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Synthesis of Highly Reactive Sulfone Iminium Fluorides and Their Use in Deoxyfluorination and Sulfur Fluoride Exchange (SuFEx) Chemistry

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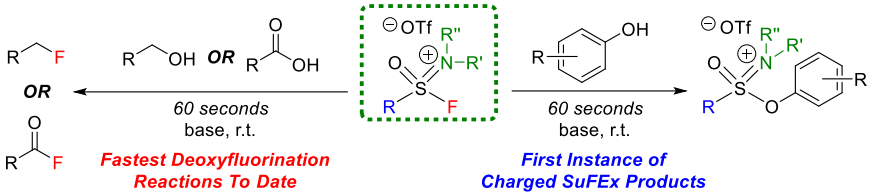
Supporting Information Placeholder



ABSTRACT: We report the synthesis of sulfone iminium fluorides (SIFs), a reactive class of sulfur(VI) molecules. The synthesis is tolerant of a variety of substituents on the sulfur and nitrogen components. The SIF reagents were applied to the deoxyfluorination of alcohols and carboxylic acids, providing high yields of fluorinated products in 60 seconds at room temperature. The SIF reagents were then utilized in sulfur fluoride exchange (SuFEx), creating the first ionic SuFEx products to date.

Sulfur(VI) compounds have become an important class of molecules in organic synthesis. Multiple positions for creative tuning on the sulfur(VI) center has led to great synthetic diversity among this broad category, leading to applications in a myriad of areas.[1] Particularly, those sulfur(VI) compounds with sulfur-fluorine bonds (Figure 1a) are capable of facilitating transformations that have become critical to the organic chemist's toolbox.[2] Of these methodologies, two have been the most directly impacted by these fluorine-containing sulfur(VI) reagents: deoxyfluorination and sulfur fluoride exchange (SuFEx).

Deoxyfluorination is one of the most efficient and versatile methods for the incorporation of fluorine into organic molecules, a highly desirable outcome given the element's ever-growing usage in the pharmaceutical industry.[3] While deoxyfluorination was largely developed using sulfur(IV) reagents, such as DAST[4] and Deoxo-Fluor[5], drastic improvements to reaction conditions, substrate compatibility and reagent stability have resulted from the use of sulfur(VI) compounds (Figure 1a). Sulfonyl fluorides, such as PyFluor[6] and sulfuryl fluoride[7], have been shown to facilitate the deoxyfluorination of a variety of oxygen substrates under mild conditions, albeit with long reaction times. More recently, Hu has demonstrated the utility of sulfonimidoyl fluorides in deoxyfluorination with the introduction of SulfoxFluor, a reagent capable of producing alkyl fluorides under shorter reaction times.[8]

SuFEx, the most recent addition to the click chemistry family, was introduced in 2014 by Sharpless and coworkers and has followed a similar journey as deoxyfluorination when it comes to reagent development.[9] Originally, SuFEx was executed exclusively with sulfonyl fluorides in conjunction with carbon, oxygen and nitrogen nucleophiles.[10] However, sulfonimidoyl fluorides have also been incorporated as a SuFEx-able "molecular plug-in", further expanding the synthetic diversity of this methodology[11] and, in some cases, facilitating easier exchange reactions.[12] Overall, the creation of modular sulfonyl and sulfonimidoyl fluorides has

