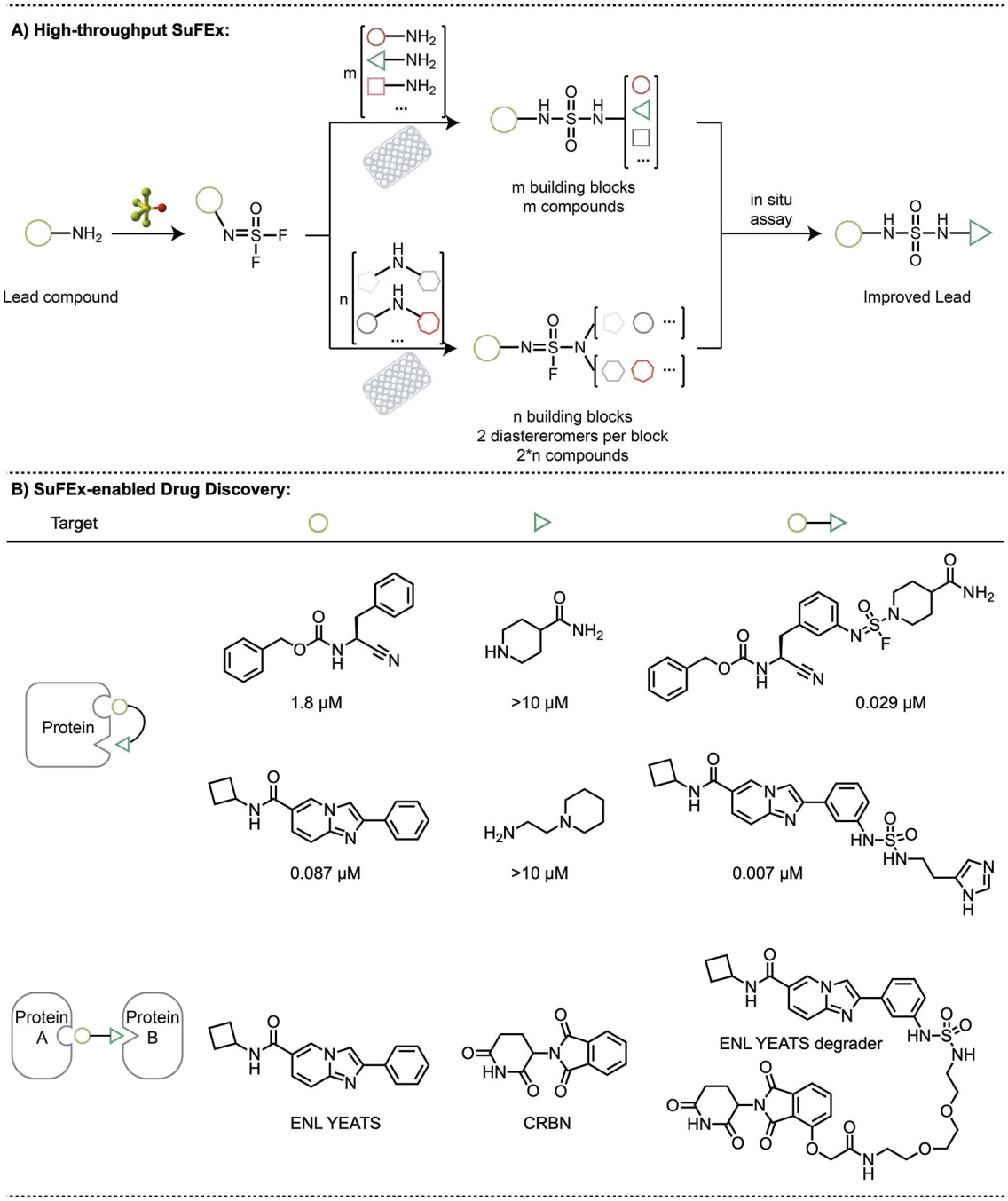


**Fig 4. SuFEx-based medicinal chemistry.**

A) High-throughput SuFEx. B) SuFEx-enabled drug discovery.

