CF PLUS CHEMICALS

Novel fluorinated chemical space

…simply delivered

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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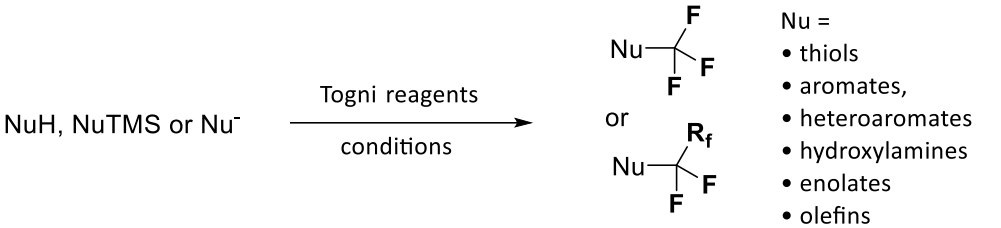
Fluoroalkylation portfolio

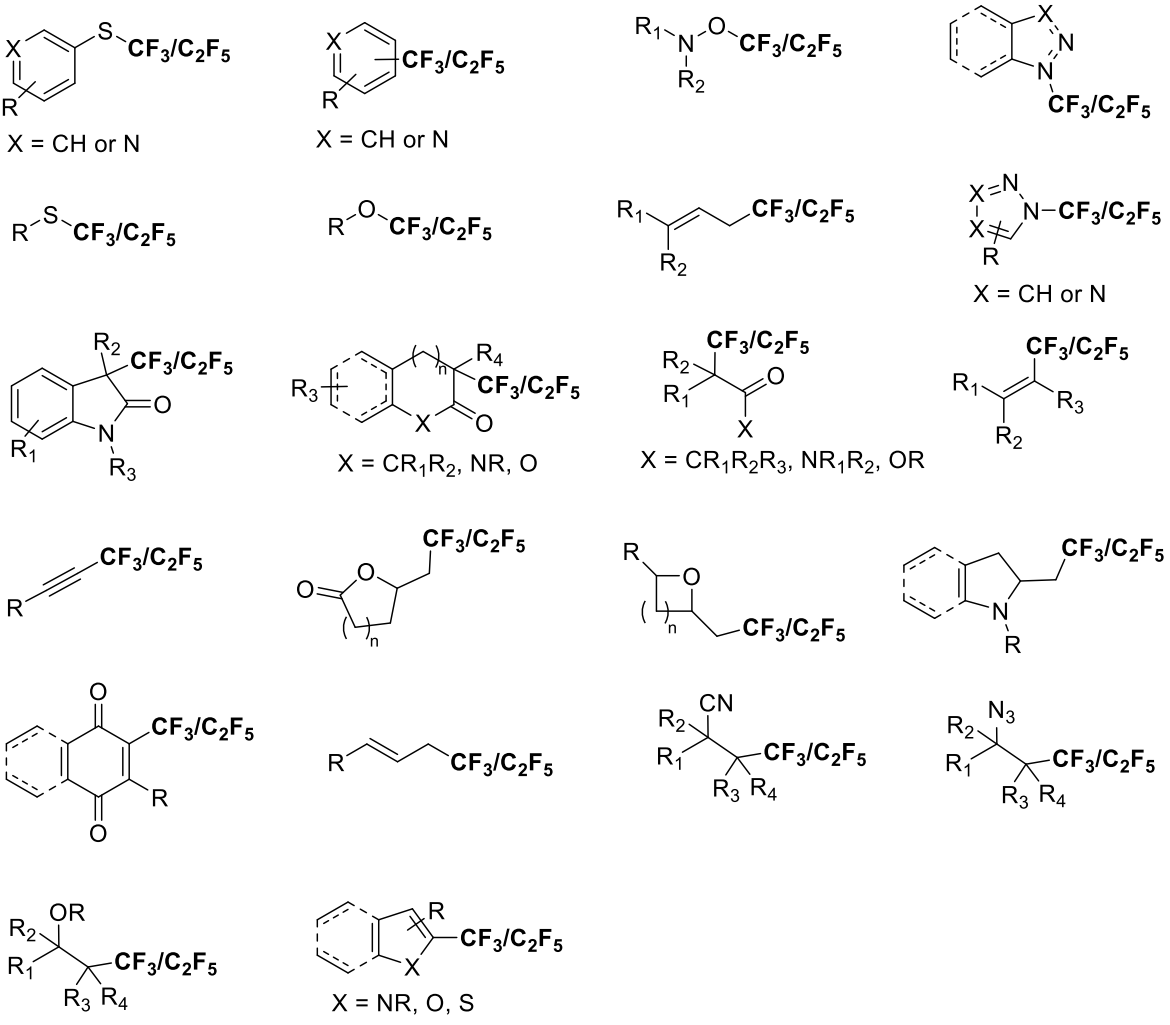
Togni perfluoroalkyl reagents

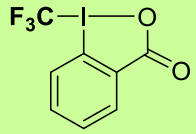
The so-called Togni reagents have over the last years become a standard tool that provides expedient access to trifluoromethylated and perfluoroalkylated compounds important for drug and pesticide discovery programs. In many cases, these reagents operate via trifluoromethyl or perfluoroalkyl radicals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



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

Chemical space opened by Togni-perfluoroalkyl reagents:





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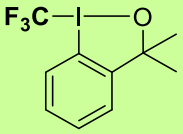

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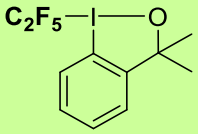

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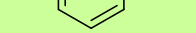

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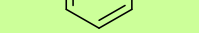
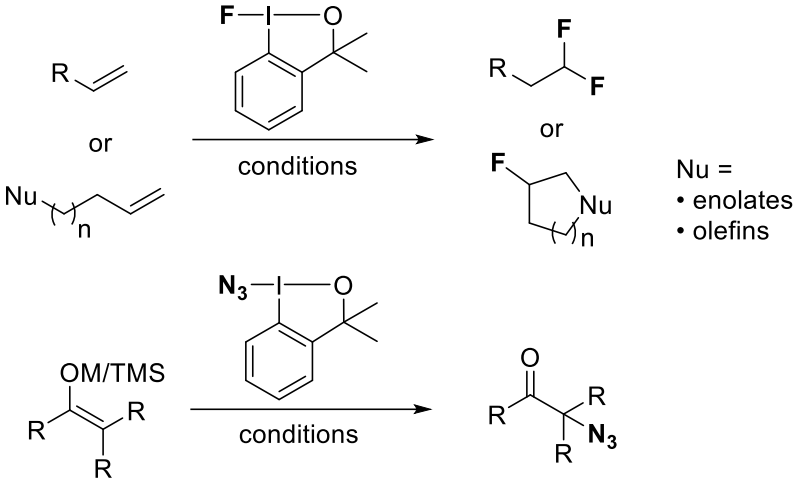


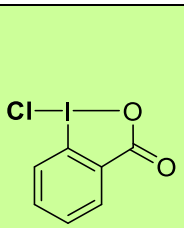
HYP034

CAS: N/A

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.





