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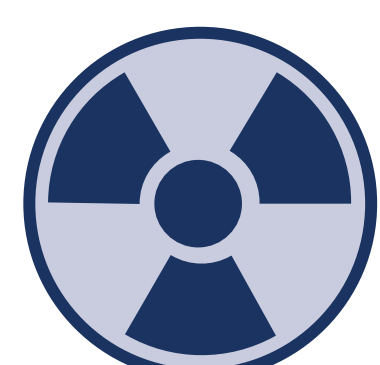
Why fluorine?



Enhancing lipophilicity and bioavailability of **drugs**



Robust **materials** with unique properties



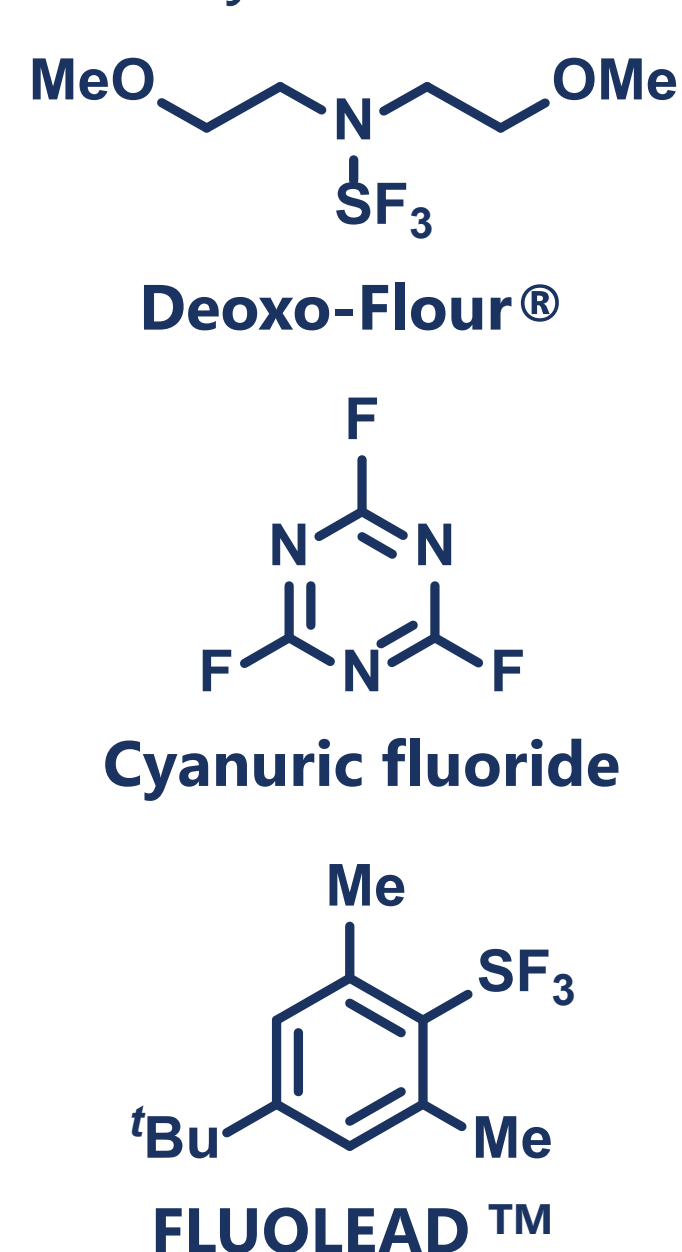
Radioactive labeling for **medicinal diagnosis**