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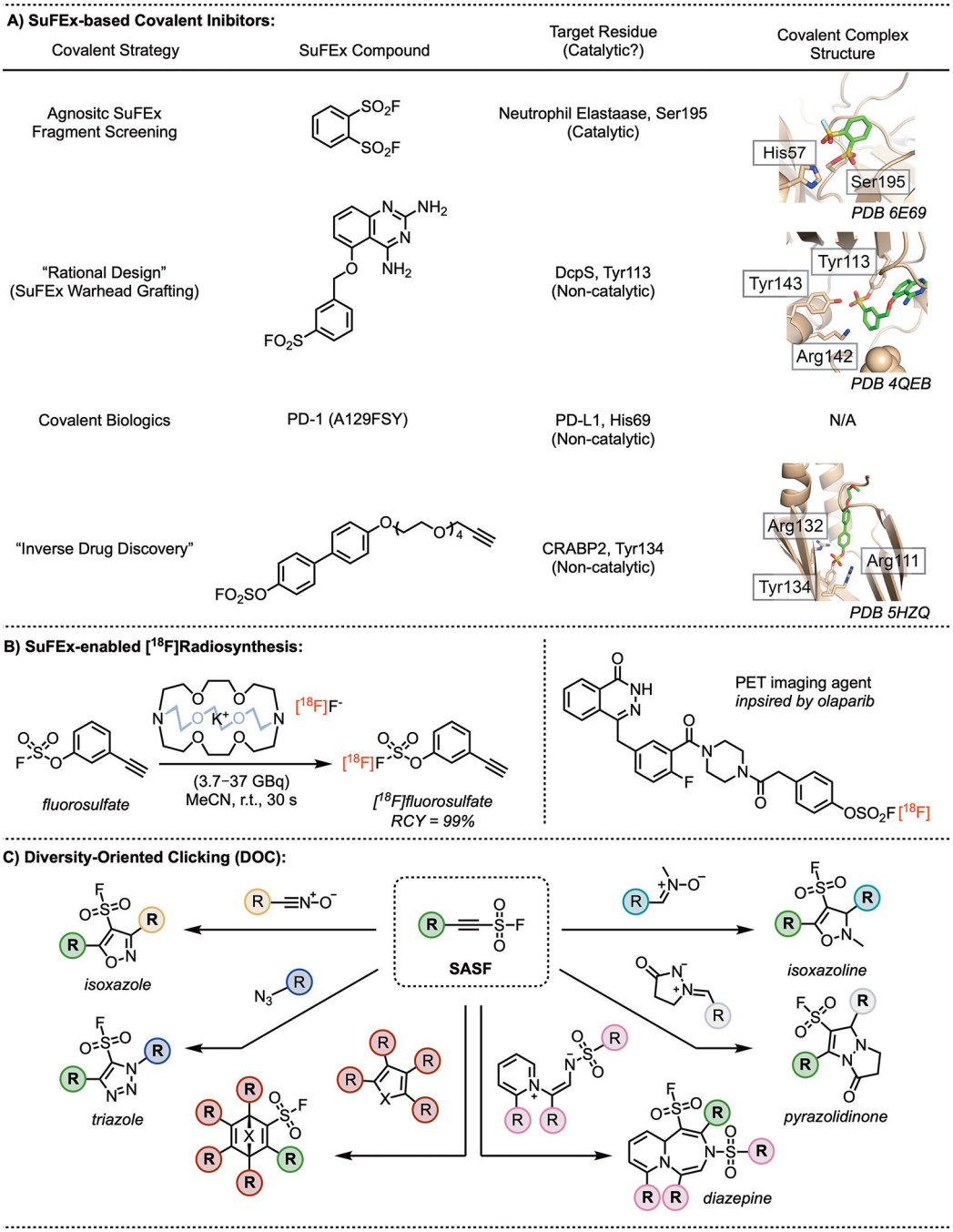


**Fig 5. Unique applications of SuFEx toward function discovery.**

A) Covalent inhibitors employing SuFExable groups. B) SuFEx-enabled radiosynthesis. C) Diversity oriented clicking (DOC). Part C adapted with permission from ref 151, Elsevier.