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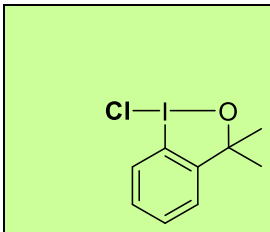

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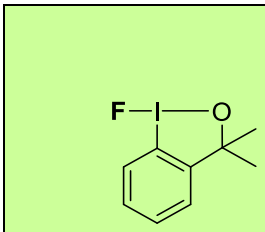

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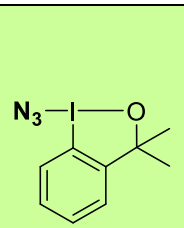


HYP007

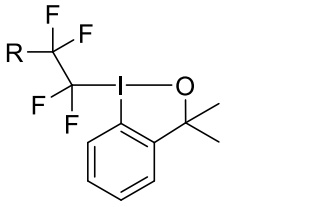
CAS: 175786-57-9

Togni - CF_2CF_2R reagents

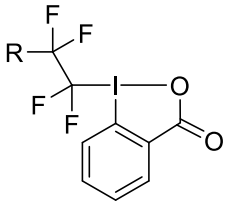
The second generation of Togni reagents („extended Togni reagents“) incorporate substituted tetrafluoroethyl groups instead of plain perfluoroalkyls. With essentially similar reactivity patterns as the original CF_3-analogues, many types of transformations that work well with CF_3-Togni reagents can 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.

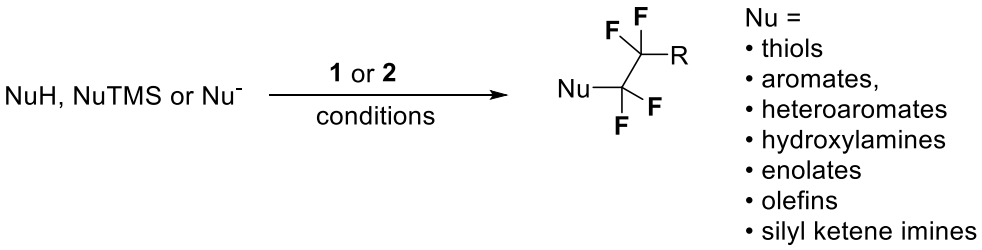
The azole-substituted —CF_2CF_2— „extended Togni reagents“ engage in a radical cyclisation reaction with olefins and acetylenes giving access to rare tetrafluorinated heterocycles. The incorporation of a —CF_2CF_2— moiety into a cyclic structure imparts the molecule a unique combination of properties called „polar hydrophobicity“ – a permanent dipole combined with the solvophobic behaviour of the tetrafluoroethylene unit.



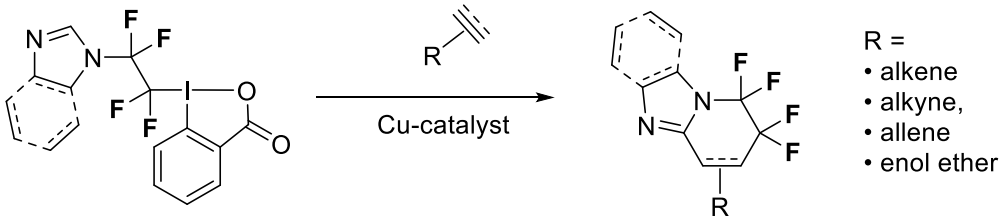
1
Alcohol-type reagent



2
Acid-type reagent

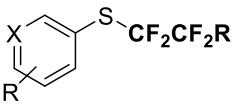


Late stage introduction of —CF_2CF_2R moieties into molecules
Ref: *Chem. Eur. J.*, **2016**, *22*, 417–424; Patent WO2016019475A1



Access to tetrafluorinated di- and tetrahydro(benz)imidazopyridines
Ref: *Org. Lett.*, **2016**, 18, 756

Chemical space opened by Togni-CF_2CF_2R reagents:



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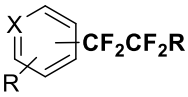

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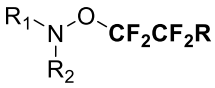

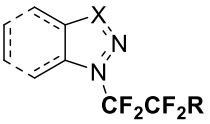

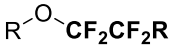

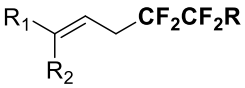

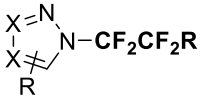

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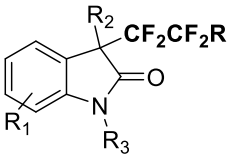

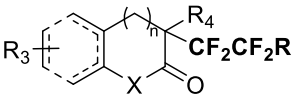

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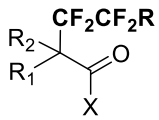

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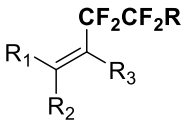

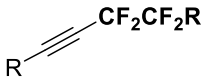

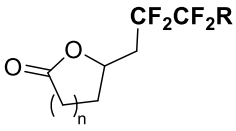

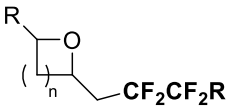

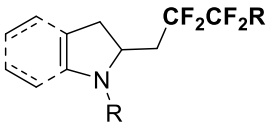

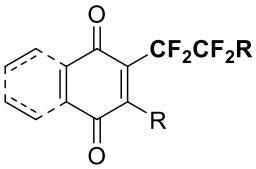

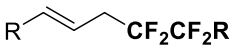

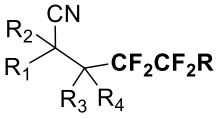

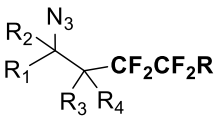

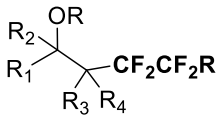

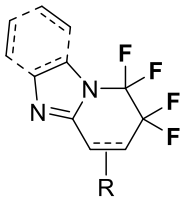

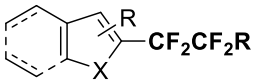

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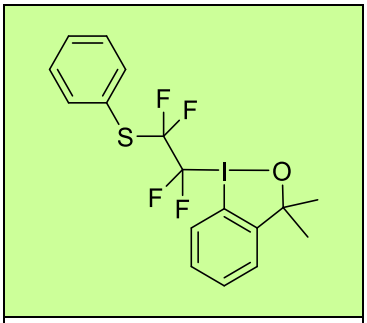

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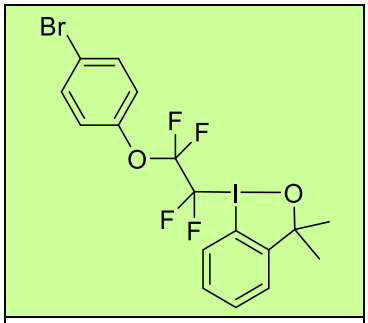

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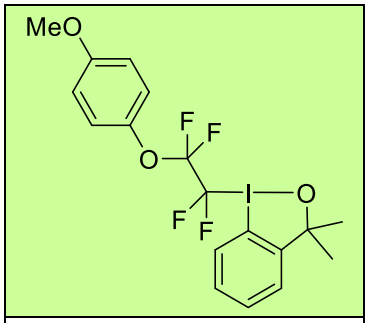

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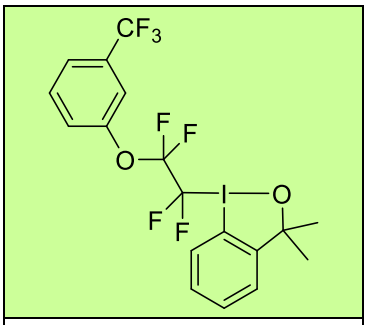

