Introducing Germanium Click Chemistry: GeFEx-S - Thiol-Selective Fluoride Exchange On-Water

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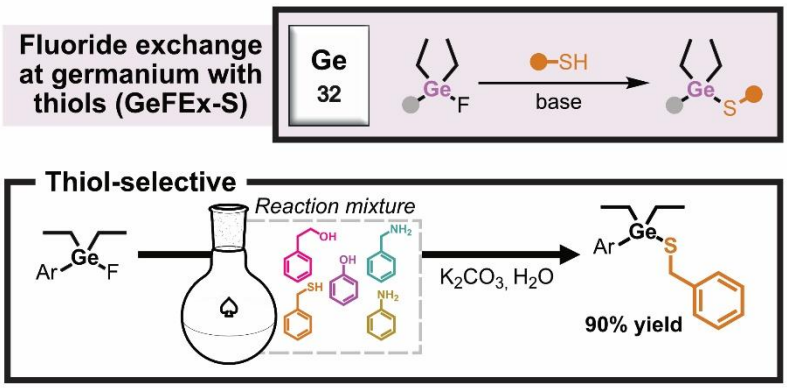
Abstract

We introduce germanium into the click chemistry family through the development of Germanium(IV) Fluoride Exchange-S (GeFEx-S), a thiol-selective reaction that enables rapid covalent bond formation under mild, "on-water" conditions. This transformation leverages the unique reactivity of tetravalent fluorogermanes to generate hydrolytically stable Ge–S linkages under biologically relevant conditions. GeFEx-S exhibits broad functional group tolerance - including compatibility with free cysteine residues - and operates orthogonally to established SuFEx and PFEx chemistries. By forming stable Ge–S bonds under aqueous conditions, GeFEx-S expands the fluoride exchange repertoire and establishes a versatile platform for site-selective bioconjugation, chemical probe development, and orthogonal functionalization in chemical biology and materials science.



Introduction

Click chemistry[1] has revolutionized molecular science by providing robust, modular reactions for constructing and modifying complex systems. Among its most influential advances are the azide–alkyne cycloaddition,[2,3] SuFEx,[4] and PFEx[5] chemistries. Yet a critical gap remains: the field lacks a thiol-selective fluoride exchange (FEx) click reaction that functions orthogonally to the established SuFEx and PFEx platforms. Such a reaction would open new avenues for constructing advanced materials and targeting biomolecules under mild conditions.

While thiol–ene[6,7] and thiol-yne[8] transformations are notable click reactions, their reliance on heat, light, or radical initiators constrains their use in bioorthogonal settings. At the same time, the central role of cysteine residues in biology[9] underscores the need for mild, chemoselective methods to label, crosslink, and modulate proteins under aqueous conditions.

Because thiols are uniquely "soft" nucleophiles, most strategies for capturing cysteine exploit 1,4-conjugate additions to comparably "soft" Michael acceptors, which are the electrophile of choice in ~70% of published cysteine-targeting agents.[10] Other thiol-selective warheads, such as haloacetamides, suffer from limitations such as excessive reactivity and poor stability.[11] The type of electrophile used in compounds designed to covalently capture cysteine has been shown to influence the selectivity towards particular residues,[12] motivating the development of new electrophile classes.

We identified germanium as a promising platform for thiol-selective ligation. Though historically underutilized in synthesis, it offers a unique combination of properties - including low intrinsic toxicity, favorable biocompatibility, and stable bonding to both carbon and heteroatoms. Germanium is a heavier bioisostere of carbon and silicon in organic molecules,[13,14] However, it is distinguished from its lighter congeners by its larger atomic radius, greater polarizability, and differing bond strengths to heteroatoms. Historically, organogermanium chemistry was only modestly explored, largely confined to simple pendant groups such as trialkyl- and triarylgermanium derivatives. However, there are notable examples that hint at germanium's broader potential.

