nature portfolio

Peer Review File

Intramolecular Chalcogen Bonding Activated SuFEx Click Chemistry for Efficient Organic-Inorganic Linking

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

An and coworkers reported a chalcogen-bonding activated SuFEx reaction for β-S substituted alkyl sulfonyl fluorides. The concept of the activation of S(VI)-F bondd by an intramolecular chalcogen-bonding is novel and I believe that this work will inspire other researchers in this area. Synthetic protocols are highly efficient and has been demonstrated by more than 70 examples. In addition, the application of this methodology to surface chemisty is interesting and I am pretty sure that material scientists will like it and use it in near future.

However, I feel that the statement “Alkyl sulfonyl fluorides exhibit poor SuFExability” is inappropriate. Yes, alkyl sulfonyl fluorides are less electrophilic but the ones with one or more α-Hs are more reactive under basic condition. Their reactions with nuclophiles followed a deprotonation-addition mechanism. Indeed, the low-yielding reaction of 2a didn’t mean too much. You can find other high-yielding conditions for 2a easily by tuning parameters such as the amount and the type of base, solvent, concentration, and temperature.

In addition, I didn’t see the direct evidence for the proposed mechanism. The supporting experiments only suggested that a β-S substituent made alkyl sulfonyl fluorides more reactive. I looked through the whole manuscript and SI and didn’t see any solid evidence for chalogen bonding. Authors should provide more experiments to show the existence of chalogen bonding, preferably the strength. This is important to support the proposed mechanism since the oxygen of sulfonyl fluoride is not a strong Lewis base.

It is also not clear for me why authors thought that the elimination will be slower when there is a chalogen bond in the substrate. Indeed, Lewis acid activation including chalogen bonding will increase the acidity of α-H. To confirm the proposed mechanism, I suggest that authors should prepare a substrate without α-Hs such as gem-dimethyl 1a and evaluate its performance. Such a substrate will give more information about the mechanism.

Furthermore, the formula of 5b and 7b (TMS = (CH3)3Si, not CH3Si) in Figure 2 were wrong and should be corrected. Several NMR spectra were not clean and showing additional peaks and their quality should be improved.

Overall, I suggest that the current manuscript could be reconsidered in Nature Communications after addressing the questions above.

Reviewer #2 (Remarks to the Author):

ID: NCOMMS-23-58311-T

This manuscript describes a novel approach to activating sulfonyl fluorides toward SuFEx reactions through chalcogen bonding. The authors prepared several alkyl sulfonyl fluorides bearing γ-sulfur functional groups that were demonstrated to activate the SuFExable group through a 1,5-interaction. These activated electrophiles reacted smoothly with phenol under mild reaction conditions in the presence of sub-stoichiometric amounts of BTMG, a strong guanidine base. Several control experiments were performed (e.g., replacing the -S-

functional group with the corresponding -CH2- and -SO2-) to highlight the importance of the thioether in activating the sulfonyl fluoride. Following the exploration of the substrate scope associated with this transformation by reacting 1b with a range of alkyl and aryl alcohols and amines, an application of this methodology in organic-inorganic linking was showcased, resulting in the formation of functionalized self-assembled monolayers that exhibit a range of properties dependent on the small molecules appended through the chalcogen-mediated SuFEx reaction. Finally, the authors probe the mechanism of this SuFEx reaction using a combination of NMR analyses and control experiments and present a plausible mechanism for consideration.

Overall, I believe the reaction is a strong and helpful addition to the SuFEx toolbox. The utility of the reaction has been demonstrated, and the experimental data is well presented and discussed. To be considered a true click reaction, the substrate scope of both coupling partners should be able to be varied. As the manuscript currently stands, further exploration of the sulfonyl fluoride component would be of significant worth to this paper. Following additional experimentation and addressing the points outlined below, I believe this manuscript warrants publication in Nature Communications.

Points to address:
- Expanding the substrate scope to include more diverse sulfonyl fluorides is essential. Currently, only a small selection of non-diverse thiols is used. Do 2-thioaryl sulfonyl fluorides benefit from the same activation? This would provide a similar 1,5-activation. Additionally, are fluorosulfates (aryl or alkyl) activated by a comparable 6-membered ring? These are obvious extensions to the methodology that should be explored.
- The catalyst loading of 0.5 equivalents of BTMG is high for a SuFEx reaction. Do the authors have any suggestions as to why this loading is high? Were any attempts made to use a smaller amount of BTMG in the presence of a sacrificial base such as TEA?
- 2-Nitrophenol required stoichiometric BTMG - this seems counterintuitive (when also considering the proposed mechanism) as this electron-deficient phenol should deprotonate easier than phenol. Please comment on this observation.
- For clarity, the references associated with the statement "Typically, SuFEx chemistries require activated substrates or additional activators…" should be separated out between activated substrate references and additional activator references.
- When selectivity for alcohol over amine functional groups is noted (i.e., 10b), including a yield based on recovered starting material would be helpful. A yield of 72% with two possible reaction sites suggests that competing reactivity could occur.
- Using "eq." for both equation and equivalent is confusing and inconsistent between the manuscript and supporting information. I suggest "eq." for equation and "equiv." for equivalent to avoid any ambiguity.
- Small typographical errors were noted (i.e., Fig 1d "alcohol"). Please check the document thoroughly prior to resubmission.
- The mention of the phenoxide guanidinium complex should reference the work by Moses and co-workers directly, as they proposed this as a SuFEx reaction intermediate (currently reference 5).
- A description for panel e is missing from the Figure 1 caption.
- The schemes are not as clear as they could be, and compound numbering is less than obvious. For example, compound 1c is mentioned in line 77 of the text, though it is not drawn until Figure 2, and even then, the reader must infer the structure from the product 5c. The phenol 4a is used in the first reaction with 1 and should have a lower number, as it is mentioned in the text and the figure sequence before compound 3, for example. The figures and compound numbers should be reconsidered for ease of reading.

- Reaction conditions for Figure 2b are missing from the legend.
- Compound 12u says "from tyrosine" - this product is from "tyrosine methyl ester.
- Inconsistencies were noted between how "O,N-nucleophiles" and supporting information were presented throughout the manuscript. Please make it consistent.

Reviewer #3 (Remarks to the Author):

In the manuscript, the authors present the intramolecular SuFEx ability activation strategy of alkyl sulfonyl fluorides using γ-S atom. The activated SuFEx reactivity of alkyl sulfonyl fluorides is achieved with relatively low base loadings under mild conditions. The activated alkyl sulfonyl fluorides can react smoothly with phenols, alcohols, and amines with excellent yields. Additionally, it can be used for the creation of functionalized SAMs on the surface of inorganic materials via organic-inorganic linking after incorporating a trialkoxy silane group. This study provides new insights into SuFEx chemistries. It is suitable for publication after addressing the following issues. Some comments are as follows.
1. What is the selectivity of the SuFEx click reaction among different phenols, alcohols and amines?
2. What is the stability of the whole organic-inorganic linking system after compounds anchored on glass surface at different pH and temperature or flushing with water and organic solvents?
3. Can compound 1c react with some bioactive molecules, such as proteins or antibodies? If the bioactive molecules can be linked on the glass surface, it may have great application value in biological detection.
4. To expand the application scope of this reaction, does water affect the reaction? Can it work in buffer solutions?
5. Please provide the eluent of flash column chromatography and Rf value for each compounds.

Point-by-Point Response to Referees

Responses to the comments of reviewer 1.

An and coworkers reported a chalcogen-bonding activated SuFEx reaction for β-S substituted alkyl sulfonyl fluorides. The concept of the activation of S(VI)-F bond by an intramolecular chalcogen-bonding is novel and I believe that this work will inspire other researchers in this area. Synthetic protocols are highly efficient and has been demonstrated by more than 70 examples. In addition, the application of this methodology to surface chemistry is interesting and I am pretty sure that material scientists will like it and use it in near future.

Response:

We sincerely appreciate your positive evaluation and highly valuable comments. Please see our response to your comments below.

(1) However, I feel that the statement "Alkyl sulfonyl fluorides exhibit poor SuFExability" is inappropriate. Yes, alkyl sulfonyl fluorides are less electrophilic but the ones with one or more α-Hs are more reactive under basic condition. Their reactions with nuclophiles followed a deprotonation-addition mechanism. Indeed, the low-yielding reaction of 2a didn't mean too much. You can find other high-yielding conditions for 2a easily by tuning parameters such as the amount and the type of base, solvent, concentration, and temperature.

Response:

Thank you for your comments and for highlighting the importance of accurately describing the reactivity of alkyl sulfonyl fluorides.