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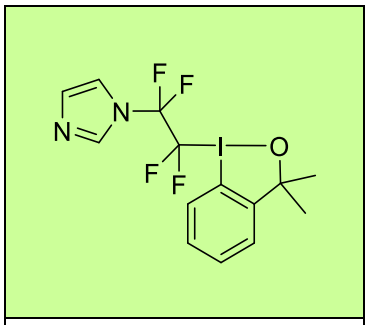

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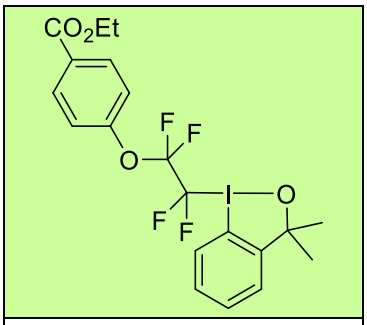

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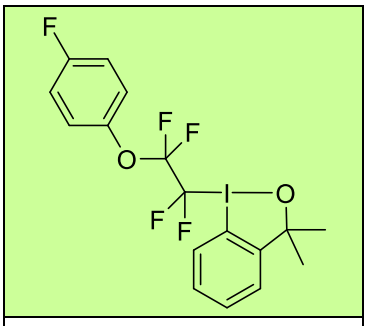

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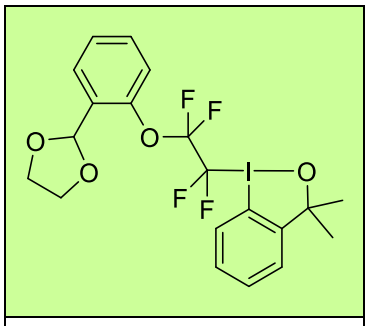

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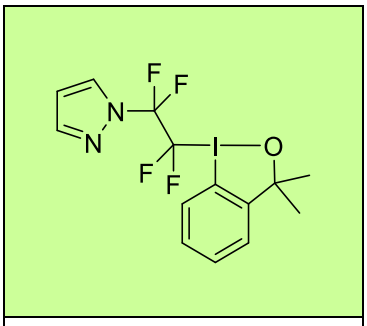

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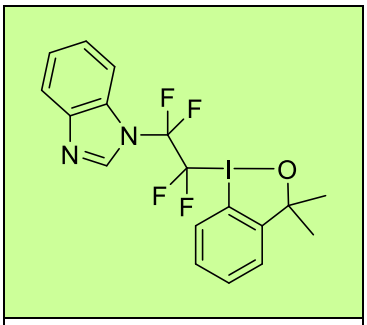

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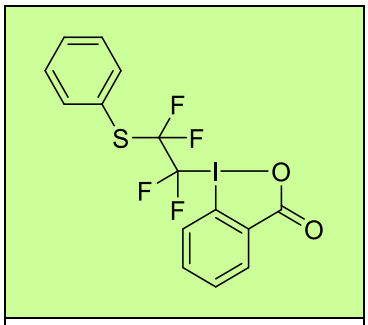

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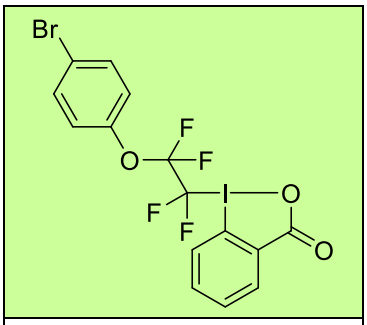

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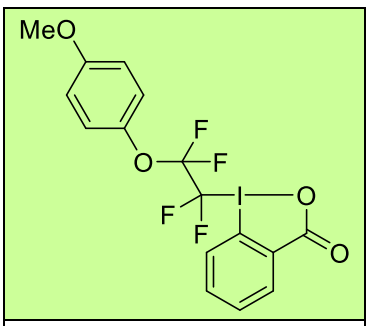

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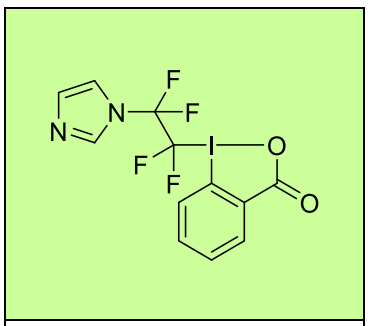
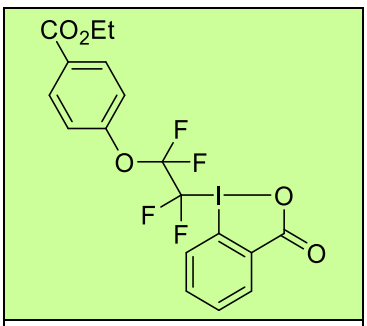