State of the art

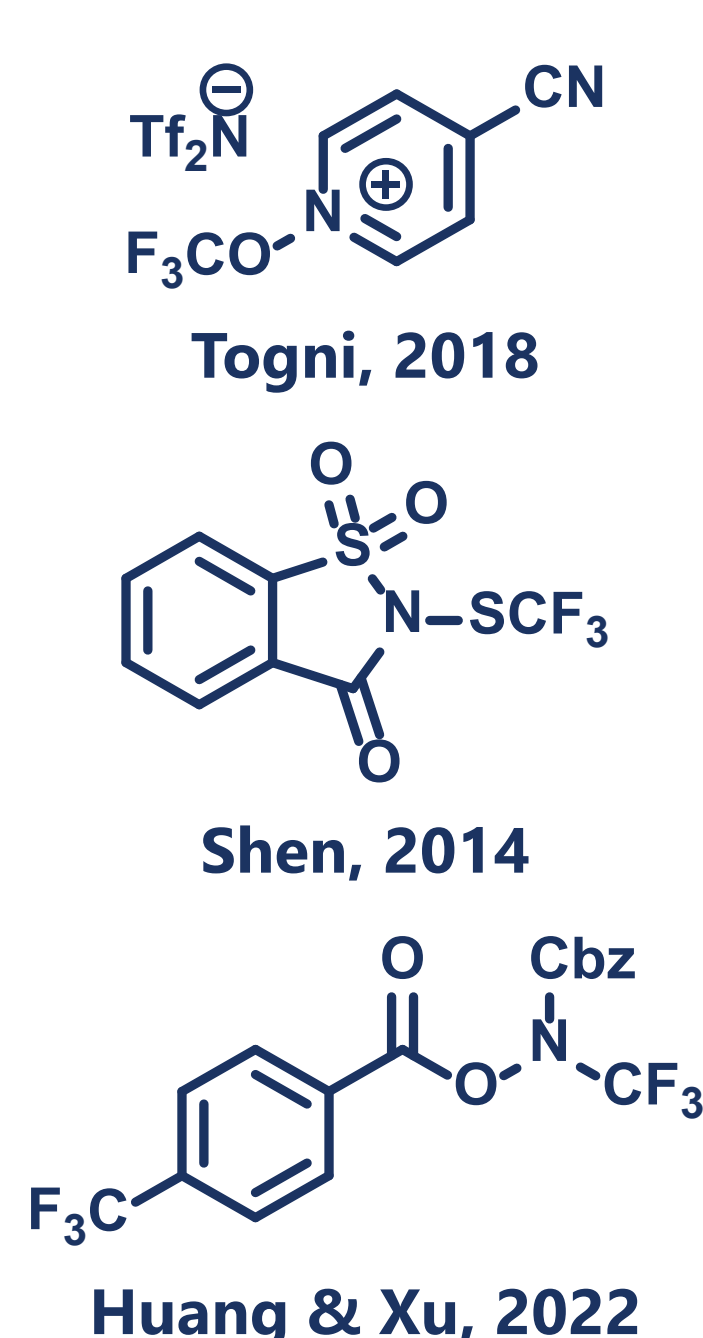
SuFEx handle installation



Carboxylic acid deoxyfluorination



CF₃-heteroatom motif installation

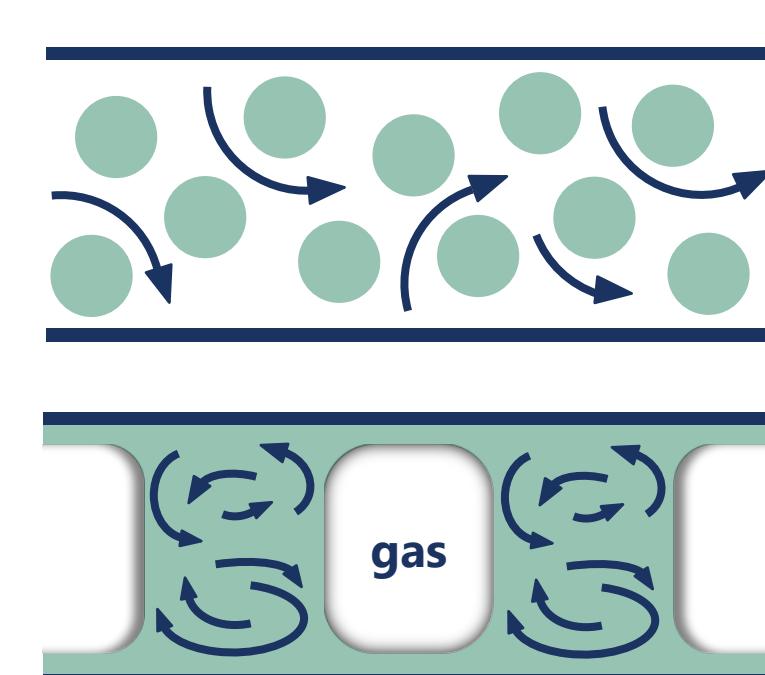


• Atom-inefficiency • High-cost • Low functional group compatibility • Moisture sensitivity