In response to your feedback, we have revised the manuscript accordingly. We have removed the statement: "Alkyl sulfonyl fluorides exhibit poor SuFExability due to the weak electrophilicity of the sulfur core" from our manuscript. It has been replaced with: "*Alkyl sulfonyl fluorides are less electrophilic*" (Page **2** line **43**). This modification has also been reflected in the revised Fig. **1b** (Page **3**).

In response to the reviewer's suggestion regarding the reaction mechanism of alkyl sulfonyl fluorides with nucleophiles, we conducted a series of experiments to explore

the deprotonation-addition mechanism. Details of these experiments and findings are provided in our response to the comment (**3**).

(2) In addition, I didn't see the direct evidence for the proposed mechanism. The supporting experiments only suggested that a β-S substituent made alkyl sulfonyl fluorides more reactive. I looked through the whole manuscript and SI and didn't see any solid evidence for chalcogen bonding. Authors should provide more experiments to show the existence of chalcogen bonding, preferably the strength. This is important to support the proposed mechanism since the oxygen of sulfonyl fluoride is not a strong Lewis base.

Response:

We are grateful for the reviewer's insightful comments and the opportunity presented for us to clarify and enhance the documentation of our work.

In response to the need for more concrete evidence of chalcogen bonding, we initially attempt to obtain direct evidence of chalcogen bonding through X-ray crystallography of compound **1b**. However, we faced challenges as the compound remained liquid even at -20 °C. Consequently, we turned to computational studies to investigate the presence of chalcogen bonding. The computational results revealed that the chalcogen bond forms between sulfur and fluorine, rather than sulfur and oxygen as initially stated. This finding corrects an oversight in our original manuscript, where we inaccurately described the ChB interaction. We appreciate the reviewer pointing out this critical aspect, enabling us to amend our manuscript accordingly.

This correction has been incorporated into both the manuscript and the supporting information. Specifically, in the revised manuscript, we detail our computational methodology and findings as follows: "*To validate our hypothesis, we undertook computational studies. The initial step involved determining the conformation of **1b** using DFT computations at the M062X/6-311G(d,p) level. Our findings indicated that the gauche conformation of **1b** is only marginally less stable than its anti counterpart, with a free energy barrier of approximately 1.0 kcal/mol between them (Fig. **S13**). This barrier is sufficiently low to allow for easy interconversion between these conformations at room temperature. Further analysis was focused on the electrostatic potential map of the gauche conformation (Fig. **7f**), revealing distinct electrostatic interactions between the negatively charged fluorine and the positively charged sulfur*

atoms. The measured distance between the fluorine and sulfur atoms was 3.19 Å (Fig. ***7g****), which is less than the sum of their van der Waals radii (∑r_{vdW} (S···F) = 3.27 Å)*[56]*. These computational insights strongly advocate for the existence of an intramolecular ChB between sulfur and fluorine in the gauche conformation. The ChB will make the fluorine a better leaving group and thus accelerating the S-SuFEx chemistry.*" (Page **13** line **316-329**). In the revised manuscript, we have corrected Fig. **1d** to show that ChB forms between sulfur and fluorine, rather than oxygen and fluorine. And we have added the Fig. **7f** and Fig. **7g** to show the results from the computational studies. In the revised supporting information, we have duly included computational details, results and optimized structure data of **1b** as "**7.5 Density Functional Theory (DFT) Studies**" in the supplementary information (SI, Page **60** ~ **63**).

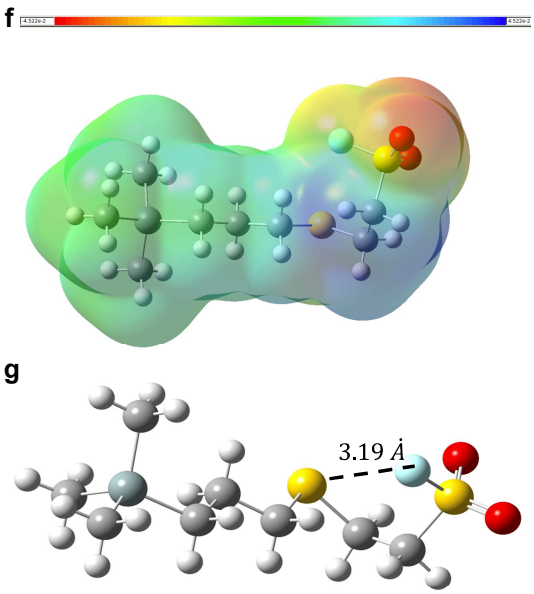


Fig. 7 | Mechanistic investigations. f, Electrostatic potential map of **1b**. Red = electron excess and blue = electron deficiency. **g,** The S···F distance of **1b** is 3.19 Å, falling into the range of chalcogen bonding distance.

(3) It is also not clear for me why authors thought that the elimination will be slower when there is a chalcogen bond in the substrate. Indeed, Lewis acid activation including chalcogen bonding will increase the acidity of -H. To confirm the proposed mechanism, I suggest that authors should prepare a substrate without α-Hs such as gem-dimethyl 1a and evaluate its performance. Such a substrate will give more information about the mechanism.

Response:

Thank you for your insightful comments. We have addressed the ambiguities in our original manuscript and conducted further studies to clarify the mechanism involved.

Firstly, we acknowledge the lack of clarity in our initial description of the deprotonation rate. We intended to convey that a chalcogen bond increases the reactivity of sulfonyl fluorides, making the reaction with a nucleophile faster compared to the side reaction (deprotonation) between sulfonyl fluoride **1b** and BTMG. We did not mean to suggest that chalcogen bonding slows the deprotonation process. To rectify this misunderstanding, we have revised the text to state: "*Considering the high yields achieved with most substrates, it is hypothesized that the side reaction between **1b** and BTMG progresses much more slowly than the favorable S_N2 reaction.*" (Page **13** line **312** ~ **313**). We have also adjusted Fig. **7** accordingly, removing the word "slow" to prevent further confusion.

Secondly, in response to your suggestion, we have conducted comprehensive studies to investigate the proposed mechanism. Contrary to our expectations, the results showed that the reaction does not proceed via the deprotonation-elimination-addition mechanism; no sulfene intermediate was detected. Instead, the deprotonated sulfonyl fluoride proved to be a non-reactive species. Our findings indicate that the actual product forms through an S_N2 reaction between the sulfonyl fluoride and the deprotonated phenol. These results are detailed in the revised manuscript and supporting information.

In the revised manuscript, we have added Fig. **7a**, **7b**, **7c**, **7d** and **7e** and the following statements: "*A series of experiments were conducted to elucidate the mechanism of S-SuFEx click chemistry, using the SuFEx reaction between **1b** and phenol **4a** as the model reaction. Initial investigations focused on the base's role in this process, as illustrated in Fig. 7. The absence of BTMG resulted in no observable reaction between **1b** and **4a**, underscoring the indispensable role of BTMG (Fig. **7a**). With BTMG present, two potential reaction mechanisms were considered (Fig. **7d** and Fig. **7e**). The first hypothesis suggests that the base deprotonates the α-position of **1b** to form intermediate **15**, which then reacts with nucleophile **4a** to yield the final product **8a** through a deprotonation-elimination-addition mechanism, involving sulfene **16** as the reactive intermediate (Fig. **7d**). Alternatively, BTMG might first interact with **4a** to produce deprotonated phenol **17**, which could then undergo an S_N2 reaction with **1b** to form the final product (Fig. **7e**). To determine the prevailing mechanism, further*

experiments were conducted. Introduction of 0.5 equiv. of BTMG to ***1b*** *in MeCN-d_3 revealed partial deprotonation at the α-position to give* ***15*** *through ^{1}H NMR analysis (Fig.* ***7b****), yet without evidence of S-F bond dissociation according to the ^{19}F NMR (Fig.* ***7c****), indicating the absence of sulfene* ***16*** *formation. Further adding 1.0 equiv. of phenol* ***4a*** *to the deprotonated alkyl sulfonyl fluoride* ***15*** *solution and stirring for 2 hours led to no detectable product, suggesting the reaction between alkyl sulfonyl fluorides and BTMG was a non-productive side pathway. Conversely, introducing BTMG to a MeCN-d_3 solution of* ***4a*** *induced a significant upfield shift in the aromatic region of the ^{1}H NMR spectrum (Fig.* ***S12****), indicative of the formation of* ***17***[5]*. Addition of* ***1b*** *to the solution of* ***17*** *resulted in a quantitative yield of the product* ***8a*** *(Fig.* ***7b****), strongly supporting the S_N2 pathway between* ***1b*** *and* ***17*** *as the primary reaction route. Considering the high yields achieved with most substrates, it is hypothesized that the side reaction between* ***1b*** *and BTMG progresses much more slowly than the favorable S_N2 reaction.*" (Page **12-13** line **291-313**).