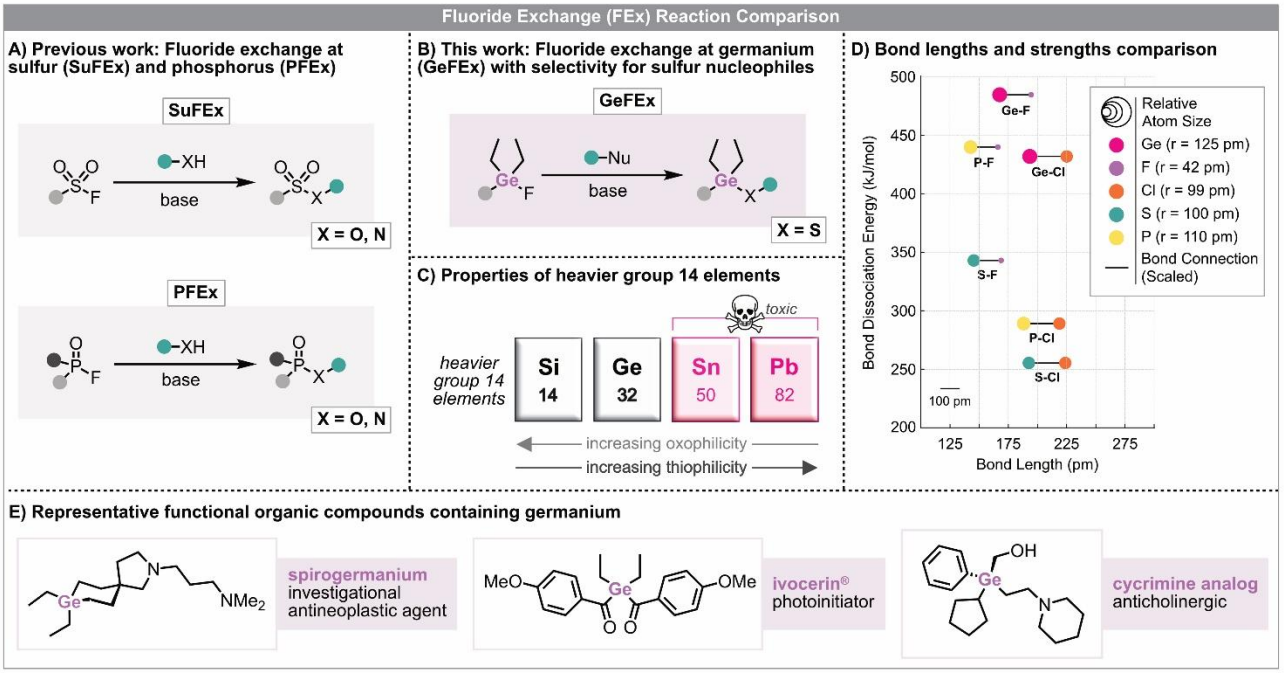


***Figure 1**: A) Established FEx click methods SuFEx and PFEx; B) thiol-selective displacement at GeFEx electrophiles; C) relative oxophilicity and thiophilicity of group 14 elements; D) El-Cl vs. El-F bond lengths, strengths, and atomic radii comparison; E) some examples of germanium incorporated into functional compounds.*

For example, spirogermanium[15] advanced to human clinical trials as an anticancer agent,[16] while germanium analogs of drugs such as cycrimine have also been synthesized and evaluated.[17] Beyond therapeutics, compounds like Ivocerin® - a commercial photoinitiator - demonstrate applications extending well outside drug discovery[18] (Fig. 1E). More recent advances include methods that enable stereoselective access to chiral-at-germanium architectures, highlighting the broader synthetic potential of organogermanium chemistry. [19–23]

Early reports on the properties of the Ge-S bond inspired the possibility of a thiol-selective Ge electrophile. Ge–O bonds are less robust and more hydrolytically labile than their Si–O counterparts, while Ge–N bonds are weaker still, readily cleaved by moisture or other nucleophiles. By contrast, Ge–S bonds display unexpected kinetic stability toward hydrolysis.