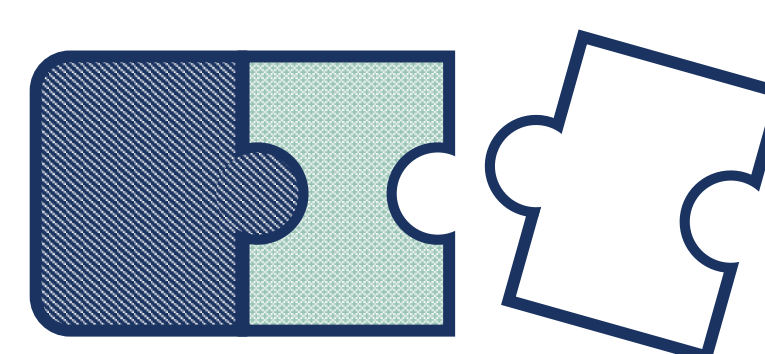
Our concept



Bulk chemicals as **cheap starting material**



Flow technology enables **efficient contact between phases**



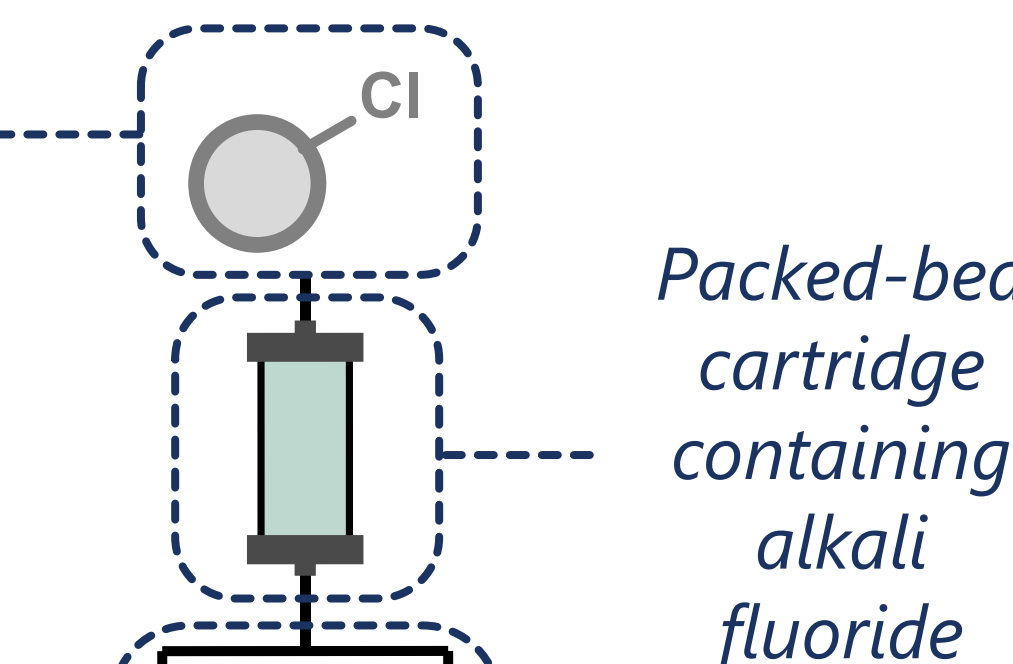
Modularity of the setup ensures high flexibility