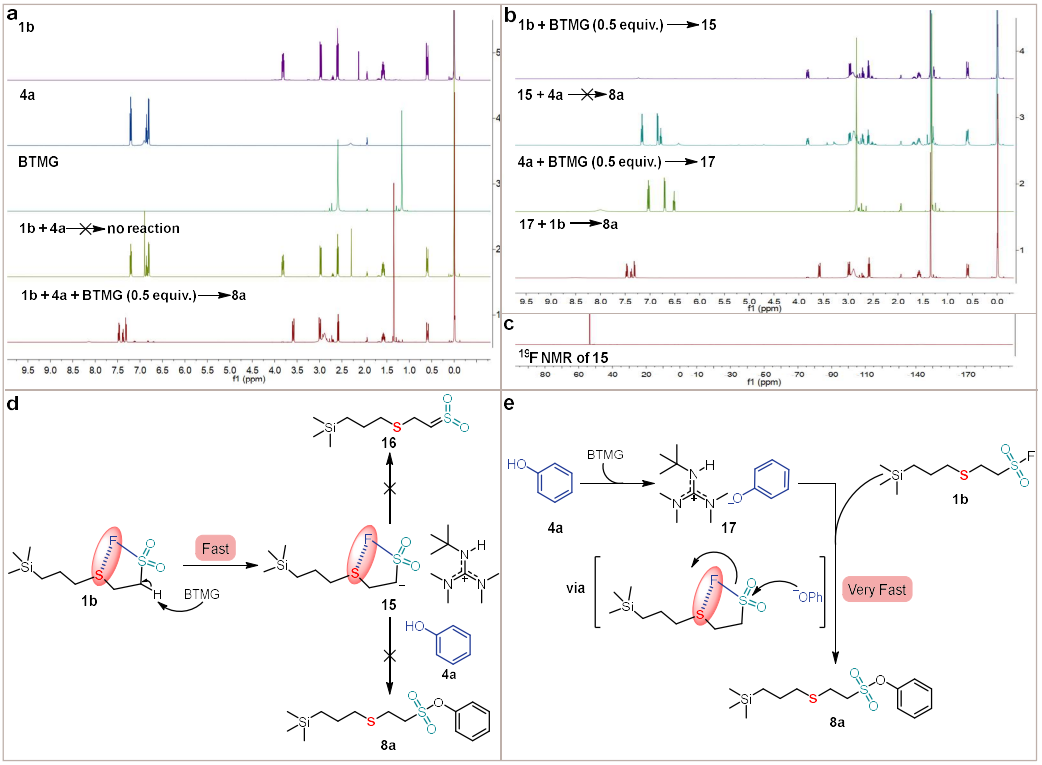
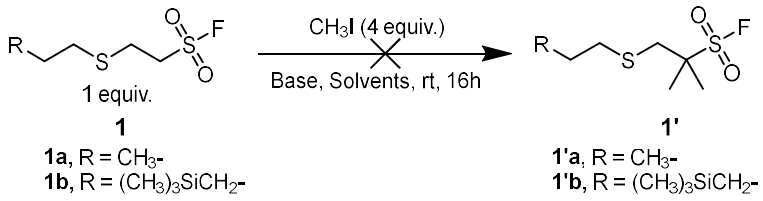


Fig. 7 | Mechanistic investigations. a, ^{1}H NMR spectra for the reaction between **1b** and **4a** with or without BTMG (500 MHz, MeCN-d_3). **b**, ^{1}H NMR spectra for the control reaction (500 MHz, MeCN-d_3). **c**, ^{19}F NMR spectra for the reaction between BTMG and **1b** (500 MHz, MeCN-d_3). **d**, Proposed mechanism disproved by experiments. **e,** Proposed mechanism.

Lastly, following your advice, we attempted to synthesize gem-dimethyl derivatives 1a and 1b to further explore the mechanism. Unfortunately, despite various attempts under different conditions, these syntheses were unsuccessful. The details of these attempts are summarized in the table below.



1

1a, R = CH_3-
1b, R = $(CH_3)_3SiCH_2$-

1'

1'a, R = CH_3-
1'b, R = $(CH_3)_3SiCH_2$-

Entry	Base	Solvent	T/°C	Yield/%
1	BTMG (1.0 equiv.)	MeCN	rt	0
2	BTMG (5.0 equiv.)	MeCN	rt	0
3	BTMG (5.0 equiv.)	MeCN	50	0
4	KOH (2.5 equiv.)	THF	rt	0
5	KOH (5.0 equiv.)	THF	rt	0
6	KOH (5.0 equiv.)	THF	50	0

(4) Furthermore, the formula of 5b and 7b (TMS = $(CH_3)_3Si$, not CH_3Si) in Figure 2 were wrong and should be corrected. Several NMR spectra were not clean and showing additional peaks and their quality should be improved.

Response:

Thank you for your comments. We sincerely apologize for the errors in the chemical formula of **5b** and **7b** in Fig. **2**, where TMS should have been correctly denoted as $(CH_3)_3Si$- rather than CH_3Si-. This has been corrected in Fig. **2a** of the revised manuscript (Page **5**).

We also greatly appreciate your thorough review of our NMR data. In response to your feedback, we have carefully re-purified the products (**8d**, **8k**, **8ab**, **8af**, **12v**, **12x**, **14e**) to ensure higher purity and have subsequently reacquired the NMR spectra. The improved spectra are now included in the revised supplementary information.

(5) Overall, I suggest that the current manuscript could be reconsidered in Nature Communications after addressing the questions above.

Response:

Thank you for your encouraging recommendation regarding publication in Nature Communications. We are grateful for your positive evaluation and insightful

comments, which have significantly contributed to the enhancement of our manuscript.

We have endeavored to address all the points you raised thoroughly and hope our revisions meet your expectations. Should there be any further concerns or additional modifications required, we are fully prepared to make the necessary adjustments to align our study with the journal's standards. We look forward to the opportunity to improve our work further if needed.

Responses to the comments of reviewer 2.

This manuscript describes a novel approach to activating sulfonyl fluorides toward SuFEx reactions through chalcogen bonding. The authors prepared several alkyl sulfonyl fluorides bearing γ-sulfur functional groups that were demonstrated to activate the SuFExable group through a 1,5-interaction. These activated electrophiles reacted smoothly with phenol under mild reaction conditions in the presence of sub-stoichiometric amounts of BTMG, a strong guanidine base. Several control experiments were performed (e.g., replacing the -S- functional group with the corresponding -CH2- and -SO2-) to highlight the importance of the thioether in activating the sulfonyl fluoride. Following the exploration of the substrate scope associated with this transformation by reacting 1b with a range of alkyl and aryl alcohols and amines, an application of this methodology in organic-inorganic linking was showcased, resulting in the formation of functionalized self-assembled monolayers that exhibit a range of properties dependent on the small molecules appended through the chalcogen-mediated SuFEx reaction. Finally, the authors probe the mechanism of this SuFEx reaction using a combination of NMR analyses and control experiments and present a plausible mechanism for consideration.

Overall, I believe the reaction is a strong and helpful addition to the SuFEx toolbox. The utility of the reaction has been demonstrated, and the experimental data is well presented and discussed. To be considered a true click reaction, the substrate scope of both coupling partners should be able to be varied. As the manuscript currently stands, further exploration of the sulfonyl fluoride component would be of significant worth to this paper. Following additional experimentation and addressing the points outlined below, I believe this manuscript warrants publication in Nature Communications.

Response:

Thank you very much for your valuable feedback. We have revised our manuscript and supporting information in accordance with your suggestions. Please see our response to your comments below.

(1) Expanding the substrate scope to include more diverse sulfonyl fluorides is essential. Currently, only a small selection of non-diverse thiols is used. Do 2-thioaryl sulfonyl fluorides benefit from the same activation? This would provide a similar 1,5-activation. Additionally, are fluorosulfates (aryl or alkyl) activated by a comparable 6-membered ring? These are obvious extensions to the methodology that should be explored.

Response:

We appreciate your insightful suggestions. Following these suggestions, we expanded our study to include a broader range of sulfonyl fluorides and evaluated their SuFEx reactivities. Our experiments demonstrated that both alkyl sulfonyl fluorides and 2-thioaryl fluorosulfates can be activated via 1,6-S···F interactions, although the latter was somewhat less effective.

