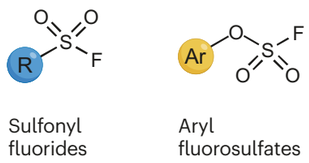
doi: 10.1038/s43586-023-00252-9; Article citation ID: 2023 3:59 For the Primer, visit doi: 10.1038/s43586-023-00241-y

PrimeView
Sulfur fluoride exchange

Click chemistry is a strategy to rapidly synthesize and functionalize molecules. Sulfur fluoride exchange (SuFEx) is a type of click reaction in which a fluoride bonded to a sulfur centre can be exchanged with a nucleophile. The reactions proceed under metal-free conditions, making this transformation favourable to biological systems.

Experimentation

There are a number of considerations to ensure the success of SuFEx chemistry; functional group compatibility, SuFEx catalyst, reaction conditions and practical and safety concerns should be considered. The most common SuFEx substrates are the sulfonyl fluorides ($R–SO_2F$) and aryl fluorosulfates ($Ar–OSO_2F$). SuFEx hubs with sulfonyl fluoride groups conjugated to π-systems provide opportunities for complementary click reactivity, such as conjugate addition and cycloaddition pathways.

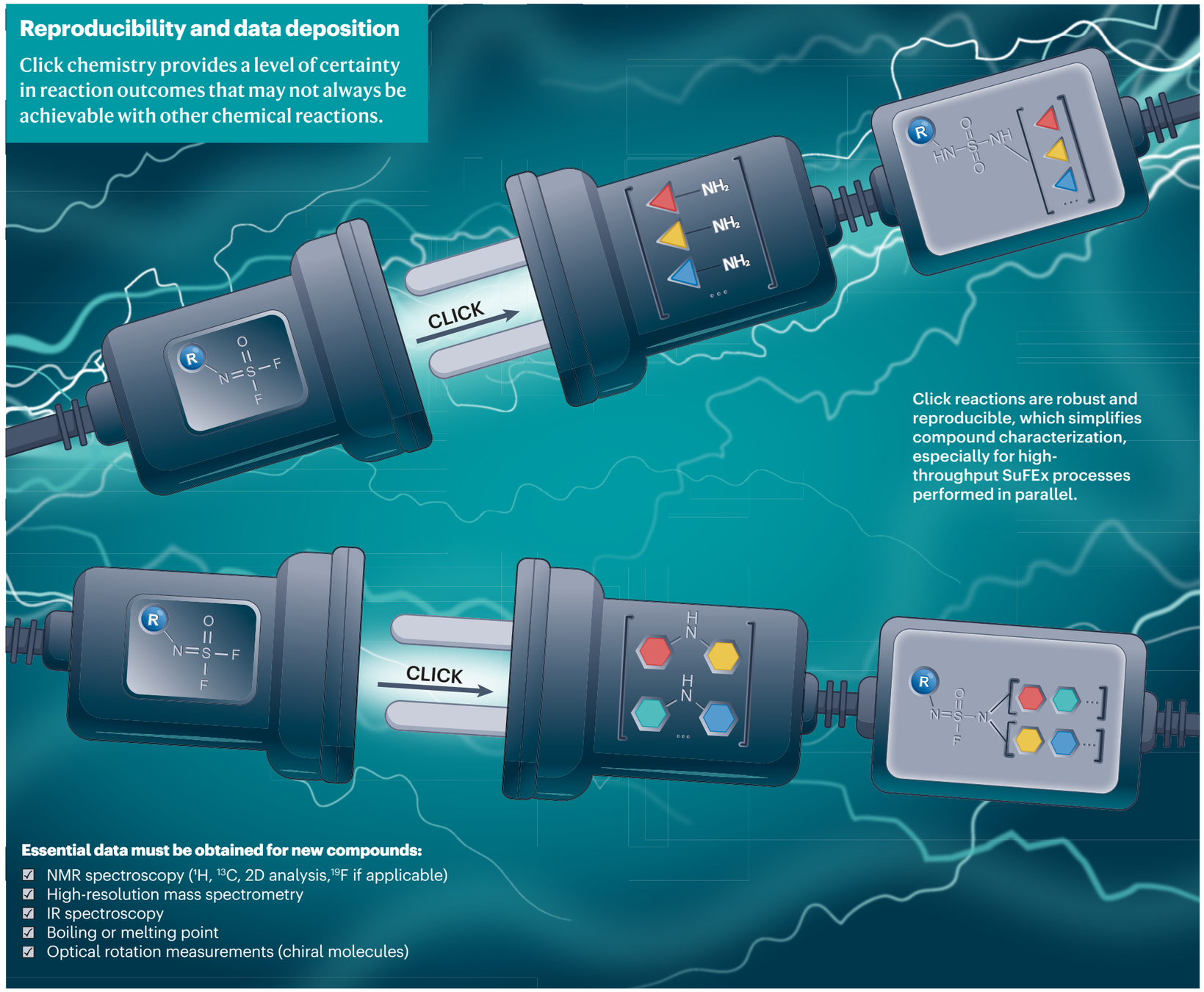


Sulfonyl fluorides | Aryl fluorosulfates

SuFEx catalysts are diverse and include nitrogenous Lewis bases, such as tertiary amines, amidines, phosphazenes and guanidines. The appropriate catalyst and reagent combinations should be selected, taking into account the distinct reactivity exhibited by SuFExable hubs and the nucleophilic partners. Having an insight into the reaction mechanisms can facilitate the design and synthesis of improved catalysts. Generally, the high charge of the central sulfur atom makes it an attractive target for nucleophiles, driving the reaction. Scaling up SuFEx reactions can pose challenges, owing to the high catalyst loading required for certain substrate combinations. Careful consideration and optimization of the reaction conditions are necessary for the successful scale-up and broad applicability of SuFEx reactions. SuFEx reactions are generally conducted using standard organic chemistry equipment. One-pot protocols offer an increase in atom economy and a reduction in both the time and consumables required for a given chemical transformation. Reactions are monitored using thin-layer chromatography and/or liquid chromatography–mass spectrometry.