Commodity chemicals

Reactive fluorinated reagent or building block

Reaction with higher-value substrate as the limiting reagent

In-line derivation of products rapidly elaborates the structure

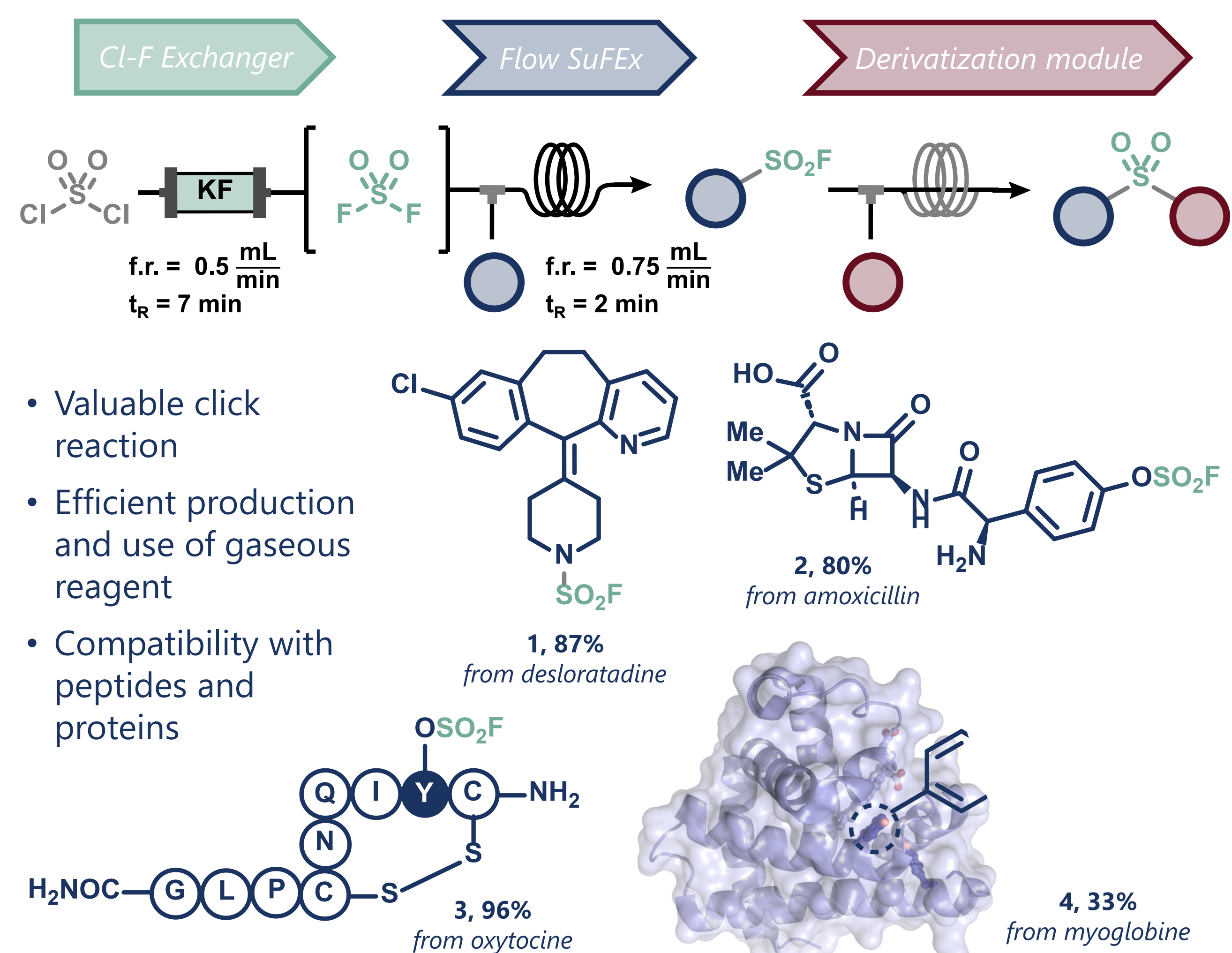


Path A Path B

Packed-bed cartridge containing alkali fluoride

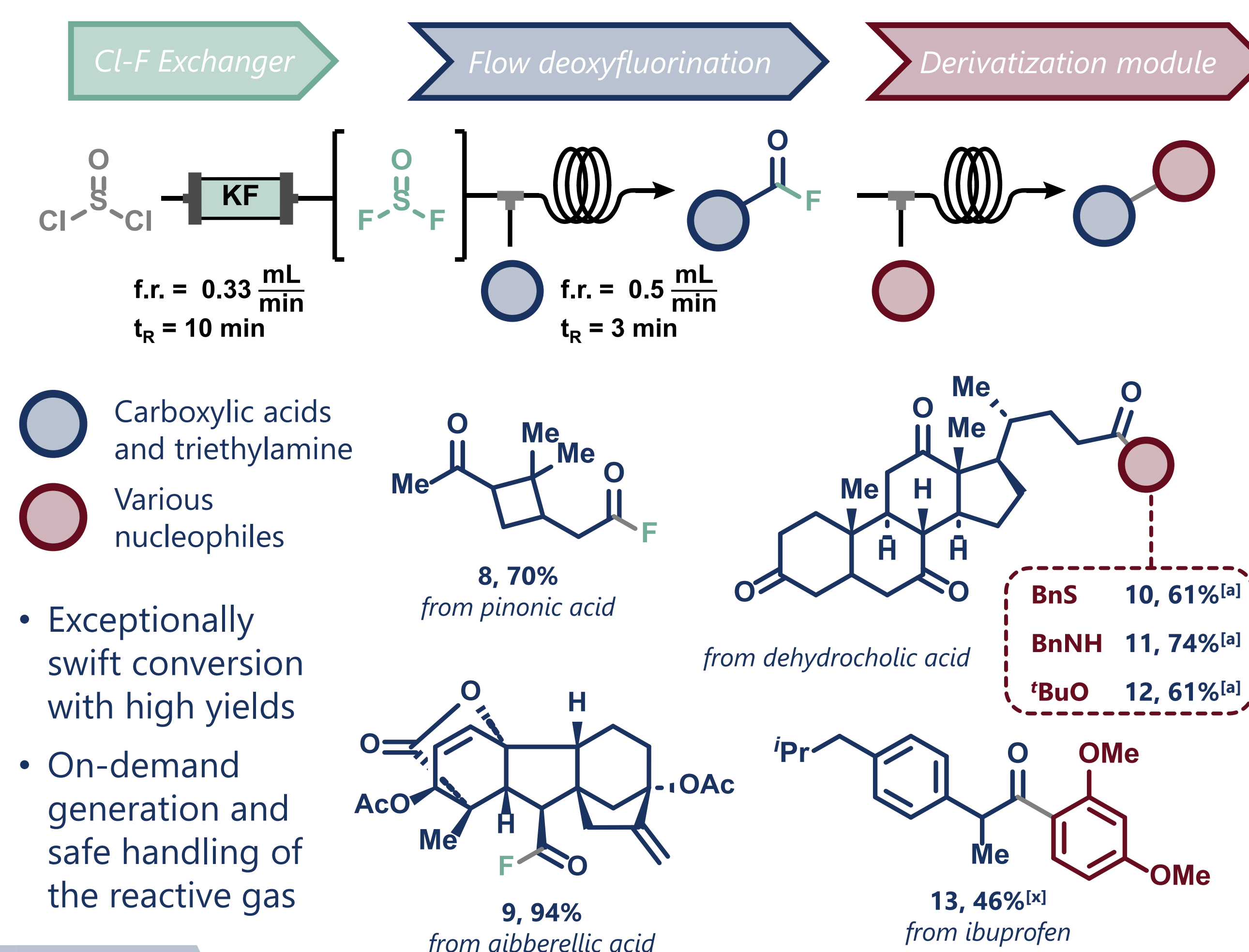
Alternative fed-batch approach broadens the method's applicability