These results have been thoroughly documented in the revised manuscript and supporting information. Specifically, the following statement was added in the revised manuscript (Page **13** line **339-350** and Fig. **7i**): "*Given the established activation of alkyl sulfonyl fluorides through non-bonding 1,5-S···F interactions, we explored the possibility of achieving a similar activation effect via 1,6-S···F interactions. Accordingly, we synthesized compound **18**, using 1-propanethiol, and 2-propene-1-sulfonyl fluoride as precursors and 2,2'-azobis(2-methylpropionitrile) as the reagent. The reaction between **18** and **4a**, in the presence of 0.5 equiv. of BTMG, gave an exceptional 99% yield of **19** within 0.5 h (Fig. **7i**, eq. **7**), demonstrating the feasibility of ChB activation by 1,6-S···F interactions. The Markovnikov addition product **20** and **4a** also exhibited high reactivity towards nucleophile **4a**, achieving a 99% yield using 0.5 equiv. of BTMG within 0.5 h (Fig. **7i**, eq. **8**). Furthermore, the reactivity of phenyl fluorosulfonate could also be moderately enhanced by a 2-thio group via a 1,6-S···F interaction (see Supplementary Section **7.7**). These outcomes collectively underscore the broader applicability of the intramolecular ChB-activated S-SuFEx reaction, demonstrating its potential for diverse synthetic applications.*".

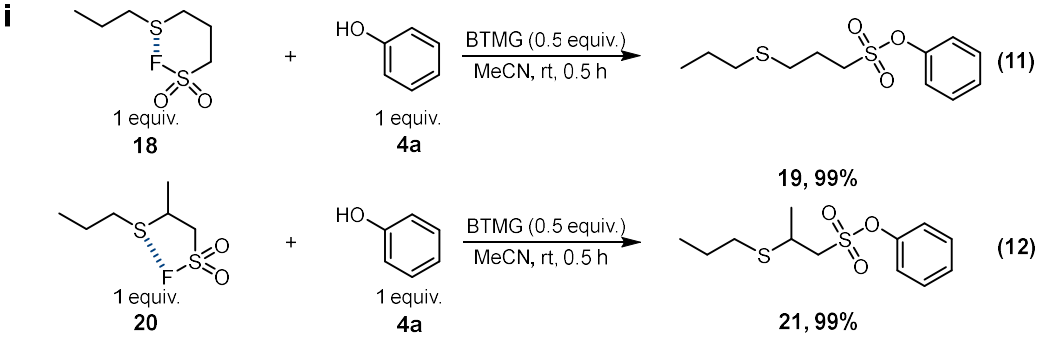
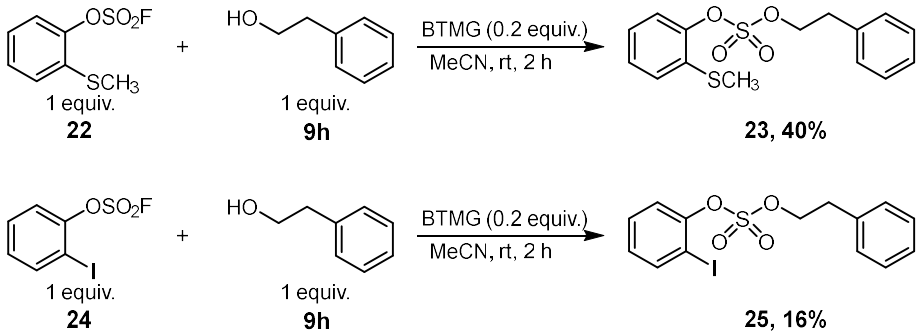
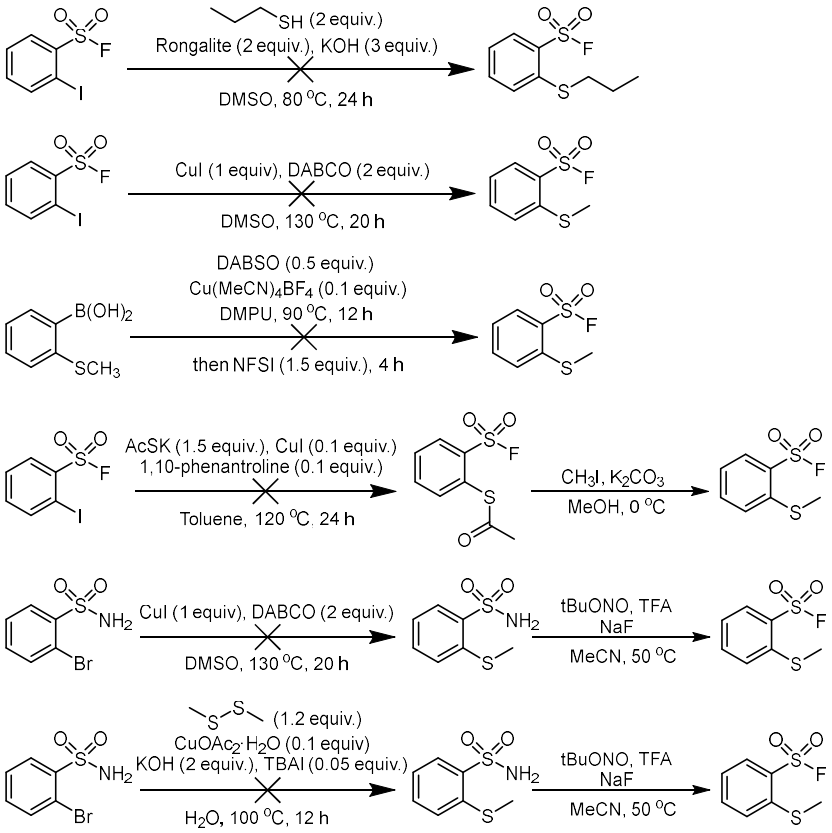


Fig. 7 | Mechanistic investigations. i, Further expansion of the S-SuFEx chemistry.



In the revised supporting information, we have included these results, along with other relevant data, as "**7.7 Further expansion of the S-SuFEx chemistry" section** (SI, Page **64-67**). And the following equations was also included in the supporting information.

As suggested, we also intent to synthesize 2-thioaryl sulfonyl fluoride. We attempted various methods (J. Org. Chem. 2019, 84, 9946-9956; Chem. Sci. 2017, 8, 3249-3253; Chem. Eur. J. 2021, 27, 3008-3012; Org. Lett. 2023, 25, 8263-8268), but were unable to obtain the desired product. Consequently, we could not further evaluate its reactivity at this stage. We hope to revisit this aspect of our research in future studies.

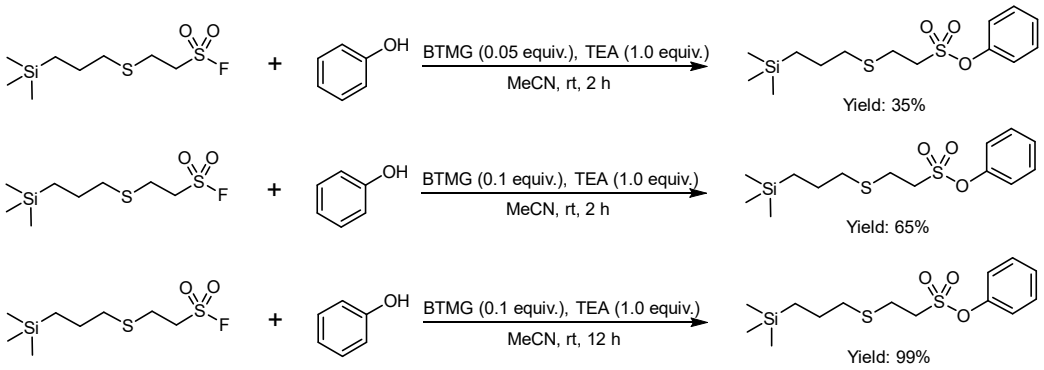


(2) The catalyst loading of 0.5 equivalents of BTMG is high for a SuFEx reaction. Do the authors have any suggestions as to why this loading is high? Were any attempts made to use a smaller amount of BTMG in the presence of a sacrificial base such as TEA?

Response:

Thank you very much for your insightful comments. In response to your suggestion regarding the high BTMG loading, we explored the possibility of reducing the amount of BTMG by incorporating triethylamine as a sacrificial base. This approach proved successful, allowing us to decrease the BTMG loading significantly.

Our experiments demonstrated that using only 0.1 equiv. of BTMG, in conjunction with 1.0 equiv. of TEA, we achieved a 99% yield of product **8a** from the reaction between **1b** and **4a**, albeit requiring a longer reaction time. These results are detailed below.