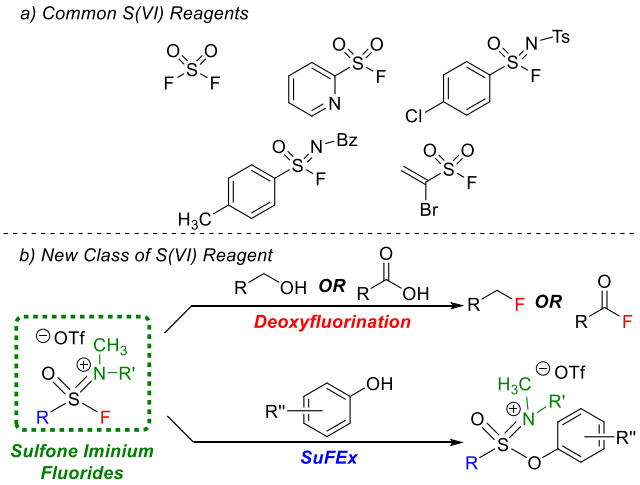
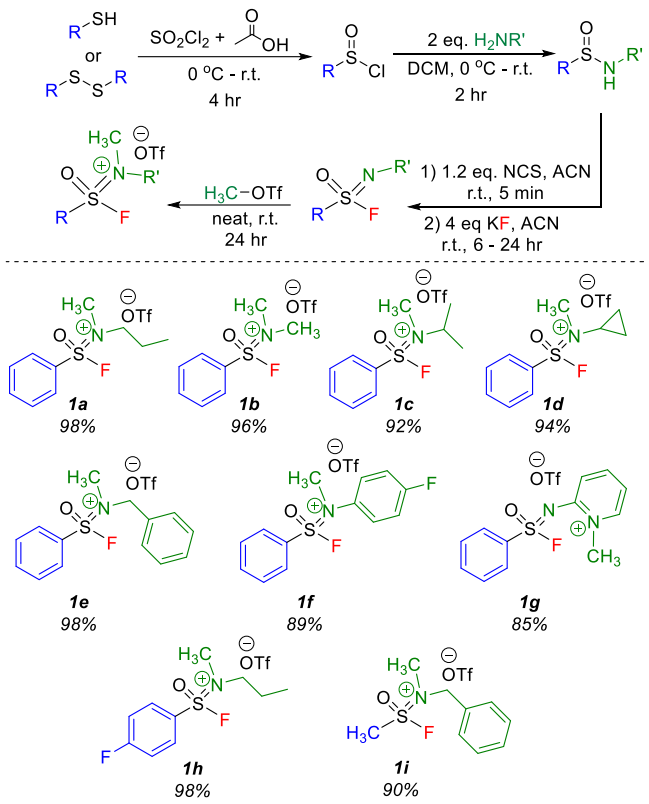


Figure 1. a) Common S(VI) reagents; b) Applying sulfone iminium fluorides towards deoxyfluorination and SuFEx.

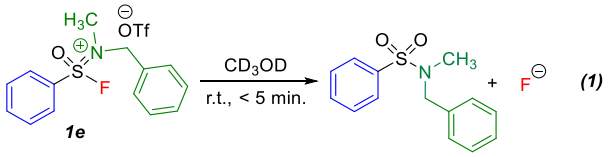
Scheme 1. Synthetic strategy and scope of sulfone iminium fluoride reagents.



played a significant role in improving the efficiency and diversity in both deoxyfluorination and SuFEx chemistry.

Compared to sulfonyl and sulfonimidoyl compounds, the sulfone iminium core has garnered little attention despite possessing promising attributes. Johnson was the first to synthesize a reagent with the sulfone iminium motif, which was capable of achieving various electrophilic alkylations[13], while Shibata and coworkers expanded on this work to include electrophilic perfluoroalkylation.[14] These examples demonstrate the strong electron-withdrawing nature of this scaffold, which is capable of producing an even more electron-deficient sulfur center than its sulfonyl or sulfonimidoyl counterparts. Additionally, there are multiple sites on the sulfone iminium core structure that offer opportunities to finely tune stereo-electronic properties. Despite these advantages, the sulfone iminium motif has yet to be applied in either deoxyfluorination or SuFEx chemistry. Therefore, we sought to synthesize a small library of novel sulfone iminium fluorides (SIFs) and apply them in both deoxyfluorination and SuFEx (Figure 1b).

We began by developing a short and modular synthesis of SIFs (Scheme 1). Oxidation of thiols and disulfides led to several variations of sulfinyl chlorides, including both aryl and alkyl substituents. Treatment with various amines



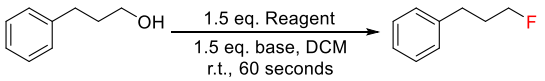
(1)

furnished sulfinamides in excellent yields; again, both aliphatic and aryl amines could be utilized, in addition to a 2-pyridyl derivative. The sulfinamides were then converted to sulfonimidoyl fluorides in a two-step process: 1) oxidative chlorination with either *N*-chlorosuccinimide or *tert*-butyl hypochlorite followed by 2) halide exchange with potassium fluoride.[15] Finally, sulfone iminium fluorides (***1a*** – ***1i***) were produced through a neat reaction of the sulfonimidoyl fluoride with methyl trifluoromethanesulfonate.[14]