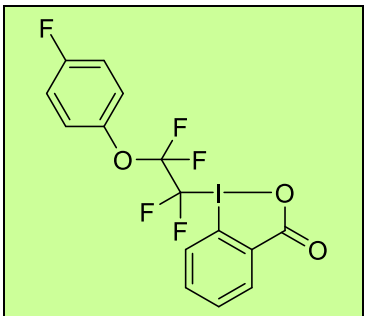
HYP021

CAS: 1836233-22-7



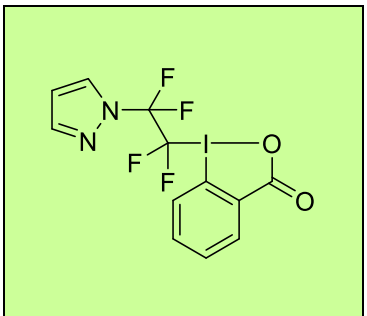
HYP022

CAS: 1836233-21-6



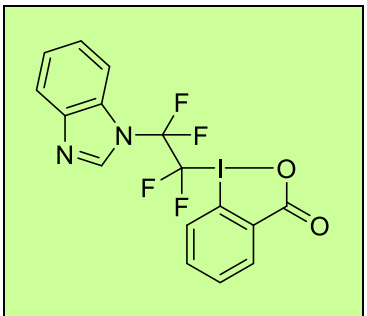
HYP023

CAS: N/A



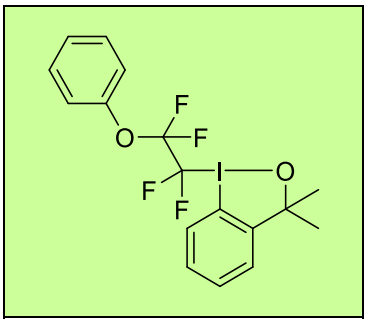
HYP024

CAS: 1836233-24-9



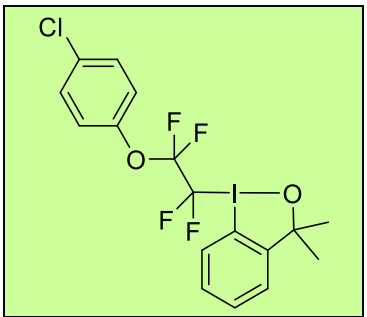
HYP025

CAS: 1836233-23-8



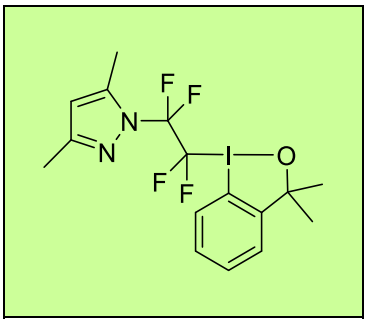
HYP028

CAS: N/A



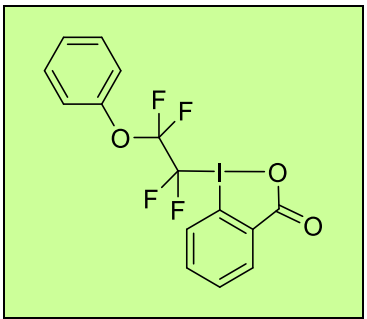
HYP029

CAS: N/A



HYP030

CAS: N/A

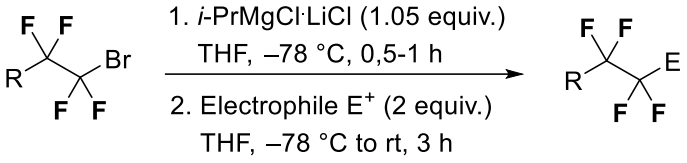


HYP031

CAS: N/A

Fluoroalkyl bromides

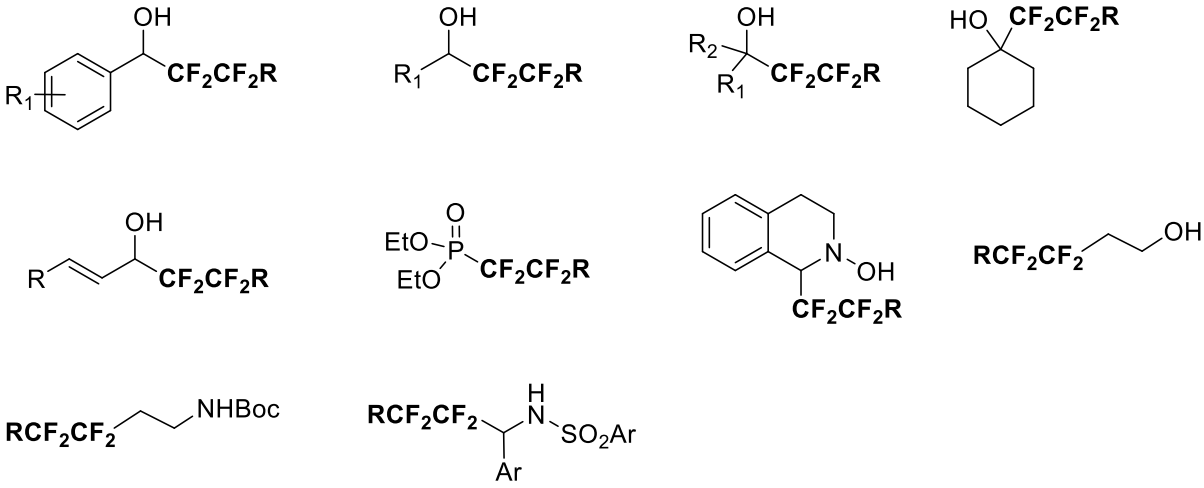
Substituted fluoroalkyl bromides turn into powerful nucleophilic fluoroalkylation reagents after being metallated with isopropyl magnesium chloride-lithium chloride complex (Turbo-Grignard). The *in-situ* generated fluoroalkyl magnesium chloride intermediate is moderately stable up to -40 °C and can be efficiently trapped with various electrophiles to afford the —CF_2CF_2— linked products.

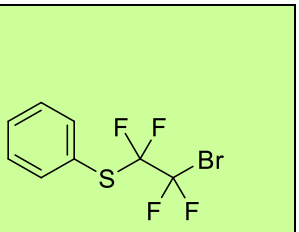


E^+ =
- aldehydes
- ketones
- sulfonylimines
- nitrones
- chlorophosphates

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

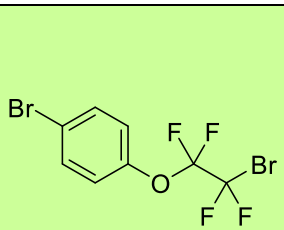
Chemical space opened by the fluoroalkyl magnesium chemistry:





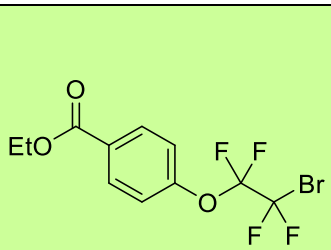
FBR001

CAS: 83015-33-2



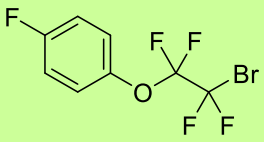
FBR002

CAS: 113939-45-0



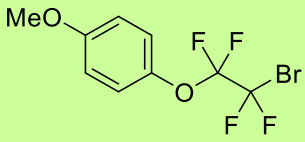
FBR003

CAS: 896431-14-4



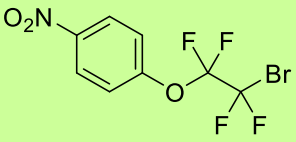
FBR004

CAS: 2032375-46-3



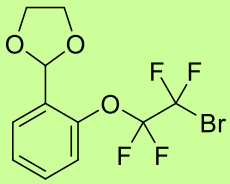
FBR005

CAS: 134151-62-5



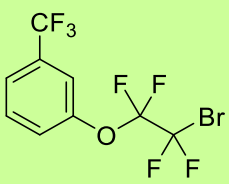
FBR006

CAS: 83105-30-9



FBR007

CAS: 1883744-08-8



FBR008

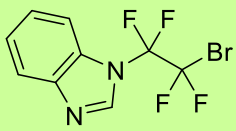
CAS: 134130-31-7

FBR009

CAS: 900534-71-6

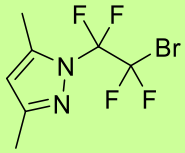
FBR010

CAS: 900534-75-0



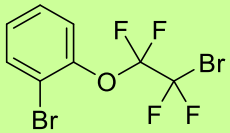
FBR011

CAS: 900534-72-7



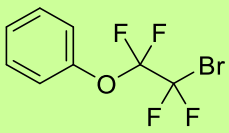
FBR012

CAS: 1125518-67-3



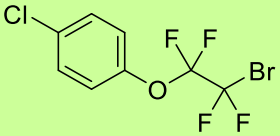
FBR013

CAS: 2185840-24-6



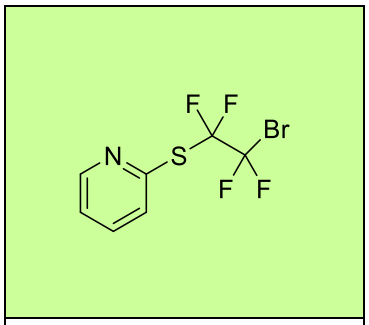
FBR014

CAS: 83015-28-5



FBR015

CAS: 83015-29-6



FBR016

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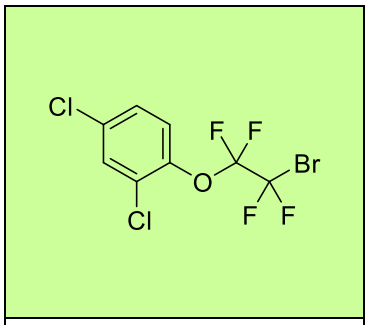
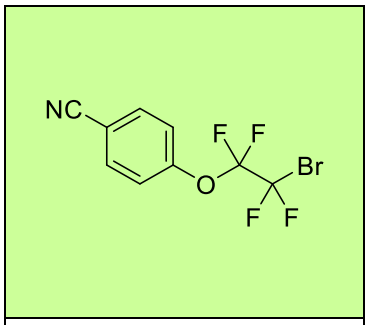