Based on these findings, we have updated both the manuscript and the supporting information. Specifically, in the manuscript, we added the statement: "*The required amount of BTMG could be further reduced by employing a sacrificial base, such as triethylamine (see Supplementary Section **2.8**).*" (Page **6**, Lines **154-156**). Additionally, in the supporting information, we introduced a new section, "**2.8 Effect of the Sacrificial Base Et_3N on the S-SuFEx Chemistry**" (SI, Pages **12-13**), to provide further details about this modification.

(3) 2-Nitrophenol required stoichiometric BTMG - this seems counterintuitive (when also considering the proposed mechanism) as this electron-deficient phenol should deprotonate easier than phenol. Please comment on this observation.

Response:

Thank you for the comments. In response to your comment, we reevaluated the reaction using a reduced amount of BTMG and replicated the original conditions for comparison.

Our findings confirm that decreasing the BTMG from 1.0 equiv. to 0.5 equiv. indeed resulted in a significantly lower yield after 2 hours, dropping to 33%. This observation can be attributed to the strong electron-withdrawing effect of the nitro group, which likely renders the phenoxide anion less nucleophilic and thus less effective in the reaction with sulfonyl fluoride. These results are consistent with the outcomes reported in the original manuscript and underscore the necessity of using stoichiometric amounts of BTMG for this particular substrate. We have documented these findings and added the statement "*Following GP1: Yield: 33%.*" in the revised supporting information (SI, Page **17**).

(4) For clarity, the references associated with the statement "Typically, SuFEx chemistries require activated substrates or additional activators…" should be separated out between activated substrate references and additional activator references.

Response:

Thank you for your suggestion. We have modified the references as "*activated substrates*[3,29,30] *or additional activators*[5,6,31]" in the revised manuscript (Page **2** line **39**).

(5) When selectivity for alcohol over amine functional groups is noted (i.e., 10b), including a yield based on recovered starting material would be helpful. A yield of 72% with two possible reaction sites suggests that competing reactivity could occur.

Response:

Thank you for highlighting this important point. We have revisited the S-SuFEx reaction with **9b**, and can confirm that no by-products from competing reactions were detected. To clarify this in the manuscript, we have included the following statement: "*In the case of amino alcohol **9b**, only the target product **10b** derived from the reaction between the hydroxyl group and sulfonyl fluoride was detected, with the remaining mass balance accounted for by the unreacted starting material.*" in the revised manuscript (Page **8**, Lines **189-192**).

(6) Using "eq." for both equation and equivalent is confusing and inconsistent between the manuscript and supporting information. I suggest "eq." for equation and "equiv." for equivalent to avoid any ambiguity.

Response:

Thank you very much for your kind suggestion. Following your suggestion, we have promptly rectified it using "eq." for equation and "equiv." for equivalent to avoid any ambiguity in the revised manuscript and ESI.

(7) Small typographical errors were noted (i.e., Fig 1d "alcohol"). Please check the

document thoroughly prior to resubmission.

Response:

We genuinely appreciate your meticulous examination of our manuscript, and deeply apologize for the oversight. To address this issue, we have made the necessary corrections and check the document thoroughly.

(8) The mention of the phenoxide guanidinium complex should reference the work by Moses and co-workers directly, as they proposed this as a SuFEx reaction intermediate (currently reference 5).

Response:

Thank you for your comment. We highly acknowledge the significant influence of the work by Moses and co-workers on our study. Following your suggestion, we have made the appropriate citation in the revised manuscript. Specifically, we have added the following statement: "*Furthermore, inspired by the discovery by Moses et al. of BTMG as an exceptional SuFEx catalyst*[5]*, we hypothesized that the phenoxide guanidinium complex **17** might also facilitate sulfonyl fluoride group activation via hydrogen bonding with fluorine. Empirical validation involved direct interaction of **1b** with sodium phenoxide 4a', achieving an impressive 87% yield of **8a** (Fig. **7h**, eq. **9**), albeit slightly lower than the 99% yield obtained with **4a** and BTMG (Fig. **7h**, eq. **3**). Conversely, the reaction of **3b** with sodium phenoxide yielded a mere 31% of **8a** (Fig. **7h**, eq. **10**), underscoring the intramolecular ChB as the predominant factor in alkyl sulfonyl fluoride activation, with the phenoxide guanidinium complex playing a supportive role in this activation process.*" (Page **13** line **330-338**).

(9) A description for panel e is missing from the Figure 1 caption.

Response:

Thank you for pointing out the error. We have promptly rectified it and added the description for Fig. **1e** "*Clickable platform for efficient covalent organic-inorganic linkages based on the S-SuFEx chemistry*" in the revised Figure **1** caption (Page **3** line **90-91**).

(10) The schemes are not as clear as they could be, and compound numbering is less than obvious. For example, compound 1c is mentioned in line 77 of the text, though it is not drawn until Figure 2, and even then, the reader must infer the

structure from the product 5c. The phenol 4a is used in the first reaction with 1 and should have a lower number, as it is mentioned in the text and the figure sequence before compound 3, for example. The figures and compound numbers should be reconsidered for ease of reading.

Response:

We sincerely appreciate your concern for the readability of our manuscript. We have improved compound numbering in the revised manuscript and supporting information.

(11) Reaction conditions for Figure 2b are missing from the legend.

Response:

Thank you for the comment. In this revised manuscript, we have added the reaction conditions "*Reaction conditions: alkyl sulfonyl fluorides* ***1b*** *or* ***2b*** *(0.3 mmol), phenol (0.3 mmol), and BTMG (0.15 mmol) were stirred in MeCN-d_3 (1 mL) for 2 h at room temperature. SO_2F_2 was introduced by needle from a balloon filled with the gas.*" in the revised Figure **2** caption (Page **5** line **127**-**129**).

(12) Compound 12u says "from tyrosine" - this product is from "tyrosine methyl ester.

Response:

Thank you for raising this concern. We have addressed it by replacing the "from tyrosine" with " from phenylalanine ethyl ester" and "from valine" with " from valine ethyl ester" in Table **3** of the revised manuscript (Page **9**).

(13) Inconsistencies were noted between how "O,N-nucleophiles" and supporting information were presented throughout the manuscript. Please make it consistent.

Response:

Thanks for your comments. We have re-reviewed the presentation of "*O*, *N*-nucleophiles" and make it consistent throughout the revised manuscript and supplementary information.

Responses to the comments of reviewer 3.

In the manuscript, the authors present the intramolecular SuFEx ability activation strategy of alkyl sulfonyl fluorides using γ-S atom. The activated SuFEx reactivity of

alkyl sulfonyl fluorides is achieved with relatively low base loadings under mild conditions. The activated alkyl sulfonyl fluorides can react smoothly with phenols, alcohols, and amines with excellent yields. Additionally, it can be used for the creation of functionalized SAMs on the surface of inorganic materials via organic-inorganic linking after incorporating a trialkoxy silane group. This study provides new insights into SuFEx chemistries. It is suitable for publication after addressing the following issues. Some comments are as follows.

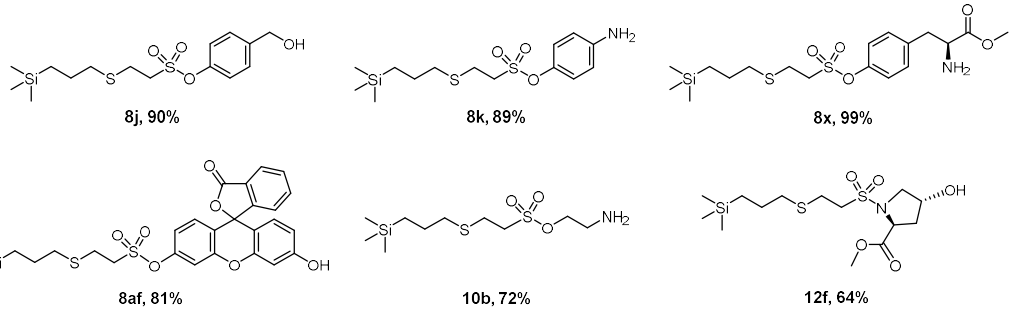
Response:

Thank you very much for your positive feedback and comment. For each of the point raised, we have made revisions to the paper as detailed in our responses below.

(1) What is the selectivity of the SuFEx click reaction among different phenols, alcohols and amines?

Response:

Thank you for emphasizing this crucial point. Taking your suggestion into account, we have conducted further experiments to evaluate the selectivity of the SuFEx click reaction among different phenols, alcohols and amines. For substrates with multiple reactive sites (i.e., **4j**, **4k**, **9b**, **11f**), it is gratifying to note the excellent chemoselectivity achieved under the established reaction conditions. The experiments indicated that phenols are the most reactive, followed by alcohols and amines.