Foundational studies by Satgé and Lesbre[24] and independently by Hooton and Allred[25] in the 1960s demonstrated the somewhat surprising stability of trialkylgermanium thioethers (e.g., Me_3Ge–SMe, Et_3Ge–SBu) against hydrolysis despite the moderate bond dissociation energies (~325 kJ/mol) of the Ge-S bond. This contrasts sharply with their hydrolytically labile silicon analogues. Further investigations confirmed that alcoholysis of Ge–S species proceeds significantly more slowly than their silicon counterparts, highlighting the unique robustness of the Ge–S linkage. Sukhani and coworkers found in 1967 that tetrathiogermanes could only undergo alcoholysis under reflux conditions for more than two days in the presence of a catalyst. They explicitly speculated on the preference of Ge to bond to S over O.[26] More recently, applications in materials chemistry have exploited Ge–S linkages for Ge surface passivation because of their good ambient stability.[27]

The greater stability of the Ge-S bond relative to the Ge-O bond may be derived from enhanced orbital overlap due to germanium's larger covalent radius, which is potentially rationalizable as a soft/soft interaction in line with HSAB theory. This behavior parallels the empirically observed increase in thiophilicity (and decrease in oxophilicity) of elements moving down group 14 of the periodic table (see Fig. 1C);[28] tin and lead bond even more robustly to sulfur than germanium,[29] but their toxicity precludes any utility in drug discovery or chemical biology. Although Ge is not known to be an essential element for life, it is considered biocompatible due to its low intrinsic toxicity.[30] It has been shown to coordinate stably to four cysteine residues in rubredoxin proteins, resisting displacement by biological thiols.[31]

In envisaging an electrophile design based on Ge centers, we took inspiration from previous FEx click reactions. SuFEx and PFEx utilize fluoride as a more

tempered leaving group than heavier halogens, imparting hydrolytic resistance and enhancing the selectivity of ligations at sulfur(VI) and phosphorus(V) centers. We hypothesized this strategy could be adapted to Ge(IV), noting fluorogermanes (R_nGeF_{4-n}) exhibit greater hydrolytic stability[32] compared to Ge–Cl or Ge–Br analogues. Indeed, Ge–F bonds (~500 kJ/mol) rival the stability of foundational P–F and S–F bonds in PFEx and SuFEx (see Fig. 1D for comparison), supporting their suitability as robust electrophilic hubs.

The substitution chemistry of Ge–F bonds has been mostly limited to organometallic reagents, but a few exceptions exist. Notably, Drake *et al*. reported in the 1970s that germanium-substituted carbodiimides could be prepared from their silicon analogs and germyl fluorides,[33,34] a process driven by the thermodynamic favorability of forming the stronger Si–F bond. These germanium carbodiimides were subsequently found to undergo protolytic cleavage with thiols and alcohols. Furthermore, Ge(IV) species exhibit pronounced resistance to redox transformations under physiological conditions; even though they can engage in hypercoordinate bonding, reduction to the less stable +2 oxidation state is uncommon and typically requires strong reductants.

Motivated by these insights, we bring germanium into the click chemistry fold with Germanium Fluoride Exchange (**GeFEx-S**) - a thiol-specific exchange reaction that exploits robust, biocompatible Ge–F and Ge–S linkages. Proceeding under mild, "on-water" conditions, GeFEx-S operates orthogonally to SuFEx and PFEx, enabling multiplexed, highly selective connectivity for chemical biology and covalent drug discovery.

Results and Discussion

Design and Synthesis of Organic Germyl Fluoride Substrates

In assessing the reactivity of Ge–F bonds within organic frameworks, we identified aryldialkylgermyl fluorides as compact and synthetically tractable model systems. The preparation of these compounds is outlined in Fig. 2. Selective monoarylation of dimethyl- or diethylgermanium dichloride (either commercially available or prepared *via* the direct process)[35] with an equimolar amount of an aryl Grignard reagent (**1**) afforded a mixture of germyl monohalides (**2a** and **2b**), which served as precursors for subsequent metathesis with an appropriate fluoride source.

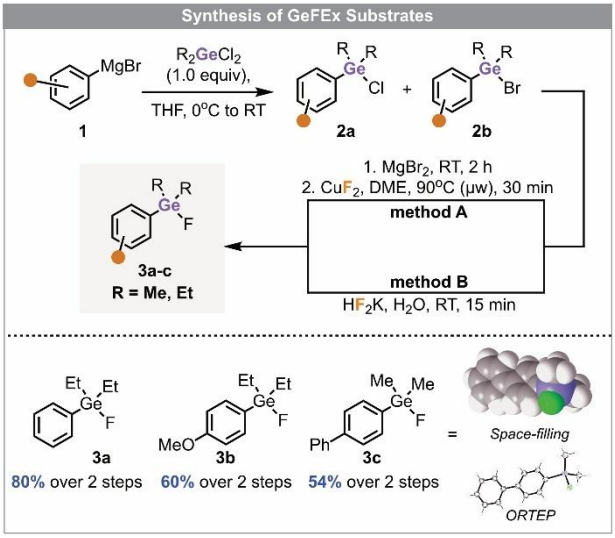


***Figure 2**: General synthetic approach to Ge-F electrophiles. The large size of Ge compared to C is readily apparent from the space-filling model of the SCXRD structure.*