Modular SuFEx reactor



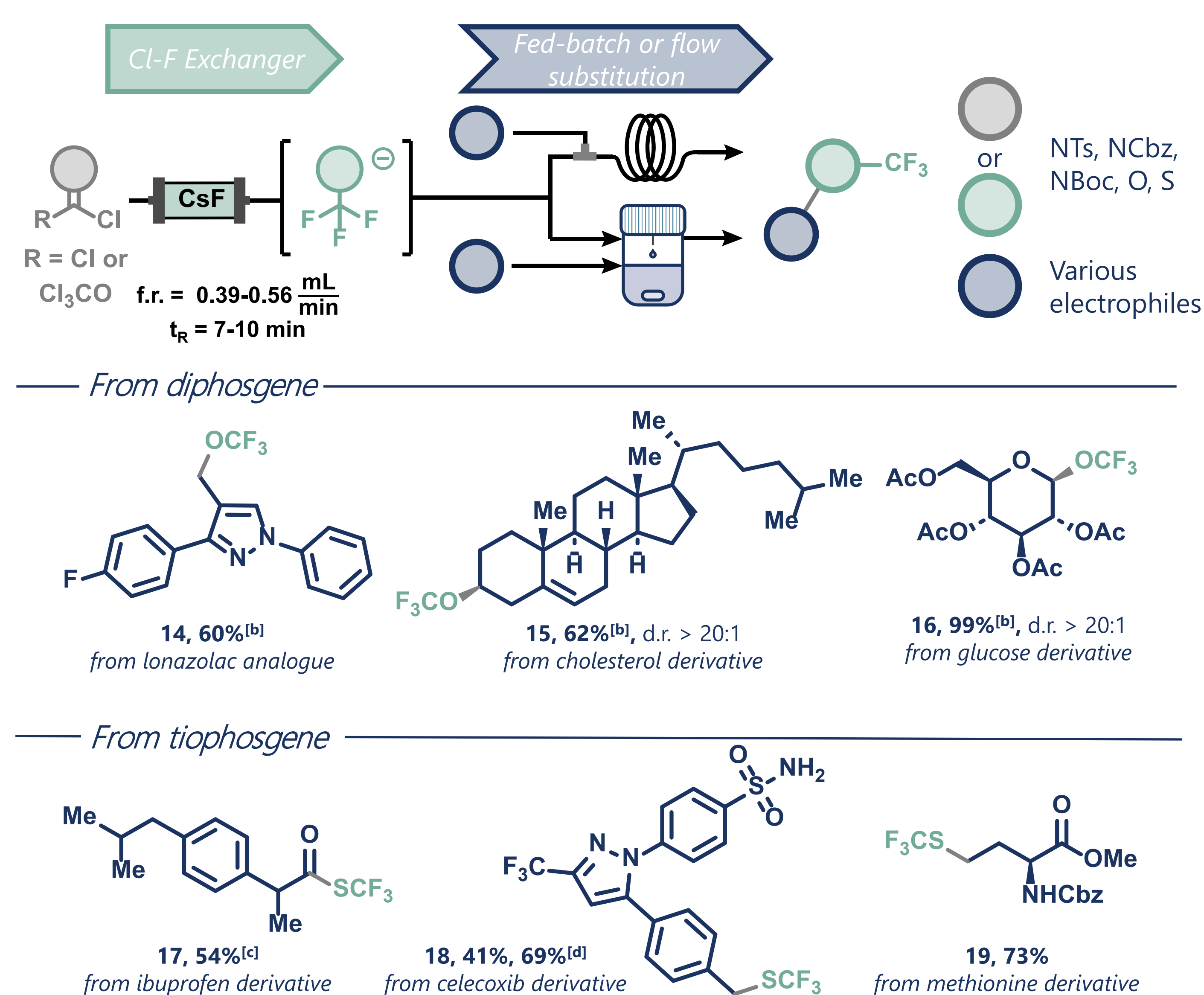
Small molecules: Nucleophile solutions (0.2-0.1 M) made in MeCN, DMF or DMSO with Et₃N or DBU (2.5-5 equiv) as activator; 2 equiv of 0.2 M SO₂Cl₂ in MeCN used. Peptides: Peptide solutions (3-10 mM) made in MeCN : water (1:1) with Et₃N (6 equiv); 40-133 equiv of 0.2 M SO₂Cl₂ in MeCN used. Proteins: Protein solutions (5-10 mM) made in aqueous buffers (acetate or Tris; 5-10 mM; pH = 5-7.7) with TMG (1-10 equiv); 2.2-11 equiv of 0.1 M SO₂Cl₂ in MeCN used.^(a)Over two steps.