Moreover, a series of competitive reactions revealed that phenols, regardless of whether they contain electron-donating or electron-withdrawing groups on the aromatic ring, demonstrate comparable reactivity due to their high reactivity. In terms of the S-SuFEx reaction selectivity among different alcohols, primary alcohols exhibit relatively higher reactivity compared to the more hindered secondary and tertiary alcohols. When it comes to amine substrates, aliphatic amines generally exhibit higher

reactivity compared to anilines, with secondary amines being the most reactive *N*-nucleophiles in S-SuFEx chemistry. A description has been incorporated in section "**7.8 Selectivity of the S-SuFEx chemistry among different phenols, alcohols and amines**" in the revised supporting information (SI, Page **67** ~ **69**). In the revised manuscript, we have added the statements as follows:

Page **6** line **157-159**: *Phenols, whether containing electron-donating or electron-withdrawing groups on the aromatic ring, demonstrated comparable reactivity and were smoothly converted into sulfonates **8**.*

Page **6** line **162-163**: *Significantly, this reaction also highlights the exceptional chemoselectivity of phenols compared to anilines (**8k**, **8t**) and alcohols (**8j**).*

Page **7** line **184-186**: *Notably, primary alcohols exhibited relatively higher reactivity compared to the more hindered secondary and tertiary alcohols (see Supplementary Section **7.8**).*

Page **7** line **205-207**: *Generally, aliphatic amines showed higher reactivity compared to anilines, with secondary amines proving to be the most reactive N-nucleophiles in S-SuFEx chemistry.*

(2) What is the stability of the whole organic-inorganic linking system after compounds anchored on glass surface at different pH and temperature or flushing with water and organic solvents?

Response:

Thank you for your insightful question. In response, we conducted additional experiments to evaluate the stability of the functionalized glass slides under various conditions, using fluorescein-functionalized glass slides as the model. We assessed their stability at different pH levels (pH =2 and pH = 12), at a high temperature of 120 °C, and after exposure to organic solvents (ethanol).

The results indicated that the functionalized glass slides exhibit good acid tolerance but poor base tolerance, likely due to the instability of the Si-O-Si bond in basic conditions (Fig. **S7**). Moreover, the slides remained stable when subjected to a high temperature of 120 °C for 3 d (Fig. **S8**) and showed no significant changes after being soaked in ethanol for 7 d (Fig. **S9**).

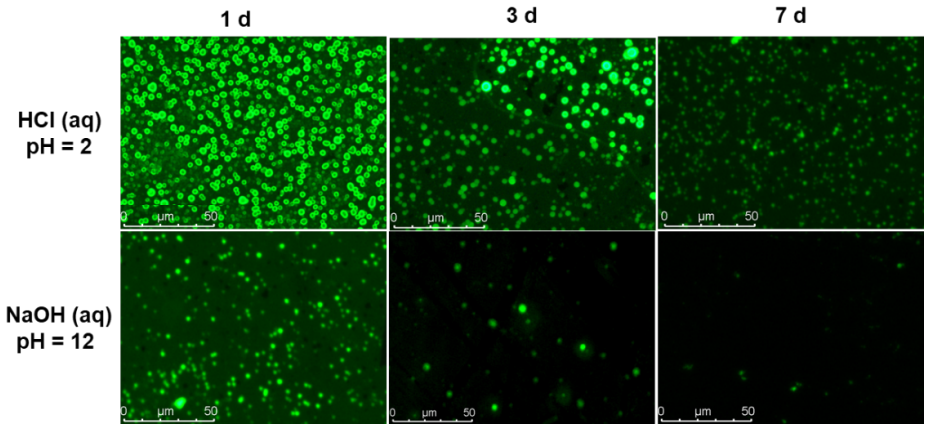


Figure S7. Stability of the fluorescein-functionalized glass surfaces in aqueous HCl (pH = 2) and aqueous NaOH (pH = 12).

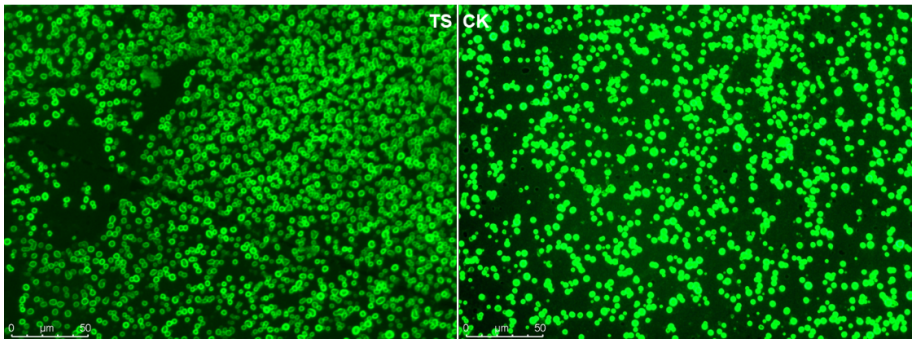


Figure S8. Stability of the fluorescein-functionalized glass surfaces at 120 ºC.

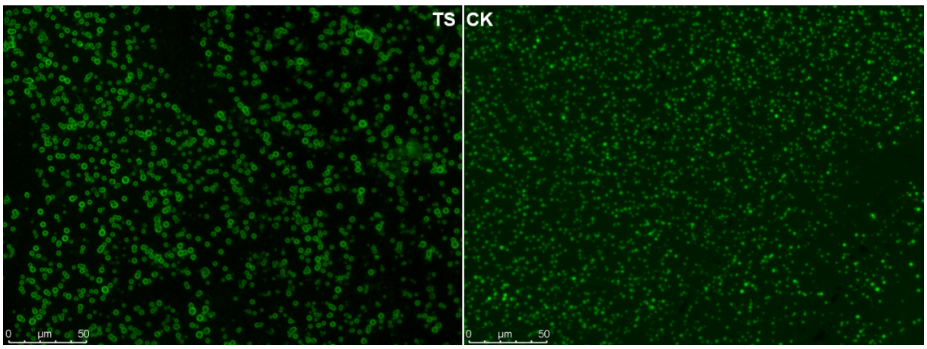


Figure S9. Stability of the fluorescein-functionalized glass surfaces in EtOH.

Based on these findings, we have updated the manuscript and the supporting information. We included the following statement in the manuscript: "*Using FR-functionalized glass as the model, we tested the stability of this organic-inorganic linking system. The results indicated that the system exhibited excellent stability, with robust tolerance to acid (pH = 2) (Fig.* ***S7****), high temperature (Fig.* ***S8****) or flushing with organic solvents (Fig.* ***S9****). However, the functionalized glass slides showed poor*

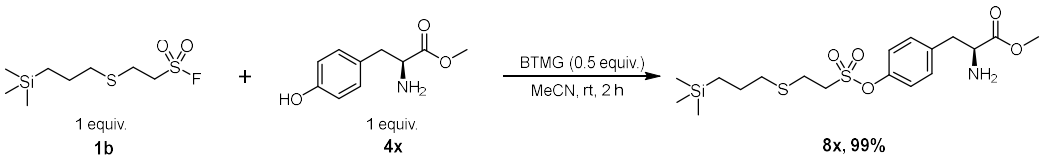
base tolerance, which was primarily caused by the dissolution of Si–O–Si network structure in a strong alkaline environment[55]." (Page **11** line **267-272**). Additionally, detailed descriptions of the experimental conditions and results have been added to the supporting information under the section "**6.5 Stability of the functionalized glass surfaces**" in the revised supporting information (SI, Page **54-55**).

(3) Can compound 1c react with some bioactive molecules, such as proteins or antibodies? If the bioactive molecules can be linked on the glass surface, it may have great application value in biological detection.

Response:

Thank you for highlighting this important aspect regarding the potential applications of our technique in biological detection systems. Your suggestion prompted us to explore the reactivity of S-SuFEx hubs with animo acids and peptides.

Initially, we tested the reactivity of **1b** with methyl *L*-tyrosinate and achieved a 99% yield of the desired product. Encouraged by these results, we proceeded to attach the peptide oxytocin, which contains a tyrosine substructure, onto glass slides using the S-SuFEx hub **1c**. This attachment was successfully confirmed by ATR-IR spectroscopy, as shown in Figure **S6**.