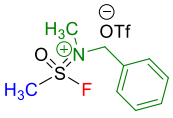
In total, 9 iterations of sulfone iminium fluoride were produced using this tunable, 4-step synthesis. Variation at the sulfur position was well tolerated, generating products with phenyl (***1a – 1g***) and 4-fluoro phenyl (***1h***) as well as methyl (***1i***). The non-methyl nitrogen component could also be altered; alkyl substituents ranging in size from methyl to *iso*-propyl were easily accessible, although a *tert*-butyl substituent proved too sterically hindered for the final methylation step to proceed. Interestingly, when using a 2-pyridyl nitrogen substituent, the reaction with methyl trifluoromethanesulfonate yielded methylation at the pyridyl nitrogen (***1g***). Additionally, the synthesis could be performed on a 50 mmol scale if required, such as with ***1e*** and ***1i***. All SIF products were found to be stable compounds that could be stored on the bench-top for at least 9 months with no signs of decomposition.

With a small library of SIF compounds synthesized, our attention turned to their reactivity with oxygen nucleophiles. During initial studies, washing compound ***1e*** with H_2O affected a complete transformation to the corresponding *N*-methyl-*N*-benzyl benzene sulfonamide. Similarly, when ***1e*** was dissolved in methanol-d_4, only the sulfonamide product was observed in the ^{1}H NMR spectrum, along with a peak in the ^{19}F NMR spectrum corresponding to free fluoride anion (Eq. 1, see SI). This phenomenon is observed in other alcohol solvents as well, including ethanol, isopropanol and 1-hexanol. For comparison, when SulfoxFluor, a

Table 1. Deoxyfluorination optimization using SIF reagents.



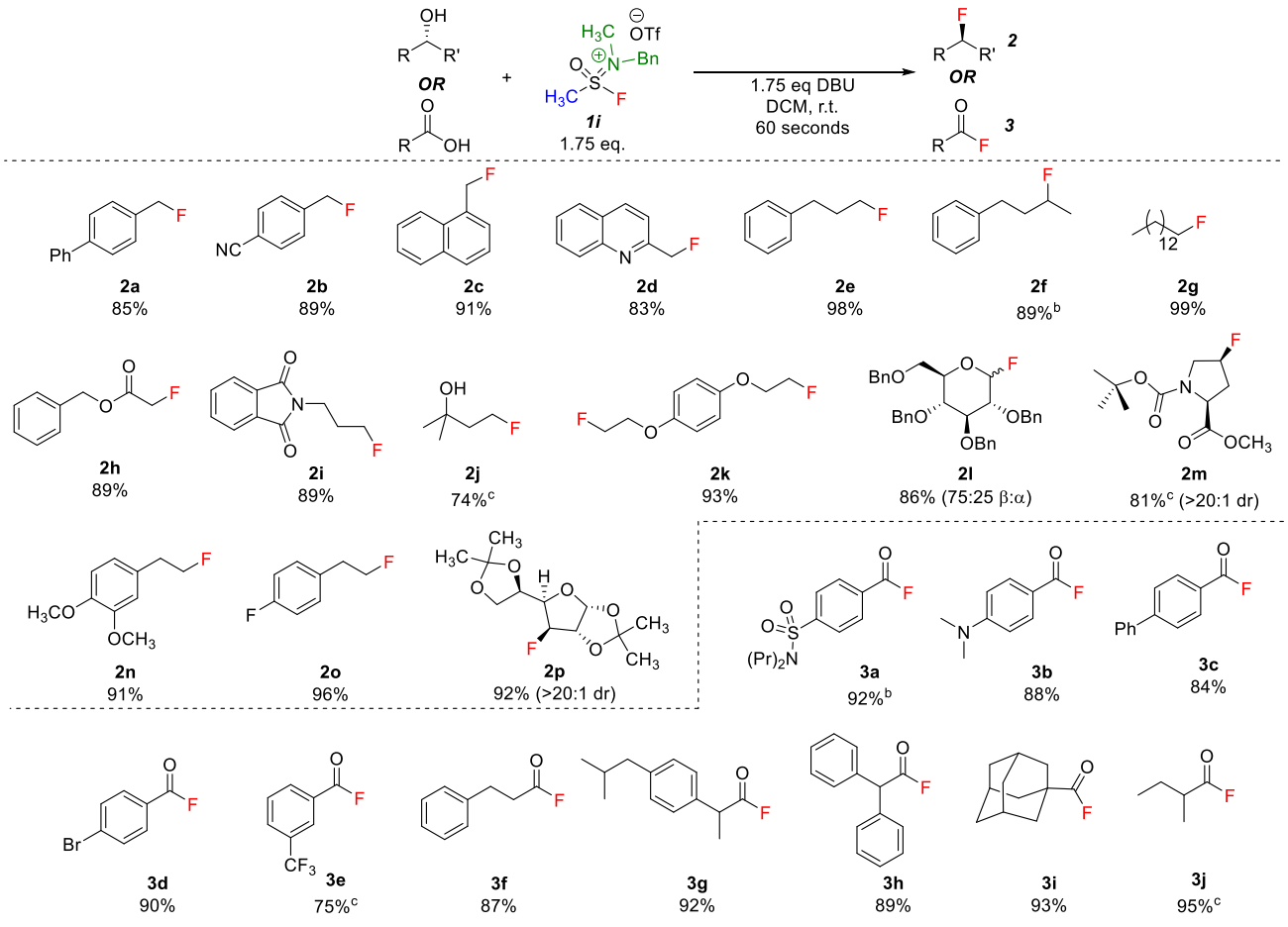
Entry	Reagent	Base	Yield [a]
1	***1a***	DBU	72
2	***1b***	DBU	70
3	***1e***	DBU	87
4	***1f***	DBU	32
5	***1i***	DBU	90
6	***1i***	Pyridine	8
7	***1i***	2,6-lutidine	24
8	***1i***	DMAP	32
9	***1i***	Proton Sponge	86
10	SulfoxFluor	DBU	21
11[b]	***1i***	DBU	>99 (98%)[c]