Access and utilization of acyl fluorides



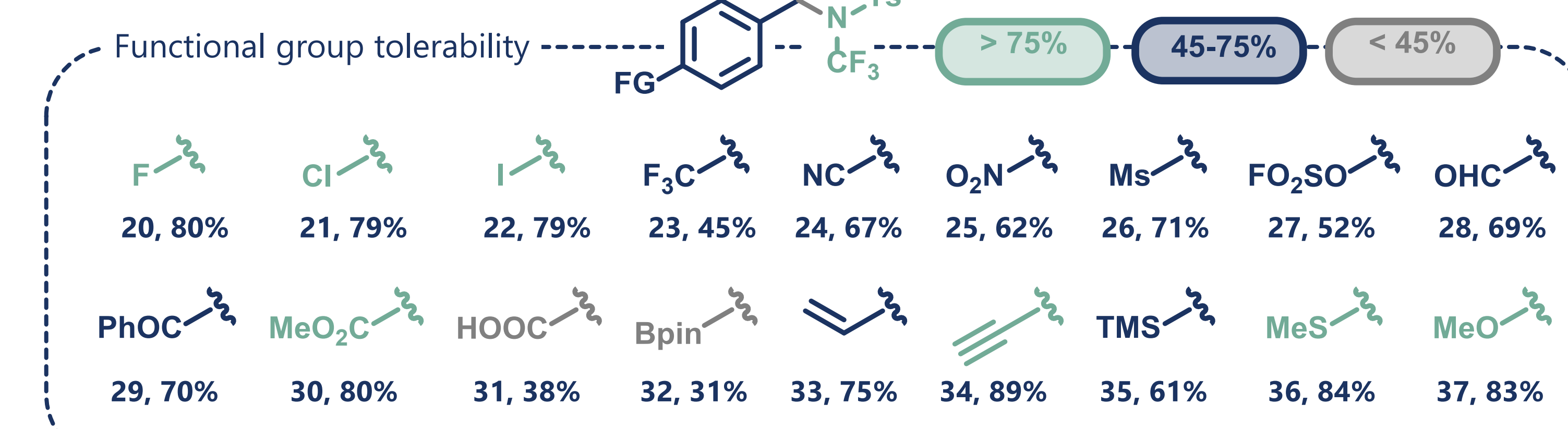
0.2 M solution of thionyl chloride in MeCN. Carboxylic acids solutions (0.2 M) were prepared in MeCN or DMF with Et₃N (3 equiv); 2 equiv of 0.2 M SO₂Cl₂ in MeCN used. For isolation and characterization purposes, acyl fluoride solution was treated with N-hydroxy phthalimide (1.05 equiv). Unless specified otherwise, reported yields refer to corresponding esters.^(a)Over two steps.

Nucleophilic introduction of CF₃-heteroatom groups



• High atom economy
• Safe handling of toxic reagents
• Straightforward access to coveted N-CF₃ motif

From N-protected imidoyl dichlorides



Solutions of CF₃X precursors prepared in MeCN (0.1 M) with 18-crown-6 (1 equiv). Unless stated otherwise, solution of CsCF₃ salts collected in a vial (2-4 equiv) appropriate electrophile (corresponding bromides, iodides, chlorides, or mesylates, 0.2 mmol, 1 equiv). Stirred at given temperature (rt. - 80 °C) for full details of reaction conditions refer to SI of the preprint.^(a)AgOTf (1.1 equiv) used; ^(b)TMSCl (3 equiv) used; ^(c)telescoped process; ^(d)performed in batch.

References

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