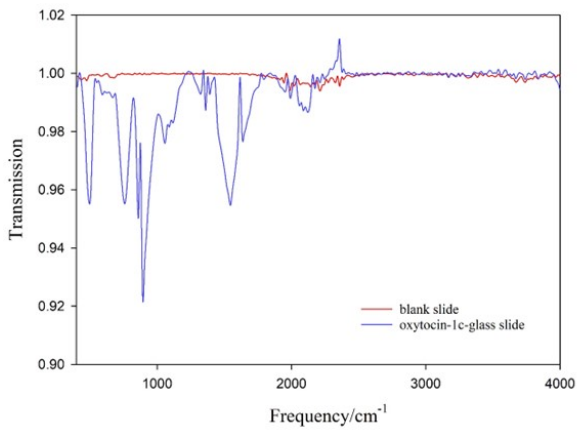


Figure S6. FT-IR spectra for covalently oxytocin-linked glass slide via the S-SuFEx hub 1c.

These findings have been incorporated into the manuscript and supporting information. In the revised manuscript, the reaction between **1b** and methyl *L*-tyrosinate is added in Table **1** as product **8x**. Notably, due to the inclusion of additional example **8x**, we have made an adjustment in the numbering of the original compounds. As a result, the previous compounds numbered **8x** ~ **8ag** have been updated to number **8y** ~ **8ah**, respectively, to ensure accurate sequencing (Page **7** Table **1**). Additionally, we added the following statement to emphasize the potential of this method: "*Furthermore, we specifically attempted to immobilize the peptide oxytocin on the glass surface using **1c** (Fig. **S6**). The successful outcomes of the peptide immobilization process suggested that this clickable platform may have significant application value in biological detection.*" (Page **11** line **272-275**).

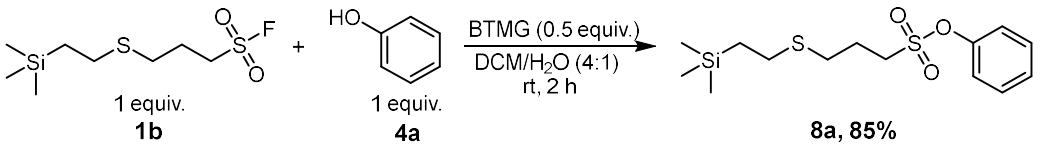
The characterization data of **8x** has been added in the revised ESI (SI, Page **23**). Detailed experimental procedures and results have also been added to the revised supporting information in the section "**6.6 Immobilization of the peptide on the glass surfaces via the S-SuFEx hub 1c**" (SI, Page **55-56**).

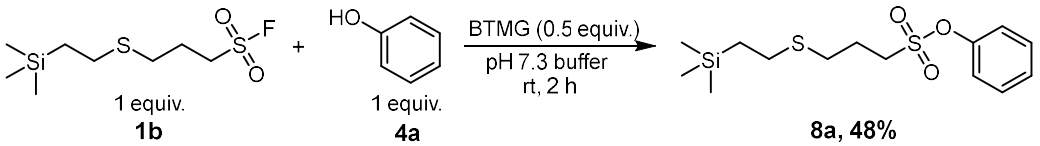
(4) To expand the application scope of this reaction, does water affect the reaction? Can it work in buffer solutions?

Response:

Thank you very much for your constructive comments. In response to your inquiry regarding the effect of water on the reaction, we conducted experiments using the reaction between 1b and 4a as a model. We tested this reaction in both DCM/H_2O (v/v, 4/1) and PBS buffer (pH 7.4) as solvents.

The outcomes have been documented in the revised manuscript, specifically on page **6**, line **169-172**: "*Additionally, the reaction between **1b** and **4a** using DCM/H_2O (v/v, 4/1) as the solvent produced an 85% yield of **8a**. Even when employing a PBS buffer solution (pH = 7.4) as the solvent for the reaction between **1b** and **4a**, a moderate yield of 48% was still achieved.*" Detailed description of these experiments has been incorporated into the revised supporting information in the section "**2.9 Effect of water on the S-SuFEx chemistry**" (SI, Page **13**).





(5) Please provide the eluent of flash column chromatography and R_f value for each compounds.

Response:

Thank you for bringing attention to this crucial point. We have provided the eluent of flash column chromatography and Rf value for each compound. The updated results can be found in the revised supporting information.

Other Changes:

1) Dr. Hainam Do has made substantial contributions during the revision of this manuscript, including conducting performing the DFT calculations, data analysis and visualization. Consequently, he is being designated as an author for this study in the revised version.
2) Page numbers have been incorporated into the revised manuscript.
3) Ref. 55 and ref. 56 were added in the revised manuscript.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

An and coworkers have greatly improved the quality of manuscript and supp information and resolved most of my concerns. In particular,they revised the original proposal during the revision based on the new insight from their computational study. For me, the only question left is still about the mechanism. The fact that the sulfen intermediate cannot be prepared and separated can not rule out the elimination-addition pathway. Indeed, the generation of sulfen intermediate is energetically uphill when fluride ion cannot be trapped. The experiment with the addition of 1 equive of phenol into the mixture of sulfonyl fluoride and base did not eliminate the e-a pathway as well. Such addition process will be initiated by good nuclophiles. Obviously, phenol instead of phenolate is not good enough. Although using excessive bases or primary/secondary alkyl amine will solve the problem above, such a solution cannot differentiate the current substrate with the substrate without S substitutents. So I don't suggest these experiments. Again, I encourage the authors to prepare aryl sulfonyl fluoride or alkyl ones without no-alpha H. They will eliminate the mechanistic ambiguity.

For the synthesis of 2-thioaryl sulfonyl fluoride, I can share some experiences. For some reason, copper-catalyzed couplings always failed. The key is to use Pd coupling for 2-thioaryl sulfonyl fluoride. It works well in our hands. In addition, the substrate 24 was not a good candidate for the comparison with the substrate 22. Can the authors make some substrate with a p-MeS-substituent? Another control substrate will be ROCH2CH2SO2F which replace S with O.

New discovery about the interaction between S and F is a good indicator for the proposed activation. Can authors computationallly measure the strength of such secondary interaction by NBO methods?

Overall, I suggest this work be accepted after minor revision.

Reviewer #2 (Remarks to the Author):

The authors have addressed all the points we raised. I’m happy with their revision.

Reviewer #3 (Remarks to the Author):

The authors have carefully revised the manuscript based on the comments, and all issues meet the requirements. Therefore, I recommend to accept it now.

Point-by-Point Response to Referees

Responses to the comments of reviewer 1.

An and coworkers have greatly improved the quality of manuscript and supp information and resolved most of my concerns. In particular,they revised the original proposal during the revision based on the new insight from their computational study. For me, the only question left is still about the mechanism. The fact that the sulfen intermediate cannot be prepared and separated can not rule out the elimination-addition pathway. Indeed, the generation of sulfen intermediate is energetically uphill when fluride ion cannot be trapped. The experiment with the addition of 1 equive of phenol into the mixture of sulfonyl fluoride and base did not eliminate the e-a pathway as well. Such addition process will be initiated by good nuclophiles. Obviously, phenol instead of phenolate is not good enough. Although using excessive bases or primary/secondary alkyl amine will solve the problem above, such a solution cannot differentiate the current substrate with the substrate without S substitutents. So I don't suggest these experiments. Again, I encourage the authors to prepare aryl sulfonyl fluoride or alkyl ones without no-alpha H. They will eliminate the mechanistic ambiguity.

Response:

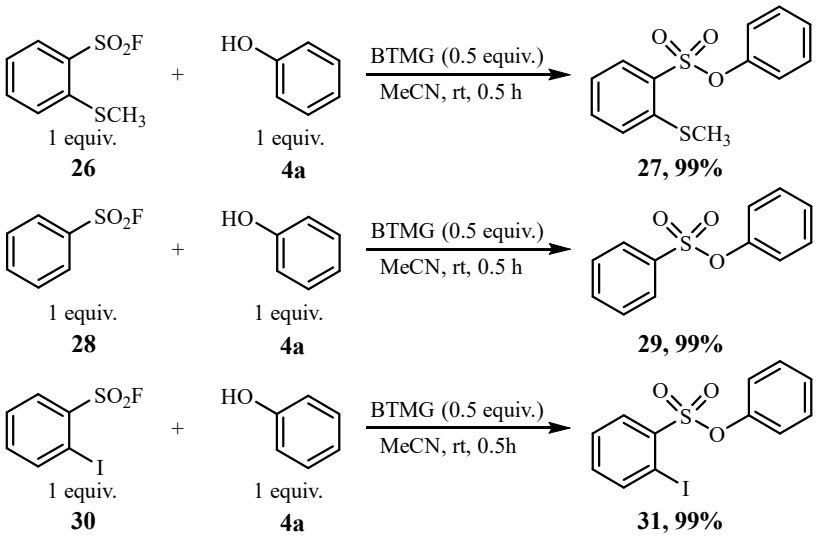
We sincerely appreciate your positive feedback on our manuscript and for your valuable suggestions. We have conducted further experiments and computational studies to clarify the mechanism involved. Please see our response to your comments below.