1i

Condition: [a] 3-phenyl-1-propanol (0.2 mmol), SIF (0.3 mmol), base (0.3 mmol), DCM (2 mL), 22 °C, 60 seconds. [b] 3-phenyl-1-propanol (0.2 mmol), ***1i*** (0.35 mmol), DBU (0.35 mmol), DCM (2 mL), 22 °C, 60 seconds. Yields were recorded by ^{19}F NMR compared to 4-fluoroanisole as internal standard and are the average of two runs. [c] Isolated yield.

Scheme 2. Substrate scope for the deoxyfluorination of alcohols and carboxylic acids using ***1i***. [a]



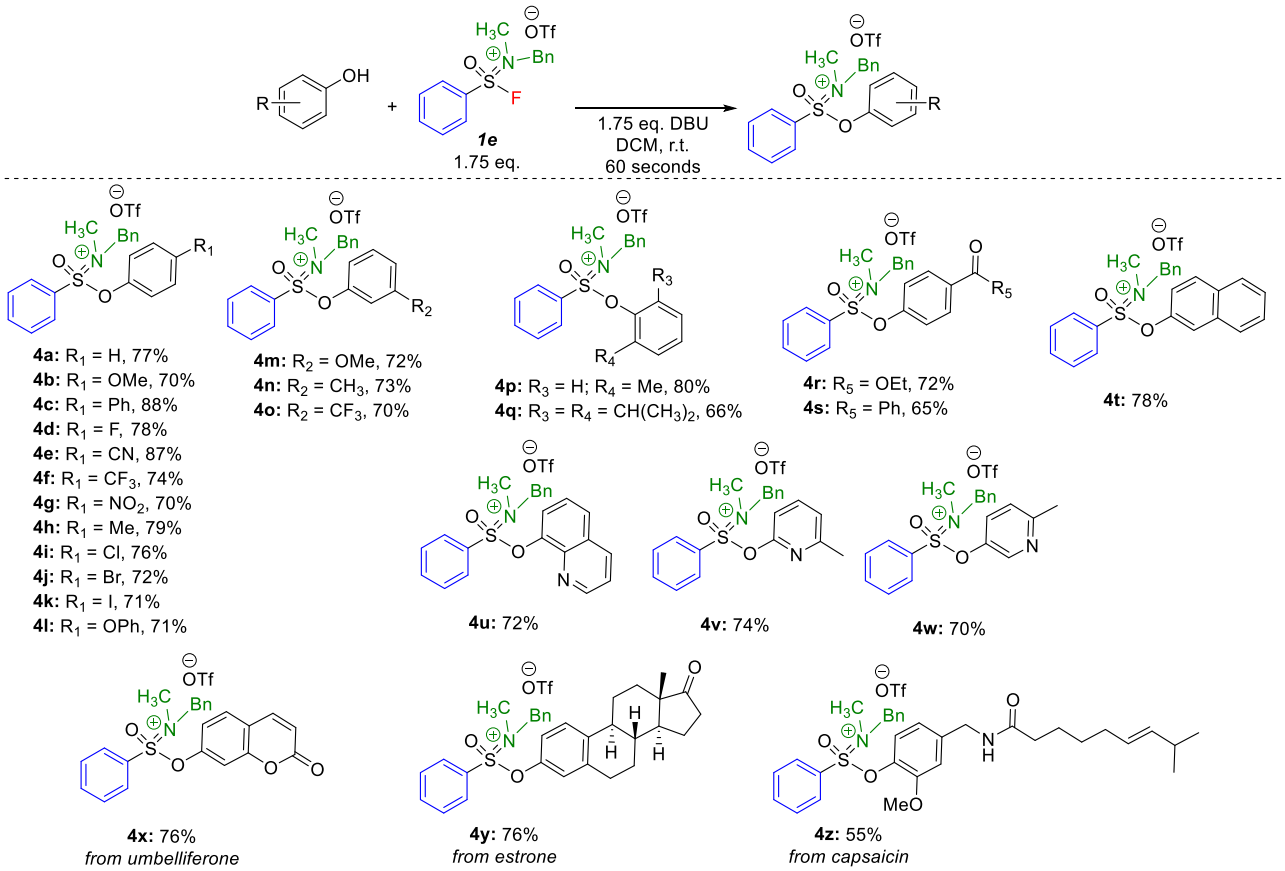
Conditions: [a] alcohol or carboxylic acid (0.2 mmol), **1i** (0.35 mmol), DBU (0.35 mmol), DCM (2 mL), 22 °C, 60 seconds. Isolated yields and reported as the average of two runs. [b] Performed on a 1 mmol scale. [c] Yield determined by ^{19}F NMR compared to 4-fluoroanisole as internal standard.

highly active deoxyfluorination reagent, is dissolved in methanol-d_4, no changes to the ^{1}H or ^{19}F NMR spectra are observed after several hours at room temperature. Taken together, these experiments provided early indications that SIF reagents displayed a high degree of reactivity with oxygen-containing compounds.

Following these encouraging results, the deoxyfluorination of 3-phenyl-1-propanol was used to further benchmark the reactivity of novel SIF reagents. Each compound synthesized in Scheme 1 was screened using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in dichloromethane. Moreover, reactions were conducted at room temperature for only 60 seconds in order to assess the potential for rapid deoxyfluorination. Despite the demonstrated reactivity of SIF reagents with water, reactions were conducted on the benchtop without the need for purified solvents or the exclusion of water. All SIF compounds were active for deoxyfluorination, producing 1-fluoro-3-phenylpropane in varying quantities with those that were most successful included in Table 1. In particular, compound ***1i*** (Entry 5) provided the highest yield of fluorinated product under these initial conditions (90%) and was selected as the SIF reagent to continue optimization. Further probing of reaction conditions showed that other bases were successful at generating alkyl fluoride product (Entries 6 – 9), albeit in decreased yields compared to DBU. By increasing the equivalents of the SIF reagent and DBU to 1.75, a quantitative ^{19}F NMR yield was achieved, along with a 98% isolated yield (Entry 10). Additional comparisons were performed to determine where SIF reagent, ***1i***, ranked among other similar compounds. Interestingly, the sulfonimidoyl fluoride precursor to ***1i*** was completely inactive for deoxyfluorination, demonstrating the need for the final methylation step to generate activated molecules (see SI). Furthermore, SulfoxFluor only provided 21% of fluorinated product after just 60 seconds of reaction time, showing the increased reactivity of the sulfone iminium core.

