Your specialist in fluoroalkylation
CF Plus Chemicals is an ETH Zurich spin-off founded in 2014 in Brno, Czech Republic, focusing on life science applications of fluoroorganic chemistry.

Our mission is to make fluoroalkylation a widely used tool for effective modification of a complete scope of molecular targets, spanning from small molecules to large molecules - unlocking the full potential of drug candidates and enabling effective bioconjugation of biologically relevant entities.

In small molecule research, the company envisions to help their customers open new, hitherto unexplored chemical space in medicinal chemistry with reagents that are easy to use.

Our goal is to deliver, and help to deliver, better and cost-effective solutions for development of cures of devastating human diseases.

Dr. Václav Matoušek, CEO and founder

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Fluoroalkylation portfolio

Togni perfluoroalkyl reagents

The so-called Togni reagents have over the last years become a standard tool that provides expedient access to trifluoromethylated and perfluoroalkylated compounds important for drug and pesticide discovery programs. In many cases, these reagents operate via trifluoromethyl or perfluoroalkyl radicals as the key reactive intermediates.

For a review, see: *Chem. Rev.*, 2015, 115, 650

Chemical space opened by Togni-perfluoroalkyl reagents:
Other hypervalent iodine reagents

Cyclic hypervalent iodine reagents with increased hydrolytical and thermal stability have been described as mild and conveniently handled electrophilic chlorination, fluorination and azidations reagents. The shelf-stable fluoroiodane reagent allows to perform elegant fluorinative functionalisations and fluorocyclisations of olefins under mild conditions, while the azidoiodane reagent can be used to as a formally electrophilic azidation reagent for azidation of enolates.
F lu o r o a l k y l a t i o n p o r t f o l i o  |  5

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\begin{align*}
&\text{R} \equiv \\
&\text{or} \\
&\text{Nu} \equiv \text{R} \\
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\end{align*}
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Nu =
- enolates
- olefins

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Togni - CF$_2$CF$_2$R reagents

The second generation of Togni reagents ("extended Togni reagents") incorporate substituted tetrafluoroethyl groups instead of plain perfluoroalkyls. With essentially similar reactivity patterns as the original CF$_3$-analogues, many types of transformations that work well with CF$_3$-Togni reagents can be done with these reagents as well, providing access to rare and potentially attractive fluorinated chemical space.

**With a set of „extended Togni reagents“ in hand, the lead compound can be diversified in the last stage of the synthesis to afford the hard-to-access fluoroalkyl-decorated derivatives.**

The azole-substituted —CF$_2$CF$_2$— „extended Togni reagents“ engage in a radical cyclisation reaction with olefins and acetylenes giving access to rare tetrafluorinated heterocycles. The incorporation of a —CF$_2$CF$_2$— moiety into a cyclic structure imparts the molecule a unique combination of properties called „polar hydrophobicity“ – a permanent dipole combined with the solvophobic behaviour of the tetrafluoroethylene unit.

![Alcohol-type reagent](image1.png)

![Acid-type reagent](image2.png)

Late stage introduction of —CF$_2$CF$_2$R moieties into molecules

Access to tetrafluorinated di- and tetrahydro(benz)imidazopyridines
Ref: *Org. Lett.*, 2016, 18, 756
Chemical space opened by Togni-CF₂CF₂R reagents:
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Fluoroalkyl bromides

Substituted fluoroalkyl bromides turn into powerful nucleophilic fluoroalkylation reagents after being metallated with isopropylmagnesium chloride-lithium chloride complex (Turbo-Grignard). The in-situ generated fluoroalkylmagnesium chloride intermediate is moderately stable up to -40 °C and can be efficiently trapped with various electrophiles to afford the $\text{--CF}_2\text{CF}_2\text{--}$ linked products.