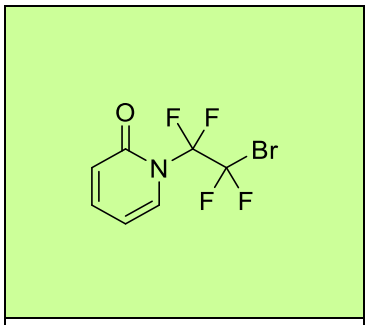
FBR017

CAS: 1548651-96-2



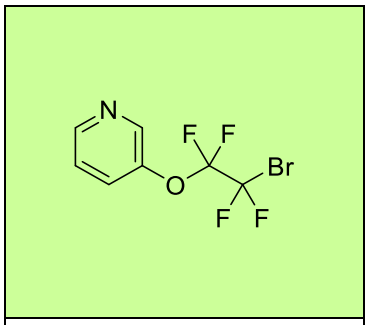
FBR018

CAS: 957372-61-1



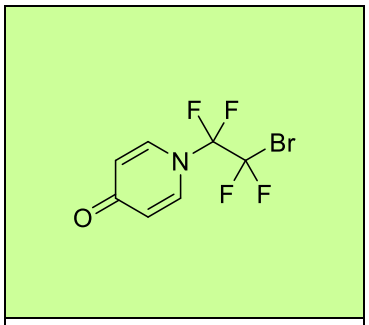
FBR019

CAS: N/A



FBR020

CAS: N/A

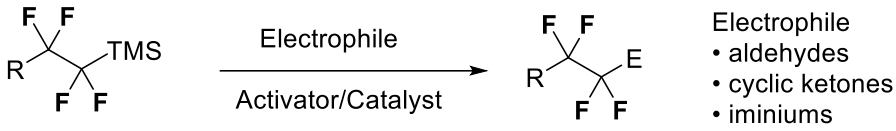


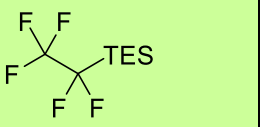
FBR021

CAS: N/A

Fluoroalkyl silanes

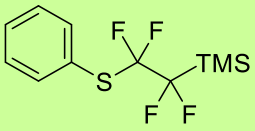
Substituted fluoroalkyl silanes serve as traditional nucleophilic sources of the fluoroalkyl synthon. Upon activation with catalytic fluoride or alkoxide, they can fluoroalkylate a range of aldehydes, reactive ketones or iminiums. The silanes can also engage in transition-metal catalyzed formation of R-CF_2CF_2- substituted aromatics.





SIL001

CAS: 386703-92-0

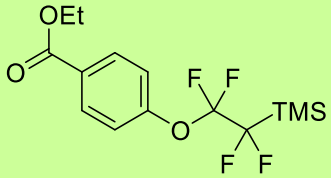


SIL002

CAS: 1000293-91-3

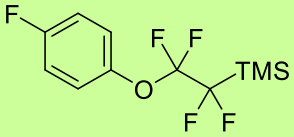
SIL003

CAS: 1836233-49-8



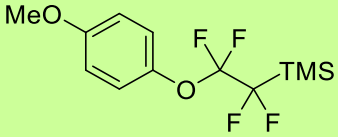
SIL004

CAS: 1836233-51-2



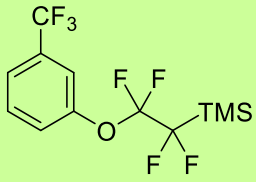
SIL005

CAS: 2185840-21-3



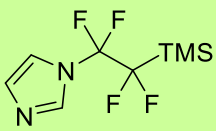
SIL006

CAS: 1836233-50-1



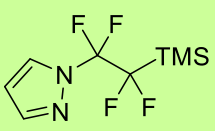
SIL007

CAS: 2185840-22-4



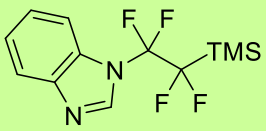
SIL008

CAS: 722491-59-0



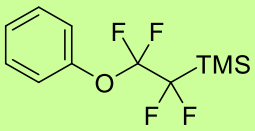
SIL009

CAS: 1125518-71-9



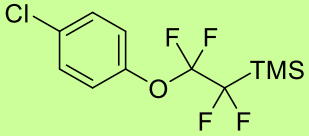
SIL010

CAS: 1125518-69-5



SIL012

CAS: 386703-91-9



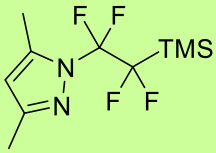
SIL013

CAS: 2185840-33-7

$C_8F_{17}TMS$

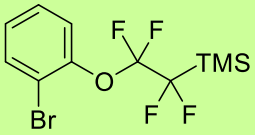
SIL014

CAS: 52112-19-3



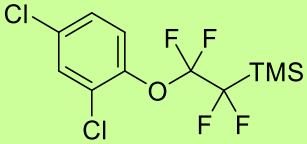
SIL015

CAS: 1125518-74-2



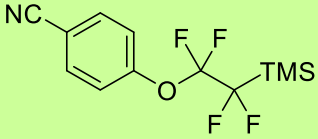
SIL016

CAS: N/A



SIL017

CAS: N/A

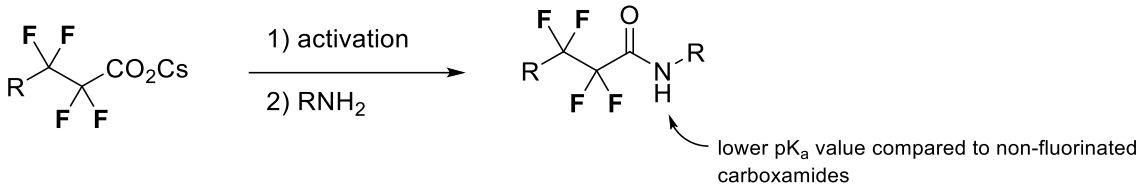


SIL020

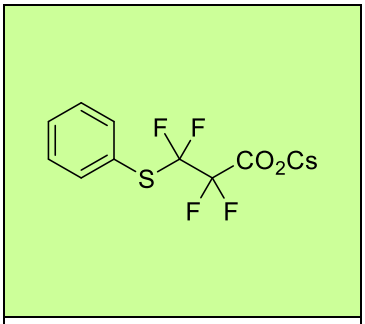
CAS: N/A

Fluoroalkyl carboxylates

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

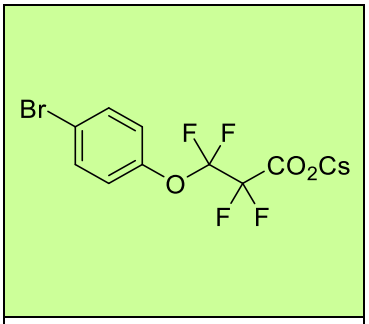


The cesium salts can be easily handled on air due to their reduced hygroscopicity compared to the highly hygroscopic free carboxylic acids.