Prior reports on the synthesis of organic germanium(IV) fluorides suggest that these compounds are synthetically accessible primarily by cleavage of Ge-O bonds with HF,[36] or *via* metathesis of other Ge-X bonds.[37,38] We sought a direct halide metathesis method as the shortest and most direct entry to organic compounds containing Ge-F bonds. Common alkali metal fluorides (NaF, KF, CsF) and TBAF proved ineffective in mediating this metathesis in our hands.

A more exhaustive survey of metal fluorides revealed CuF_2 to be an effective and general mediator of Ge-X to Ge-F metathesis, and we developed a method utilizing microwave heating to achieve complete metathesis in as little as 30 minutes. An alternative route was identified in which germyl chlorides or bromides rapidly convert to fluorides in saturated aqueous $K[HF_2]$, likely *via* a germanol intermediate. Both methods proved general and efficient.

Next, we synthesized several aryldialkylgermyl fluoride model substrates with a few different substituents for the aryl group. In parallel, we found that CuF_2 could also mediate the conversion of germanols to germyl fluorides, though with significantly longer reaction times.

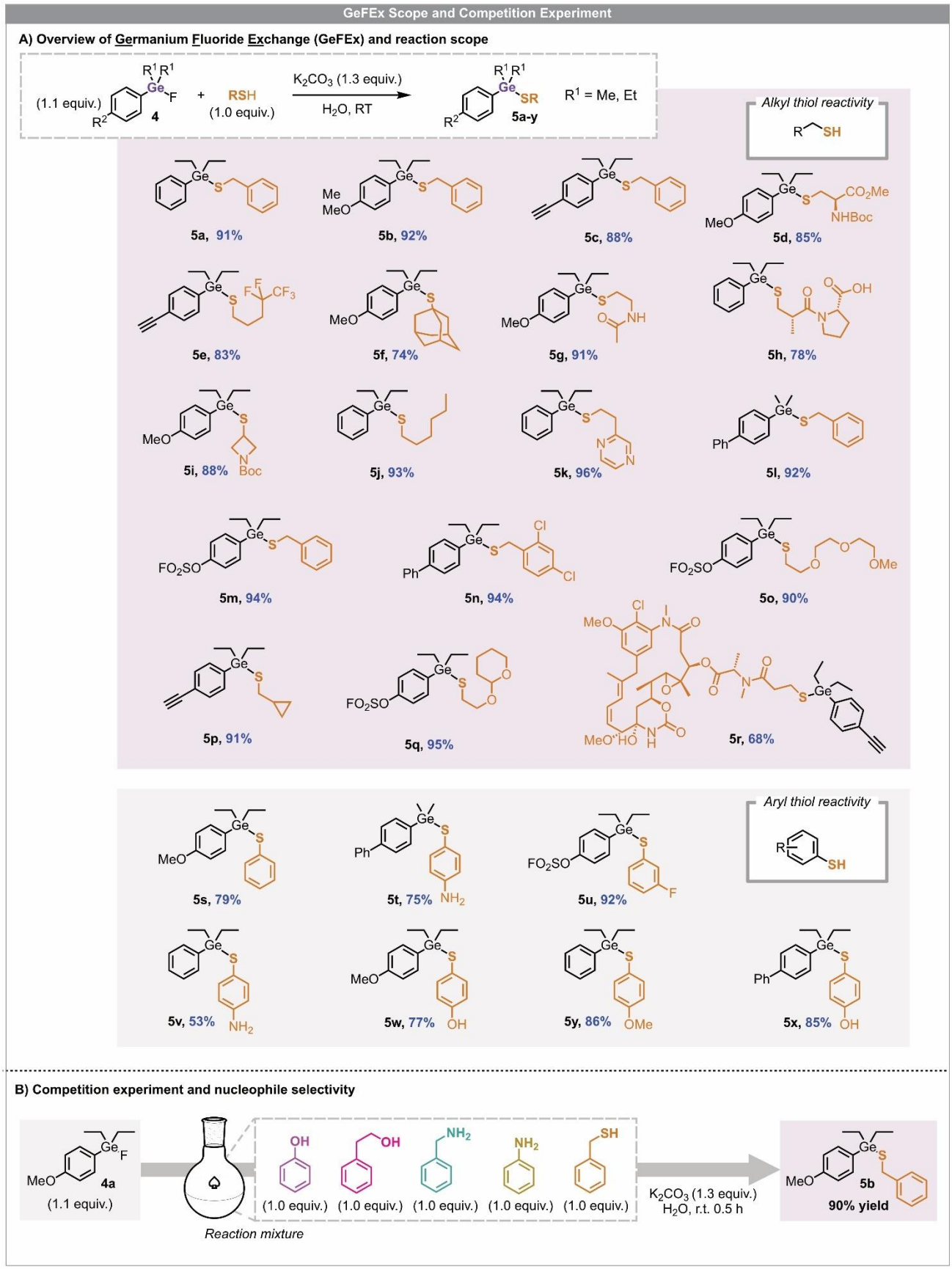


***Figure 3**: A) Substrate scope for the on-water GeFEx reaction; B) competition experiment showing preference for thiol nucleophiles.*

Single-crystal X-ray diffraction analysis of compound **3c** corroborated the presence of a Ge–F bond with a bond length of 1.79 Å, consistent with reported values for tetracoordinate organic Ge–F species of around 1.78 Å.[39]

On-Water Reaction with Thiols

We evaluated thiol reactivity with germyl fluorides using "on-water"[40] conditions (Fig. 3A). In the presence of K_2CO_3, thiols rapidly displaced the Ge–F bond to form stable germyl thioethers, which were easily isolated. This fast, selective, and water-compatible transformation fulfills key click criteria and establishes Ge–F as a unique electrophilic handle for thiol ligation - unaddressed by current FEx platforms.