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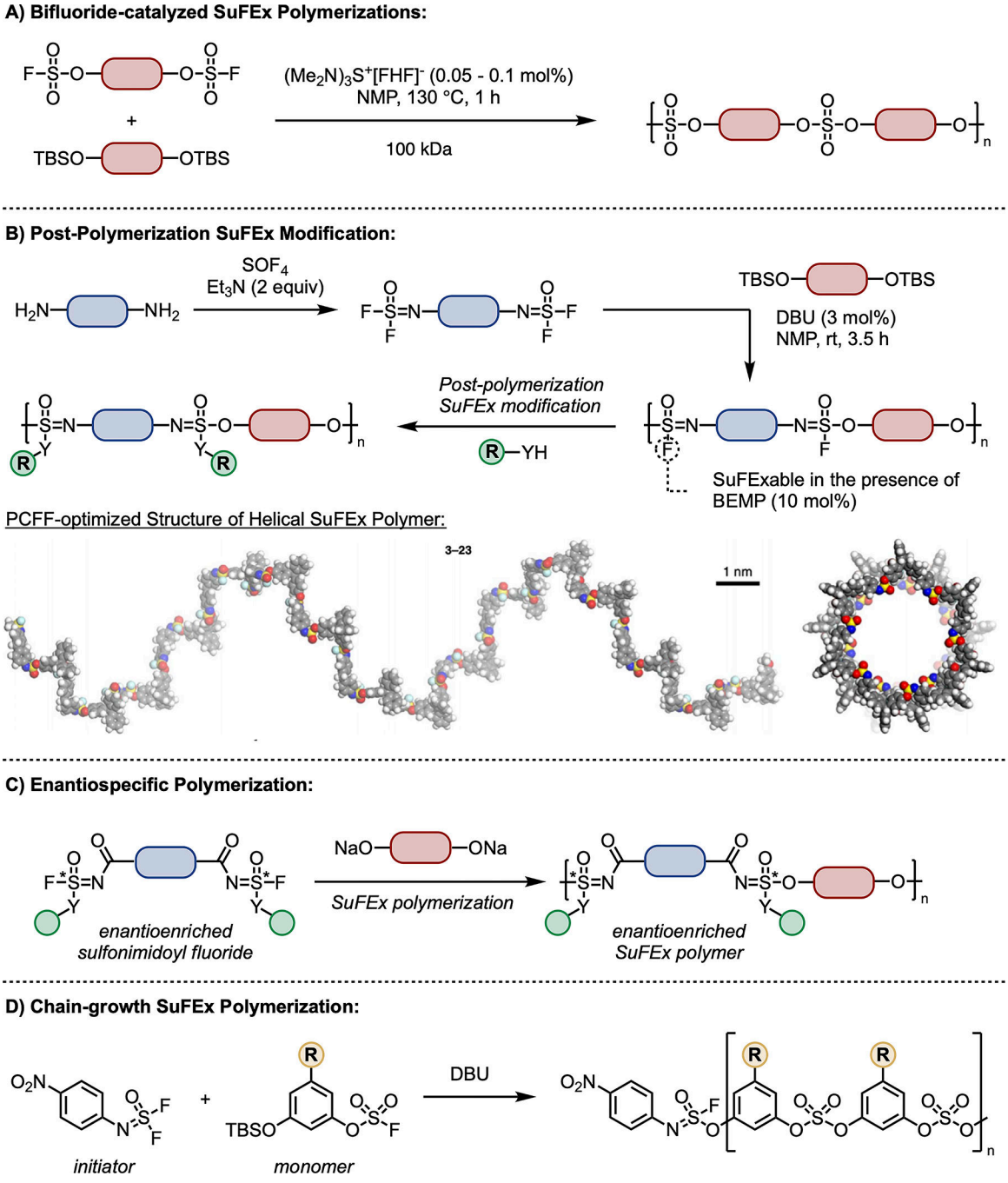


**Fig 6. Advances in SuFEx-based polymerizations.**

A) Bifluoride-catalyzed polysulfate synthesis. B) Post-polymerization modification. C) Enantiospecific polymerization. D) Chain-growth SuFEx polymerization. PCFF = polymer consistent force field. Part B reprinted from ref 121, Springer Nature Limited.