We then translated these optimized conditions to both aliphatic alcohols and carboxylic acids, attempting to achieve the fastest deoxyfluorination rates for both sets of substrates (Scheme 2). All reactions were performed without the need for rigorous exclusion of water or oxygen, which speaks to the practicality and ease of use of these new reagents. Starting with several substituted benzyl alcohols, ***1i*** was competent at generating monofluoromethyl groups rapidly and in excellent isolated yields (**2a – 2d**). Secondary alcohols were well tolerated with minimal elimination side-products present (<10%) in the case of **2f**. In addition to hydrocarbon substrates, alcohols containing various functional groups could be converted to their fluorine analogues

Scheme 3. Phenol substrate scope for SuFEx reactions using ***1e***. [a]



Conditions: [a] phenol (0.2 mmol), 1e (0.35 mmol), DBU (0.35 mmol), DCM (2 mL), 22 °C, 60 seconds. Isolated yields reported as the average of two runs.

using ***1i***, including esters (**2h**), amides (**2i**), cyclic acetals (**2l** and **2p**) and carbamates (**2m**). Additionally, several of these substrates are biologically related, such as **2l**, **2m** and **2p**. We were pleased to see that the methodology optimized for alcohols was also effective for the conversion of carboxylic acids to acid fluorides without need for further modifications. ***1i*** successfully produced acid fluorides in excellent isolated yields, requiring just 60 seconds to do so. Several substituted benzoic acids could be transformed to benzoyl fluorides (**3a** – **3e**); of particular note, the acid fluoride of probenecid, a treatment for gout, was synthesized in 92% yield (**3a**). In addition to benzoic acids, aliphatic carboxylic acids were also well tolerated (**3f** – **3j**), generating the acyl fluoride derivative of ibuprofen (**3g**) in a 92% yield. Importantly, when SulfoxFluor is used with carboxylic acids under these conditions, no acid fluoride is produced after 2 hours of reaction time. These results represent a marked improvement on other common deoxyfluorination methodologies for aliphatic alcohols and carboxylic acids, providing accelerated reaction rates without compromising on yield.

Finally, we probed how effective these deoxyfluorination conditions would be in SuFEx reactions when utilizing phenols as the oxygen-based nucleophile (Scheme 3). To our delight, employing ***1e*** as the SIF reagent and DBU as the base generated SuFEx products, aryl sulfone iminiumates, in good to excellent yields with a wide range of phenol substrates. A variety of *para* and *meta* substituents are well tolerated (**4a** – **4o**) and large, sterically-hindered groups at the *ortho* position did not diminish yields (**4p** – **4q**). Aryl sulfone iminiumates of quinolines (**4u**) and pyridines (**4v** – **4w**) could also be isolated under these conditions, while several natural products (**4x** – **4z**) proved to be viable substrates for these rapid SuFEx reactions. Overall, these reactions are high yielding, complete in just 60 seconds and require minimal purification while representing an entirely new, charged molecular plug-in to expand SuFEx possibilities.

In summary, we have extended the sulfone iminium core structure to produce novel SIF reagents. With 9 iterations synthesized, it was quickly found that these compounds are highly reactive with oxygen-containing molecules. This inherent reactivity was leveraged into a methodology that could convert aliphatic alcohols into alkyl fluorides and carboxylic acids into acid fluorides in just 60 seconds while still delivering excellent yields. Despite their high level of reactivity, all deoxyfluorination reactions are carried out on the benchtop without the need for specialized solvents or conditions. These reagents were also competent at SuFEx chemistry with phenols as nucleophiles, furnishing aryl sulfone iminiumates as the first instance of charged SuFEx products. The SIF reagents designed here facilitate the fastest deoxyfluorination and SuFEx reactions to date and current work is aimed at expanding their influence to other substrates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental data, characterization data and NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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