Screening a small set of bases (see SI) showed that both carbonate and hydroxide bases achieved complete conversion within 10 minutes. K_2CO_3 was chosen over KOH to maintain the mildest environment. A survey of diverse thiols revealed broad functional-group tolerance, notably including free anilines (**5t**, **5v**) and phenols (**5w**, **5x**), which could otherwise compete as nucleophiles.

Both aliphatic and aromatic thiols reacted successfully, with the products from aliphatic thiols generally showing greater stability.

Primary, secondary, and tertiary thiols were all tolerated, including sterically hindered examples such as the adamantyl derivative **5f**. Aromatic heterocycles were also tolerated (**5k**), as were free carboxylic acids (**5h**). The reaction also succeeded on highly complex substrates, with the potent tubulin inhibitor mertansine being successfully ligated to a Ge center *via* the primary thiol moiety to generate compound **5r**.

A competition experiment exploring the reactivity of germyl fluorides in aqueous solution containing a mixture of alcohols, amines, and thiols confirmed the selectivity of germyl fluorides towards thiol nucleophiles (see Fig. 3B). The germyl thioether **5b** was the only isolable product from the mixture. Although this experiment does not rule out the possibility that other nucleophiles can transiently displace fluoride from Ge, other products likely undergo fast hydrolysis or further displacement by thiol nucleophiles.

Mechanistic Discussion

Although the Ge–F bond BDE is greater than that of the Ge-S bond (~500 kJ/mol vs. ~325 kJ/mol)[i] such values pertain to homolytic cleavage and thus only partially reflect reactivity. The favorability of the reaction may be rationalized in terms of the highly exothermic solvation of fluoride in water, the polarization of the Ge-F bond, and the soft-soft orbital matching of the thiol nucleophiles with the germanium atom.