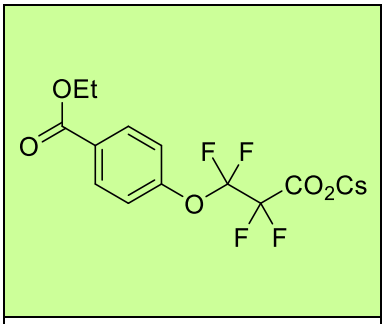
CC001

CAS: N/A



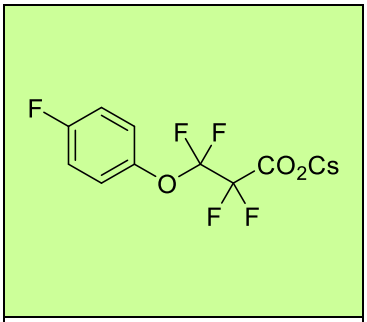
CC002

CAS: N/A



CC003

CAS: N/A



CC004

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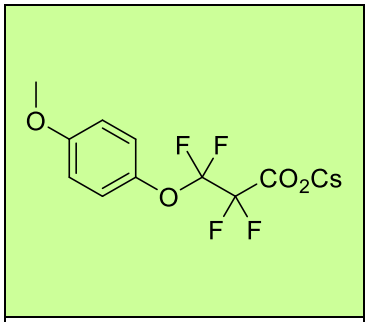
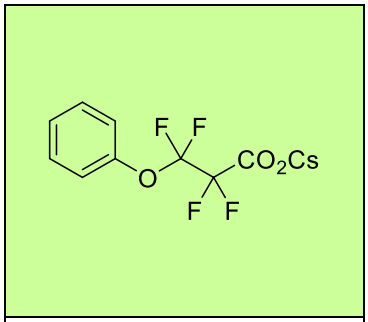


CC005

CAS: N/A



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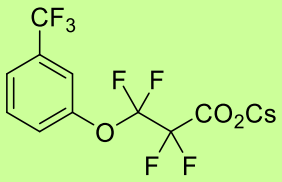
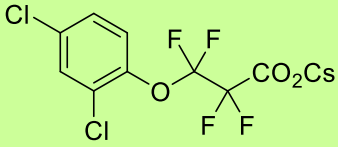
CAS: N/A



CC007

CAS: N/A



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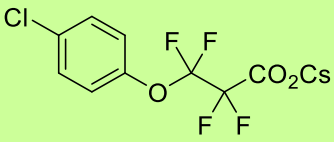

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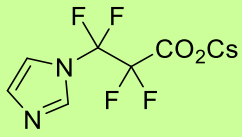

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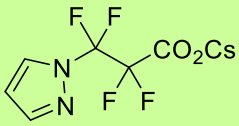

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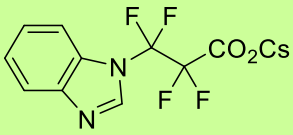

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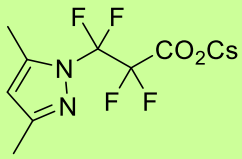

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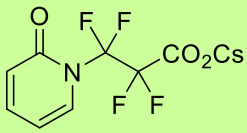


CC014

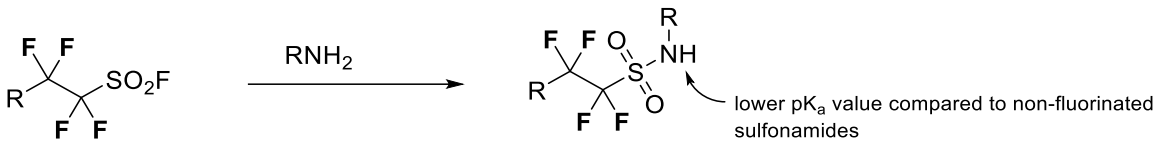
CAS: N/A

CC015

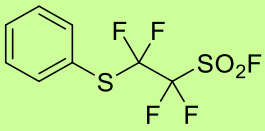
CAS: N/A

Fluoroalkyl sulfonylfluorides

Fluoroalkyl sulfonyl fluorides can be used as moderately reactive electrophilic fluoroalkyl sulfonylation reagents. Whereas the related fluoroalkyl sulfonyl chlorides can also behave as electrophilic chlorination reagents towards amines affording undesirable *N*-chloroamines, the fluoroalkyl sulfonyl fluorides give slower, yet very clean nitrogen sulfonylation to give the corresponding sulfonamides.



Fluoroalkyl sulfonylation of the amine nitrogen greatly lowers the pK_a value of NH group and can be used to modulate the behaviour of the drug candidate or build additional molecular complexity around the highly acidic fluoroalkyl sulfonamide nitrogen.



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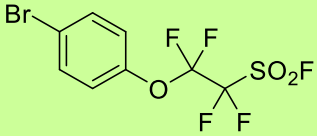

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SF003

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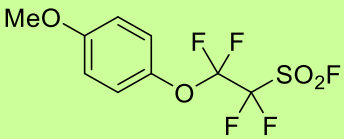

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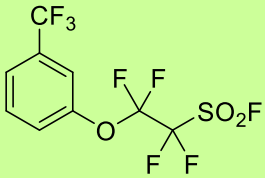

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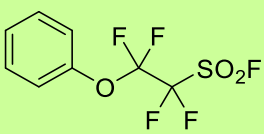

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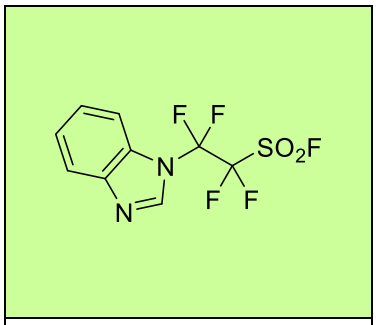

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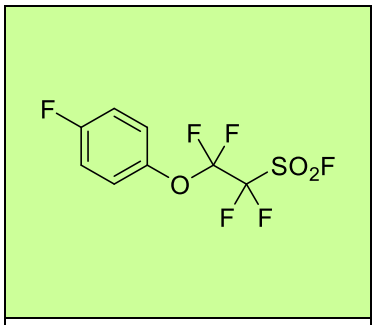

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CAS: 2368871-64-9

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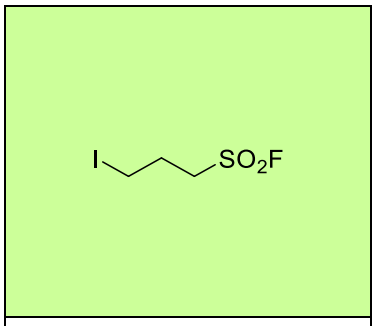
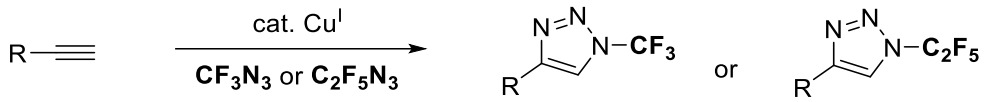


SF010

CAS: N/A

Fluoroalkyl azides

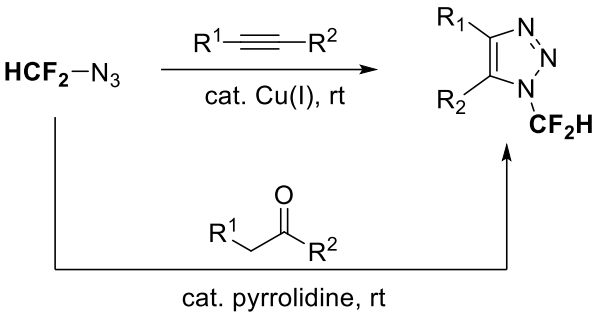
Trifluoromethyl azide, pentafluoroethyl azide, difluoromethyl azide and trifluoroethyl azide represent four examples of exotic fluoroalkyl azides that are potentially very attractive for medicinal chemistry and agrochemistry discovery programmes. Generally, fluoroalkyl azides show much higher thermal 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 trifluoromethyl azide or pentafluoroethyl azide affording regioselectively the 1,4-disubstituted *N*-CF_3 or *N*-C_2F_5 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.