For the synthesis of 2-thioaryl sulfonyl fluoride, I can share some experiences. For some reason, copper-catalyzed couplings always failed. The key is to use Pd coupling for 2-thioaryl sulfonyl fluoride. It works well in our hands. In addition, the substrate 24 was not a good candidate for the comparison with the substrate 22. Can the authors make some substrate with a p-MeS-substituent? Another control substrate will be ROCH2CH2SO2F which replace S with O.

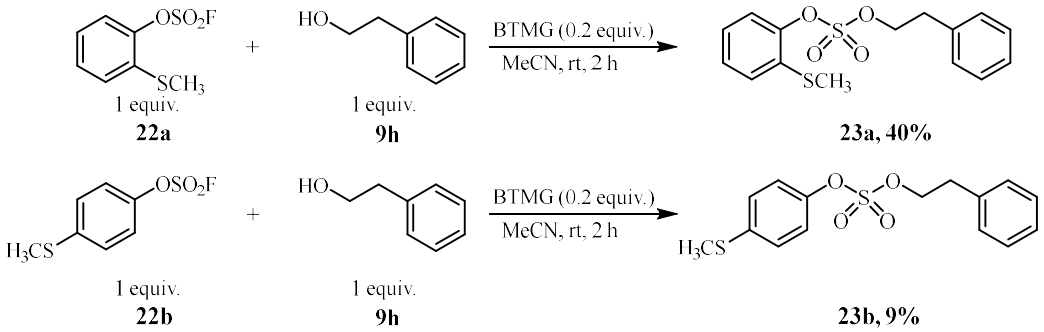
Response:

We have successfully synthesized 2-(methylthio)benzenesulfonyl fluoride (compound **26**). This compound exhibited high reactivity with **4a**, yielding 99% of

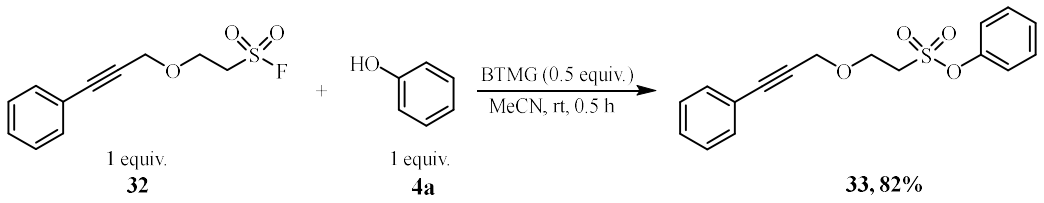
the desired product within 0.5 hours in the presence of 0.5 equiv. of BTMG. In contrast, the control experiment using benzenesulfonyl fluorides **28** and **30** also resulted in a 99% yield. Given the inherent high reactivity of aromatic sulfonyl fluoride, it was challenging to determine if the activation was due to the 2-methylthio group. The outcomes have been documented as "**7.7.1.4 Synthesis of 2-(methylthio)phenyl sulfonyl fluoride**" and "**7.7.2.4 SuFEx reactivity of 2-thioaryl sulfonyl fluorides**" in the revised supplementary information (SI, Page **66-67** and **69-70**).



We acknowledge that substrate **24** was not ideal for comparison with substrate **22a**. We have synthesized 4-(methylthio)phenyl fluorosulfonate **22b** and tested its SuFEx reactivity. The results showed that 4-(methylthio)phenyl sulfurofluoridate was less reactive compared to **22a**, indicating that the increased reactivity of **22a** was due to non-bonding S···F interactions. We have updated the supporting information by replacing the control reaction using 2-iodophenyl sulfurofluoridate with the control reaction using 3-(methylthio)phenyl fluorosulfonate (SI, Page **68-69**). Thank you for pointing out this critical aspect, enabling us to amend our manuscript accordingly.



Additionally, in response to your suggestion, we have synthesized an aliphatic sulfonyl fluoride **32** with a γ-oxygen substituent and tested its SuFEx reactivity with **4a** in the presence of 0.5 equiv. of BTMG. Given that oxygen is known to form chalcogen bonding (Ref 57: Coordin. Chem. Rev. 2022, 464, 214556), compound **32** with a γ-oxygen substituent also exhibited high reactivity towards phenol **4a**, yielding 82% of the desired product. These results have been thoroughly documented in the revised manuscript and supporting information. Specifically, the following statement was added in the revised manuscript (Page 13, line **350-351**): "*Interestingly, alkyl sulfonyl fluorides with γ-O replacing γ-S also showed significantly enhanced SuFExability (see Supplementary Section **7.9**), as oxygen is known to form chalcogen bonding*[57]." In the revised supporting information, we have included these results, along with other relevant data, as "**7.9 SuFEx reactivity of alkyl sulfonyl fluoride bearing γ-O" section** (SI, Page **72-73**). And the following equations was also included in the supporting information.



New discovery about the interaction between S and F is a good indicator for the proposed activation. Can authors computationallly measure the strength of such secondary interaction by NBO methods?

Response:

Thank you very much for your positive feedback on our work. Following your suggestion, we have computationally measured the strength of the chalcogen bonding

in compound **1b** using NBO methods and have made the corresponding modifications in both the main text and the supporting information.

In the revised manuscript, we have added the following statement (page **13**, line **324-328**) and Fig **7g**: "*We further computationally measured the distance and strength of the ChB between S and F in **1b** using NBO analysis. The measured distance was found to be 3.11 Å (Fig. **7g**), which is less than the sum of their van der Waals radii ($\sum r_{vdW}$ (S···F) = 3.27 Å)[56]. The strength of this interaction was measured to be 5.37 kcal/mol.*". In the revised supporting information, we have included the details of the NBO calculation on page **61**.

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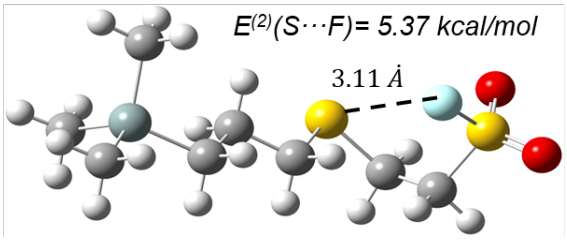

Fig. 7 | Mechanistic investigations. g, The S···F distance of **1b** is 3.11 Å, falling into the range of chalcogen bonding distance. The $E^{(2)}$ is the second order perturbation stabilization energy.

Overall, I suggest this work be accepted after minor revision.

Response:

We sincerely appreciate your thorough review and constructive feedback on our manuscript. We are particularly grateful for your insightful comments and detailed suggestions regarding the mechanistic questions which have significantly contributed to the improvement of our work. We are hopeful that our responses and the improved manuscript meet your expectations.

Thank you once again for your invaluable input and recommendation to accept our work.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors have greatly improved the quality of the manuscript and met the standard of Nature Communications. I suggest the authors to remove the sentence “Interestingly, alkyl sulfonyl fluorides with γ-O replacing γ-S also showed significantly enhanced SuFExability (see Supplementary Section 7.9), as oxygen is known to form chalcogen bonding57.”since oxygen has the weakest chalcogen bonding compared to S, Se, and Te. Although the current data cannot differentiate the inductive effect and the chalcogen bonding, the slightly lower yield of γ-O substrate over γ-S substrate implies the role of chalcogen bonding in this methodology.

Point-by-Point Response to Referees

Responses to the comments of reviewer 1.

The authors have greatly improved the quality of the manuscript and met the standard of Nature Communications. I suggest the authors to remove the sentence "Interestingly, alkyl sulfonyl fluorides with γ-O replacing γ-S also showed significantly enhanced SuFExability (see Supplementary Section 7.9), as oxygen is known to form chalcogen bonding." since oxygen has the weakest chalcogen bonding compared to S, Se, and Te. Although the current data cannot differentiate the inductive effect and the chalcogen bonding, the slightly lower yield of γ-O substrate over γ-S substrate implies the role of chalcogen bonding in this methodology.

Response:

We sincerely appreciate your constructive feedback and acknowledging the improvements made to our manuscript. In response to your suggestion, we have carefully considered the statement regarding the role of oxygen in chalcogen bonding within the context of our study. Following your advice, we have removed the sentence. Thank you once again for your invaluable input and recommendation to accept our work.