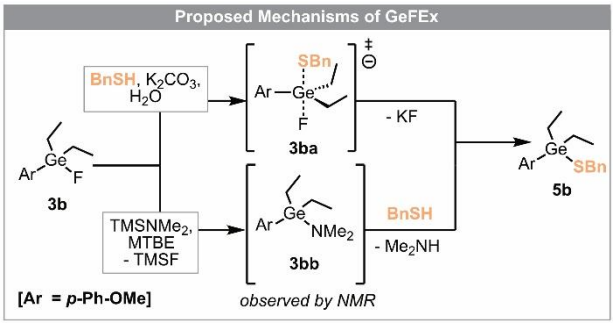


Figure 4: *Substitution of Ge-F bonds by thiolates proceeding via a proposed pentacoordinate transition state in the on-water case or an observed germylamine intermediate in organic solvents mediated by* $TMSNMe_2$.

Bond polarization is cited as a significant factor in the facile hydrolysis of comparable Si-F bonds under physiological conditions, despite the exceptionally high Si-F bond enthalpy;[43] in the case of GeFEx, Ge-F thiolysis likely predominates over hydrolysis due to aforementioned HSAB principles.

A plausible mechanism of the on-water GeFEx reaction is a simple S_N2 substitution, involving attack of a thiolate ion at the germanium center (illustrated in Fig. 4 on substrate **3b**) to form a pentacoordinate transition state **3ba** with subsequent loss of fluoride to generate the product **5b**. Previous studies provide significant evidence for associative S_N2-type mechanisms in the nucleophilic substitution of many similar germyl halides by observing Walden inversion on chiral substrates.[44,45] A pertinent example reported by Eaborn e*t al.* observed a chiral germyl chloride to undergo marked stereochemical inversion with a thiolate nucleophile, despite the presence of two arene substituents on the substrate, which should stabilize an intermediate germylium ion if a dissociative S_N1 mechanism were operative.

In organic solvents instead of water, GeFEx substitution was found to take place most rapidly and effectively with the aid of a stoichiometric silylamine promoter. Germylamines, exemplified by **3bb**, were found to form spontaneously upon the reaction of a germyl fluoride with a silyl amine (driven by Si-F bond formation); these intermediates readily undergo protolysis in the presence of thiol

[i] *While older reference tables*[41] *report a gas-phase Ge–S BDE near 560 kJ mol*$^{-1}$*, more recent thermochemical analysis of* Me_3GeS–^{n}*Bu indicates ~325 kJ mol*$^{-1}$ *for comparable organic germyl thioethers.*[42]

nucleophiles to generate germyl thioether products without the addition of further base. This presents an alternative practical method to ligate thiols to germanium centers. However, the on-water system was chosen as the primary preparative method due to improved ease of product purification and potential biological compatibility.

Installing GeFEx Groups on Drugs and Complex Scaffolds

The incorporation of Ge–F electrophiles has generally relied on organometallic methods, which limit their late-stage installation onto complex, densely functionalized scaffolds such as drugs and natural products. To overcome this constraint, we developed a practical route to an alkyne-functionalized germanol (**7**) from readily available precursor **6**, providing an efficient handle for CuAAC conjugation with structurally complex azides (Fig. 5A).

Germanol **7** underwent facile clicking *via* the CuAAC reaction to azides derived from stavudine (**9a**), ospemifene (**9b**), perphenazine (**9c**), troxipide (**9d**), and dasatinib (**9e**). Although the alkyne containing a Ge–F group in place of Ge–OH was also compatible with CuAAC, the superior ease of purifying the germanol intermediates made it preferable to complete the click reaction to **7** before Ge–F installation.

Subsequent late-stage fluorolysis of the Ge–O bond using aqueous K[HF_2] cleanly afforded the corresponding germyl fluorides (see Fig. 5B), which could undergo telescoped GeFEx substitution to generate thiol-ligated products. This approach demonstrates the applicability of the GeFEx platform to complex, highly-functionalized systems.