Ref: Org. Lett., 2016, 18, 5844

Chemical space opened by the fluoroalkylmagnesium chemistry:
Fluoroalkyl silanes

Substituted fluoroalkyl silanes serve as traditional nucleophilic sources of the fluoroalkyl synthon. Upon activation with catalytic fluoride or alkoxide, they can fluoroalkylate a range of aldehydes, reactive ketones or iminiums. The silanes can also engage in transition-metal catalyzed formation of R-CF₂CF₂ substituted aromatics.
**Tetrafluoropropionates**

β-Substituted caesium tetrafluoropropionates are convenient starting materials for construction of fluoroalkyl carboxamides. The pKa values of such amide groups are significantly lower than their non-fluorinated counterparts, offering potential to modulate the behaviour of drug candidates.

![Chemical structures](image)

The caesium salts can be easily handled on air due to their reduced hygroscopicity compared to the highly hygroscopic free carboxylic acids.
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**Chemical Structures:**

1. ![Structure 1](image1)
2. ![Structure 2](image2)
3. ![Structure 3](image3)
4. ![Structure 4](image4)
5. ![Structure 5](image5)
6. ![Structure 6](image6)
7. ![Structure 7](image7)
8. ![Structure 8](image8)
9. ![Structure 9](image9)
10. ![Structure 10](image10)
Fluoroalkylsulphonyl fluorides

Fluoroalkylsulphonyl fluorides can be used as moderately reactive electrophilic fluoroalkylsulphonylation reagents. Whereas the related fluoroalkylsulphonyl chlorides can also behave as electrophilic chlorination reagents towards amines affording undesirable $N$-chloroamines, the fluoroalkylsulphonyl fluorides give slower, yet very clean nitrogen sulphonylation to give the corresponding sulphonamides.

Fluoroalkylsulphonylation of the amine nitrogen greatly lowers the pKa value of $\text{NH}$ group and can be used to modulate the behaviour of the drug candidate or build additional molecular complexity around the highly acidic fluoroalkylsulphonamide nitrogen.
**Fluoroalkylazides**

Trifluoromethylazide, pentafluoroethylazide, difluoromethylazide and trifluoroethylazide represent four examples of exotic fluoroalkylazides that are potentially very attractive for medicinal chemistry and agrochemistry discovery programmes. Generally, fluoroalkylazides show much higher thermal stability than their alkyl counterparts, resulting in a good safety profile. Using the well-established copper catalyzed alkyne-azide cycloaddition, various alkynes can be reacted with trifluoromethylazide or pentafluoroethylazide affording regioselectively the 1,4-disubstituted N-CF₃ or N-C₂F₅ triazoles that would be otherwise very hard to access. N-trifluoromethylated azoles have been shown to be robust alternatives to potentially metabolically weak N-methyl analogues.

![Chemical structures](image)

Straightforward and regioselective access to rare N-CF₃ and N-C₂F₅-1,4-disubstituted triazoles

Later, Beier et al. demonstrated that the triazoles prepared by copper catalyzed azide-alkyne cycloaddition can be transformed into a plethora of hitherto unreported five-membered N-(per)fluoroalkyl heterocycles using the Rh-carbene chemistry.

Conversion of fluoroalkyl triazoles to N-fluoroalkyl heterocycles using Rh-carbene chemistry
Ref: Chem. Commun., 2018, 54, 3258

Very recently, the same group showed that N-fluoroalkyltriazoles can undergo chemoselective and regioselective Rh-catalyzed [4+3] annulation with 1,3-dienes, providing access to otherwise hardly accessible N-fluoroalkyl azepines.

Difluoromethylazide shares practically the same reactivity as trifluoromethylazide in copper catalyzed alkyne-azide cycloadditions, providing expedient access to five-membered N-CF3H heterocycles. Difluoromethylazide provides similar synthetic benefits as other fluoroalkylazides – a broad substrate scope of regiochemically defined N-difluoromethylazoles can be accessed in a much simpler manner than with other synthetic routes.
Besides the established copper catalyzed alkyne-azide cycloaddition, difluoromethylazide was shown to undergo an enamine mediated azide-ketone [3+2] cycloaddition, affording the corresponding N-CF₂H triazoles.