Straightforward and regioselective access to rare *N*-CF_3 and *N*-C_2F_5 -1,4-disubstituted triazoles
Ref: *Angew. Chem. Int. Ed.* **2017**, *56*, 346

Difluoromethyl azide shares practically the same reactivity as trifluoromethyl azide in copper catalyzed alkyne-azide cycloadditions, providing expedient access to five-membered *N*-CF_2H heterocycles. Difluoromethyl azide provides similar synthetic benefits as other fluoroalkyl azides – a broad substrate scope of regiochemically defined *N*-difluoromethyl azoles can be accessed in a much simpler manner than with other synthetic routes.

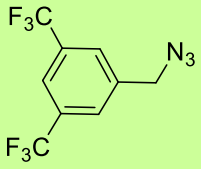
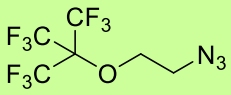
Besides the established copper catalyzed alkyne-azide cycloaddition, difluoromethyl azide was shown to undergo an enamine mediated azide-ketone [3+2] cycloadditions, affording the corresponding *N*-CF_2H triazoles.



Ref: *Eur. J. Org. Chem.,* **2018**, 5087-5090

3,3,3-Trifluoroethyl azide 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.

CF_3N_3 0,5 M in THF	$C_2F_5N_3$ 0,15 M in THF	HCF_2N_3 1,2 M in DME
FAZ001	**FAZ002**	**FAZ003**
CAS: 3802-95-7	**CAS:** 2055167-74-1	**CAS:** 41796-84-3

$CF_3CH_2N_3$ 0,6 M in DME		
FAZ004	**FAZ005**	**FAZ006**
CAS: 846057-92-9	**CAS:** 620533-92-8	**CAS:** 1262207-12-4

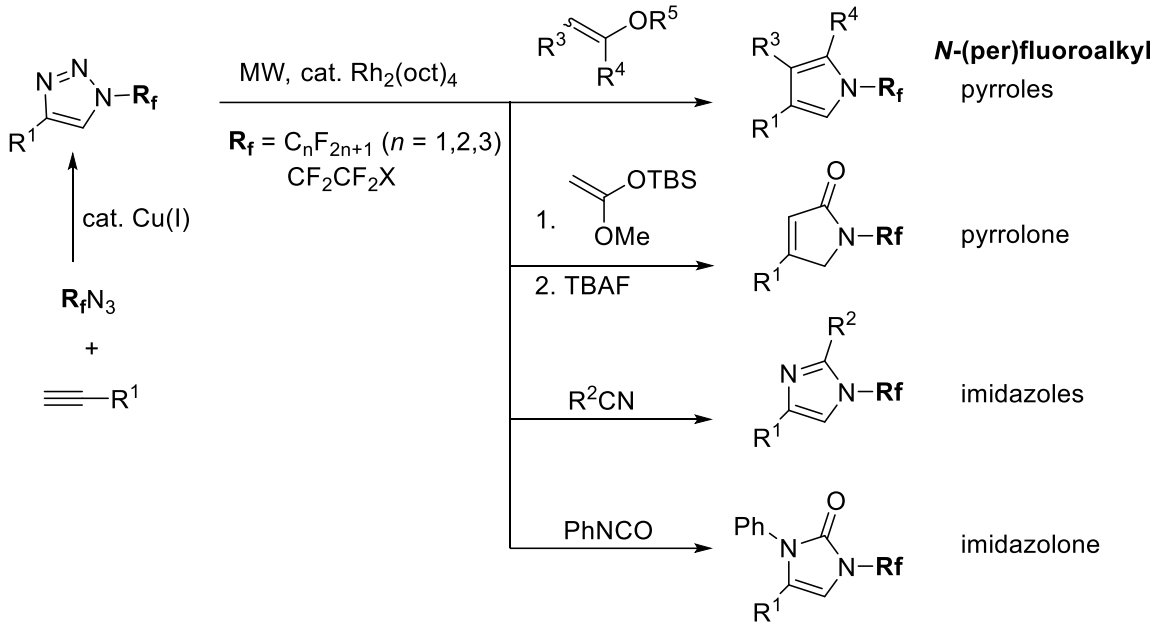
Fluoroalkyl triazoles

So far, *N*-fluoroalkyl triazoles have been very rare motifs in medicinal chemistry due to their limited synthetic availability, but thanks to the robust click chemistry based on *N*-fluoroalkyl azides, the attractive chemical space of *N*-fluoroalkyl triazoles is now unlocked.

N-fluoroalkyl triazoles can serve various purposes in drug design, depending on the nature of the fluoroalkyl, spanning from improved metabolic stability, use as hydrophobic amide bioisosteres or lipophilic hydrogen bond donors.

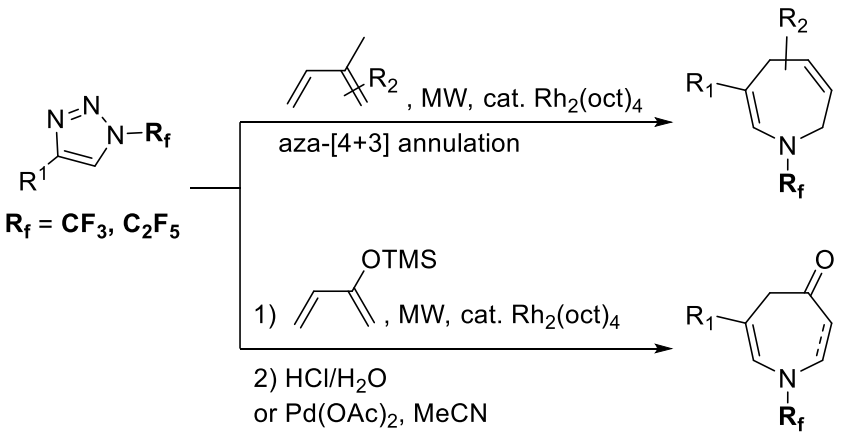
1,4-disubstituted *N*-fluoroalkyl triazoles with three different reactive handles (alcohol, amine and carboxylic acid) can be easily incorporated into synthesis routes, generating novel and potentially promising drug and pesticide candidates.

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

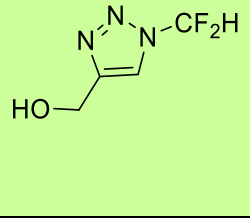


Conversion of fluoroalkyl triazoles to N-fluoroalkyl heterocycles using Rh-carbene chemistry
Ref: *Chem. Commun.*, **2018**, *54*, 3258

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



Construction of *N*-fluoroalkyl azepines from *N*-fluoroalkyl triazoles
Ref: *J.Org.Chem.*, in press, DOI: 10.1021/acs.joc.8b02472



FAT_CF2H_001
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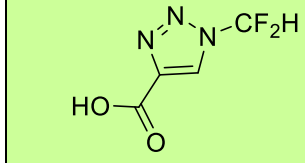

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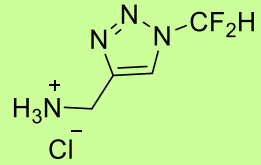

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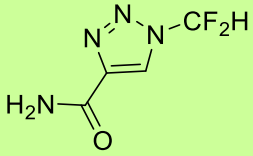

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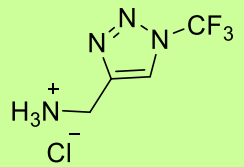

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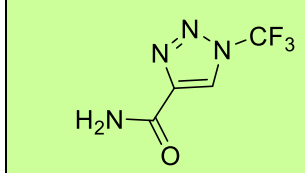
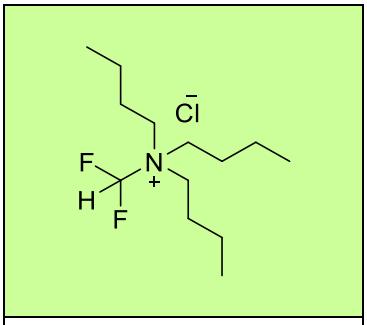


FAT_CF3_004
CAS: N/A

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.