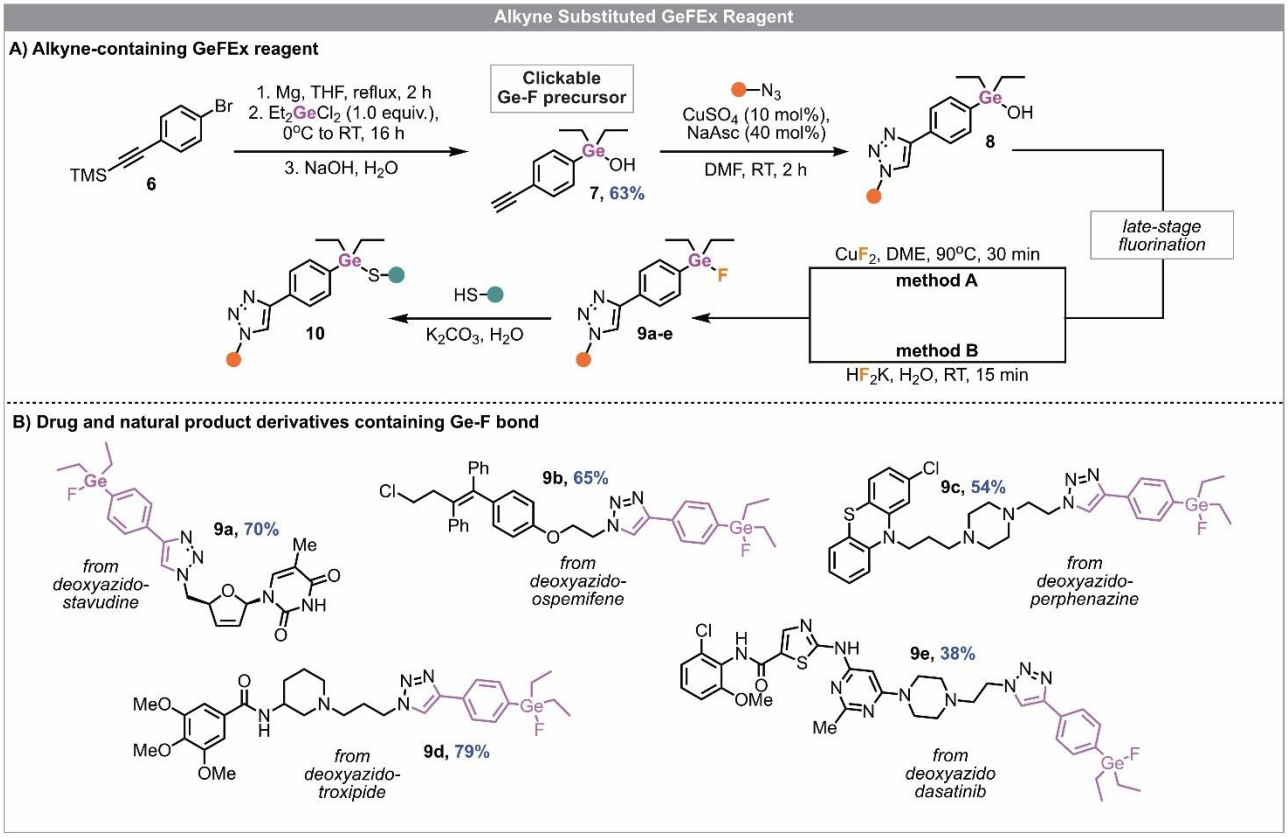


***Figure 5**: A) Synthetic approach to an alkyne-containing Ge-F precursor for CuAAC conjugation; B) drugs and natural product derivatives containing a germanol precursor. Yields are of unpurified germyl fluorides*

Testing Click-Orthogonality using a Diversity-Oriented Clicking Approach

A central challenge in click chemistry is the development of orthogonal reaction platforms that enable multiple, sequential bond-forming events with precise control. This challenge is at the heart of *diversity-oriented clicking*,[46–49] where distinct click reactions are combined to generate structural diversity while retaining modularity and chemoselectivity. To probe the chemoselective resilience of fluoride-based exchange chemistry within this framework, we designed a modular system that integrates CuAAC, GeFEx, PFEx, and SuFEx into a single connective platform.

Each of these electrophilic groups was then transformed in sequence. The most reactive, the

Ge–F bond, was first engaged in an on-water reaction with benzyl thiol in the presence of K_2CO_3 to afford compound **15**. This was followed by sequential telescoped SuFEx and PFEx reactions with phenols **16** and **17**, respectively, yielding the final compound **18**. Our approach to a multi-clickable hub began by reacting phenol and **10** with phosphoryl chloride in succession to generate azide-containing intermediate **11**. Subsequent P-Cl to P-F metathesis, followed by a CuAAC reaction with **7**, generated intermediate **13**, which was readily transformed to the corresponding germyl fluoride **14** under mild aqueous conditions. Hub **14** contains three orthogonal electrophilic handles – Ge-F, P-F, and S-F.