\[
\text{HCF}_2\text{N}_3 \xrightarrow{\text{cat. Cu(I), rt}} \text{R}^1\equiv\text{R}^2 \xrightarrow{\text{cat. pyrrolidine, rt}} \text{R}_1\text{N}-\text{N}^\equiv\text{CF}_2\text{H}\text{R}_2
\]


3,3,3-Trifluoroethylazide represents a complementary fluorinated azide that can be used to access N-trifluoroethylated triazoles in a regioselective fashion using the established copper catalyzed azide-alkyne cycloaddition.
Difluoromethylation reagents

N-Difluoromethyltributylammonium chloride is an effective source of difluorocarbene for difluoromethylation of O-, S-, N-, C- centred nucleophiles under mild conditions. Using only 1.2 equivalent of this reagent, difluoromethylated products can be obtained in moderate to excellent yields under mild conditions.


Trifluoromethoxylation reagents

4-Cyano-N-trifluoromethoxypyridinium bis(trifluoromethanesulfonfyl)imide acts as a formally electrophilic trifluoromethoxylation reagents operating via trifluoromethoxy radical as the key intermediate, enabling for example direct C-H trifluoromethoxylation of aromatics and heteroaromatics.

Ref: Angew. Chem. Int. Ed. 2018, 57, 13784
Bioconjugation portfolio

Protein crosslinkers

Protein cross-linkers are chemical reagents that play an important role in immunotechnology, structural biochemistry and biology. Protein cross-linking agents can be used to elucidate protein structure and study various protein-protein interactions. Formation of stable covalent bonds between reactive groups contained in protein framework allows easy identification of spatially close domains. The cross-linked conjugates can be identified for example by mass-spectroscopy.

- **PCL001**
  - CAS: 79642-50-5

- **PCL002**
  - CAS: 68528-80-3

- **PCL003**
  - CAS: 23024-29-5

- **PCL004**
  - CAS: 4856-87-5

- **PCL005**

- **PCL006**
The urea-based MS-cleavable crosslinkers are based on the concept pioneered by Prof. Dr. Andrea Sinz of the Halle University. (Ref.: *Anal. Chem.*, 2010, 82, 6958 and *Rapid Commun. Mass Spectrom.*, 2011, 25, 155)

The ureido-4,4’-dibutyric acid bis(hydroxysuccinimide) ester, also known as DSBU or BuUrBU (PCL008), is the first described, longest version of MS-cleavable urea-based lysine-lysine reactive homobifunctional cross-linkers, featuring a C4-arm. At neutral or slightly basic pH, it irreversibly crosslinks the neighbouring lysine groups. The presence of the symmetrical urea moiety which is prone to collision-induced dissociation allows to perform unambiguous distinguishing of crosslinks in tandem CID-MS experiments. Another advantage of these crosslinkers is that the energy required for cleavage of the central urea unit lies approximately in the same region as the energy required to cleave the peptide bonds. Therefore, this feature enables to simultaneously observe both the characteristic doublets arising from the central urea cleavage as well as the typical fragmentation patterns of the peptide backbone.

The shorter C3-arm (PCL007) and C2-arm (PCL006) version extend the toolbox of these reagents and enable proteomic researchers to get a much deeper proteome XL-MS information than was previously possible.
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Speciality chemicals

Dihydroisoquinolines

Substituted dihydroisoquinolines serve as useful entry points to synthesis of enantiopure tetrahydroisoquinolines by asymmetric hydrogenation, for example by the established enantioselective Ru-catalyzed transfer hydrogenation pioneered by Noyori et. al. Furthermore, the imine moiety of the dihydroisoquinolines can be oxidized to the corresponding nitrones which undergo a (3+2) cycloaddition with a range of olefins and acetylenes.

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Azide building blocks

We offer a selection of azide building blocks for synthesis.
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AZ002
CAS: 18523-47-2

AZ003
CAS: 79583-98-5

AZ005
CAS: 51453-79-3

AZ006
CAS: 66761-27-1

AZ007
CAS: 79598-53-1
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