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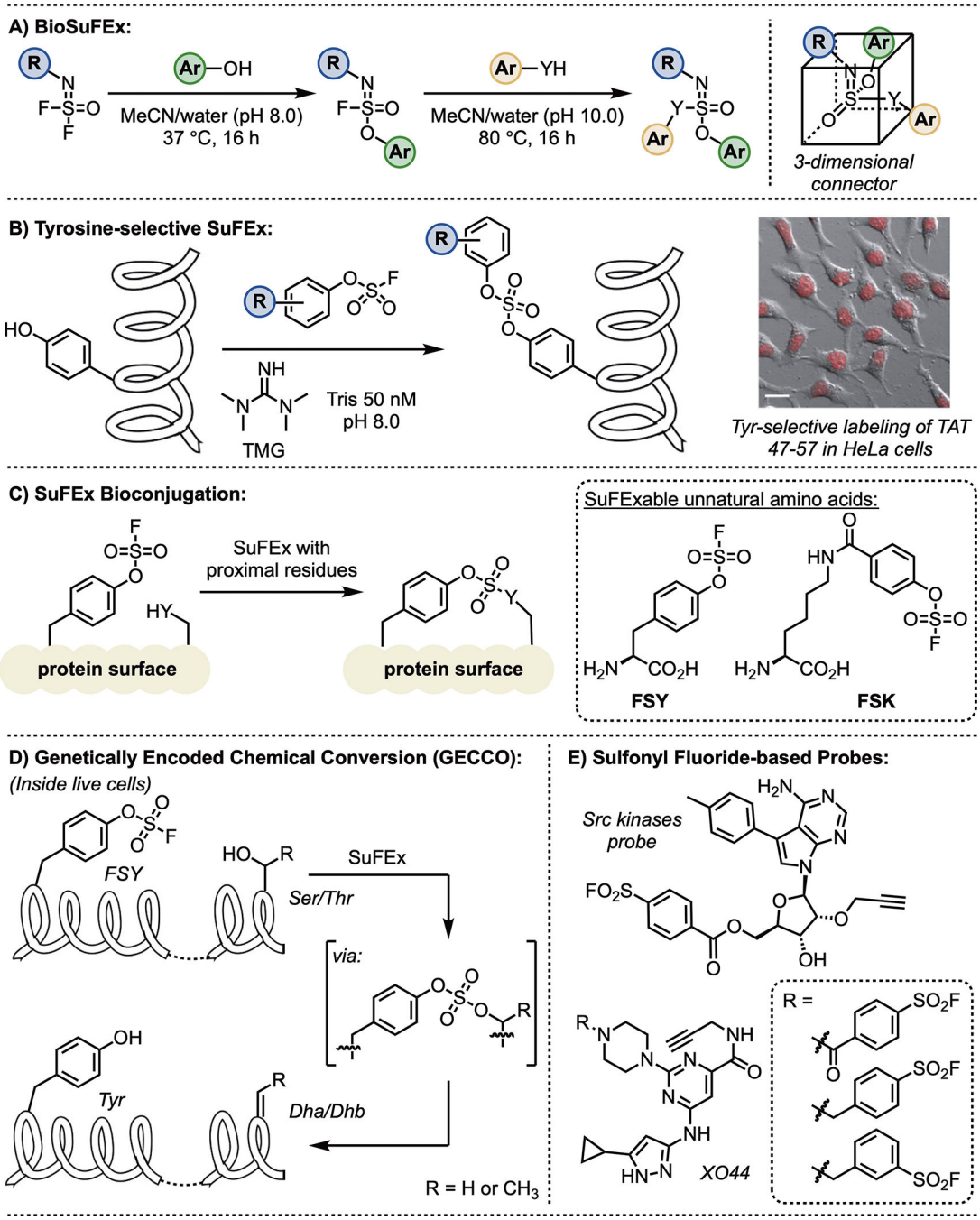


**Fig 7. Bio-compatible SuFEx methods.**

A) BioSuFEx. B) Tyrosine-selective modification. C) SuFEx-based bioconjugations. D) Genetically encoded chemical conversion (GECCO). E) Sulfonyl fluoride-based probes. Y = O, NH. Part B reprinted with permission from ref 125, Wiley.