Reproducibility and data deposition

Click chemistry provides a level of certainty in reaction outcomes that may not always be achievable with other chemical reactions.



Essential data must be obtained for new compounds:

- ☑ NMR spectroscopy (^1H, ^{13}C, 2D analysis, ^{19}F if applicable)
- ☑ High-resolution mass spectrometry
- ☑ IR spectroscopy
- ☑ Boiling or melting point
- ☑ Optical rotation measurements (chiral molecules)

Applications

In drug discovery, combinatorial libraries with SuFEx-derived S–O or S–N linkers have yielded nucleoside mimics, antivirals and anti-insect agents with improved potency. SuFExable compounds can also become potential diagnostic tools by substituting the natural-occurring fluorine-19 nuclide with a positron-emitting fluorine-18 nuclide; positron-emission tomography imaging is widely used for early diagnosis of cancer and neurodegenerative diseases. In materials science, SuFEx can be used to add functionality and chirality to polymers. Furthermore, SuFExable compounds are ideal as activity-based probes, owing to their hydrolytic stability and chemoselective reactivity.

Limitations and optimizations

Challenging substrate combinations often require high catalyst loading and harsher reaction conditions. An enhanced understanding of the SuFEx mechanism will guide the design of next-generation catalysts that can reduce catalyst loadings and improve reaction conditions. Furthermore, the synthesis of SuFEx hubs often involves the handling of toxic, gaseous reagents. Using flow setups or non-gaseous surrogate reagents could improve the safety and practicality of preparing SuFEx hubs and facilitate broader adoption of SuFEx chemistry.

Outlook

It is likely that SuFEx will play a critical role in drug discovery and other areas of chemical research. For example, SuFExable warheads could advance covalent drug development, owing to the unique properties of S–F functional groups. Future work should focus on the stereoselective generation of 3D motifs to create molecules with unique physical and pharmacokinetic properties.

Written by Natalie Barnes; designed by Steven Hall; based on Homer et al. (2023)