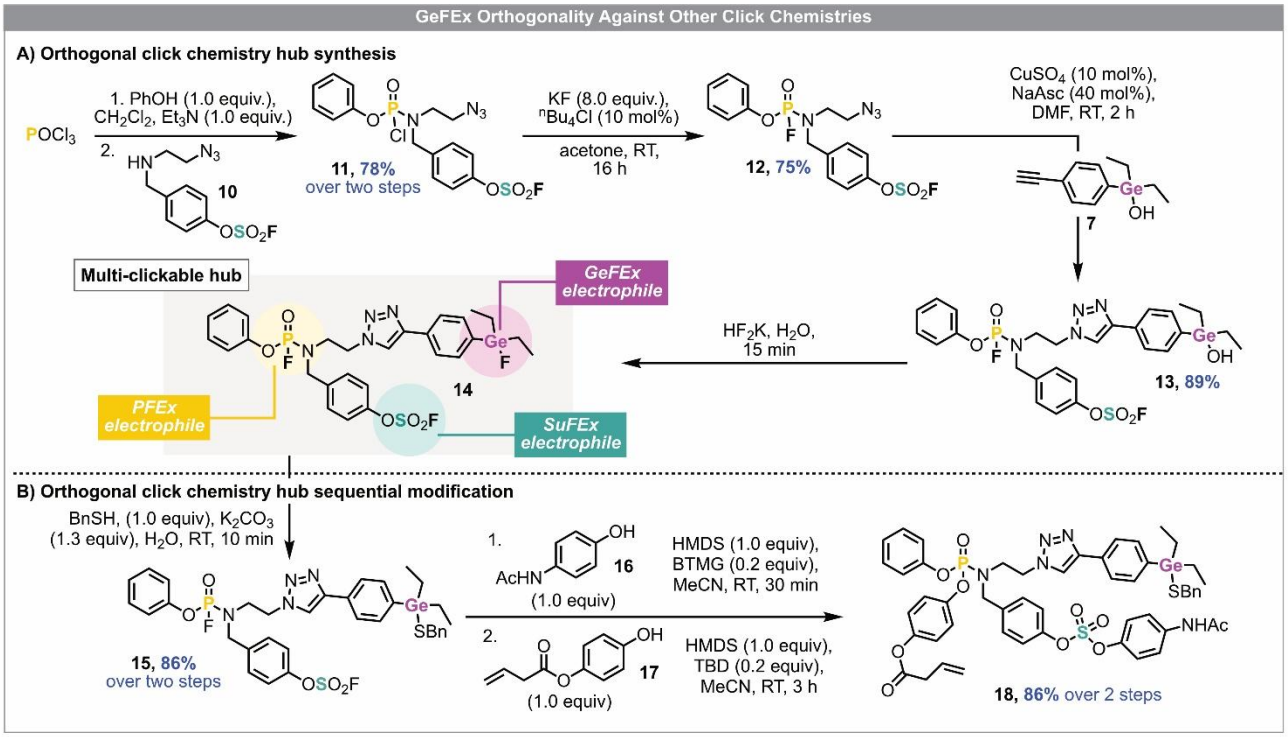


***Figure 6**: Synthetic approach to a hub for orthogonal SuFEx, PFEx, and GeFEx, and utility in diversity-oriented clicking.*

Summary

GeFEx-S establishes germanium-fluoride exchange as a versatile and thiol-selective click chemistry platform, expanding the fluoride exchange (FEx) paradigm beyond oxygen and nitrogen nucleophiles. This robust, aqueous-compatible transformation enables rapid and orthogonal ligation to thiols, forming stable Ge–S linkages with broad functional group tolerance. Integrating GeFEx-S with existing click modalities such as CuAAC, SuFEx, and PFEx provides a modular and orthogonal framework for complex molecular assembly, promising applications in chemical biology, drug discovery, and materials science. In addition, this platform enables greater exploration of germanium in drug discovery and chemical biology.

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