Ref: *Chin. .J. Chem.*, **2011**, *29*, 1717-1721



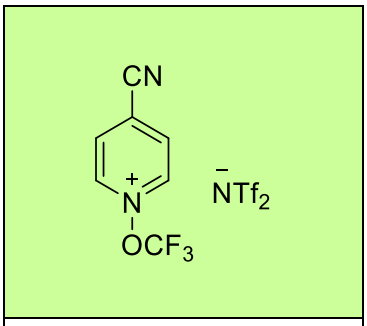
DFM001

CAS: 1004517-48-9

Perfluoroalkoxylation reagents

4-Cyano-*N*-trifluoromethoxypyridinium bis(trifluoromethanesulfonyl)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



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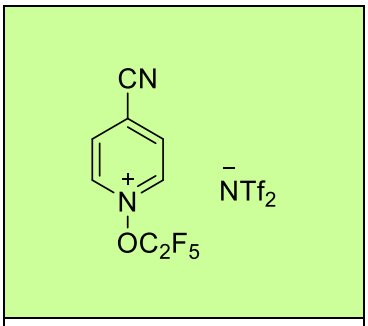


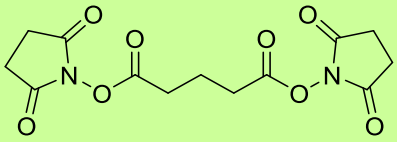
TFM002

CAS: N/A

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

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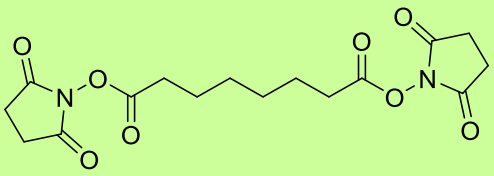

PCL002

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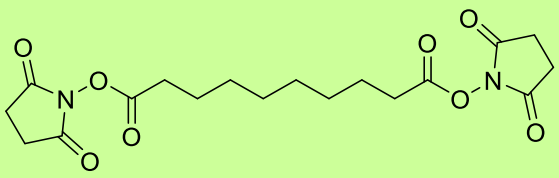

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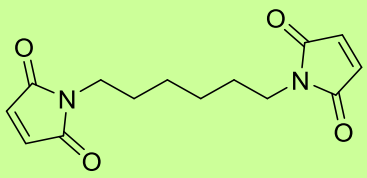

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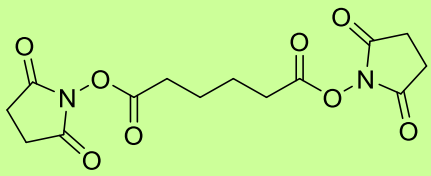
CAS: 4856-87-5



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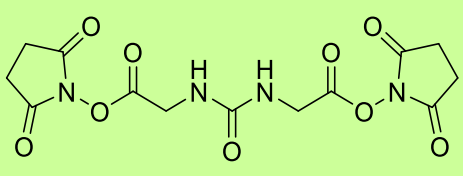


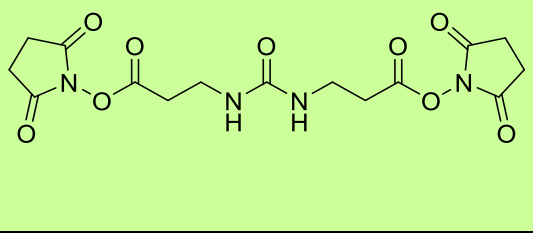
PCL006

CAS: 211029-82-2

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)

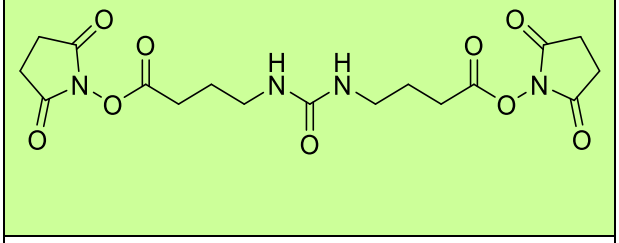
The ureido-4,4´-dibutyric acid bis(hydroxysuccinimide) ester, also known as DSBU or BuUrBU (**PCL008**), is the first described, longest version of MS-cleavable urea-based lysine-lysine reactive homobifunctional cross-linkers, featuring a C4-arm. At neutral or slightly basic pH, it irreversibly crosslinks 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. Therefeore, 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.



PCL007

CAS: 2185840-20-2



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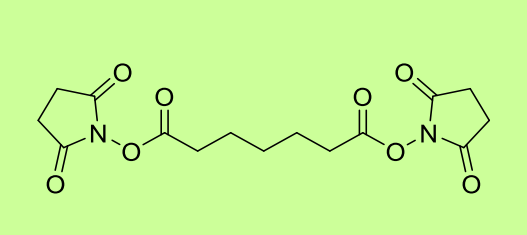

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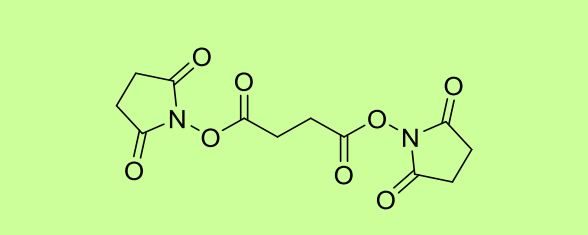

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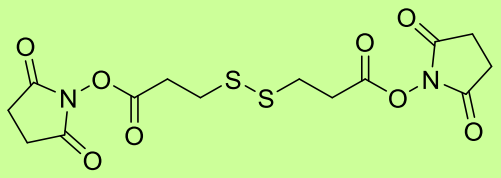

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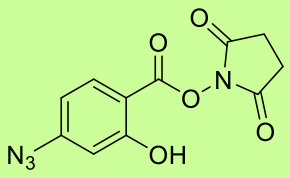

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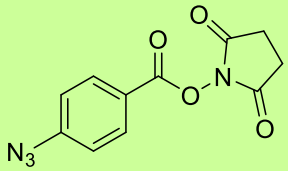
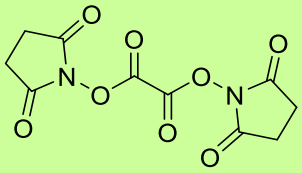
CAS: 96602-46-9



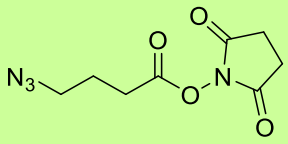
PCL013

CAS: 53053-08-0



PCL014

CAS: 57296-03-4



PCL015

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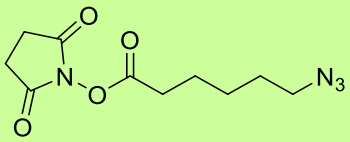

PCL021

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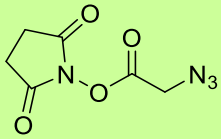
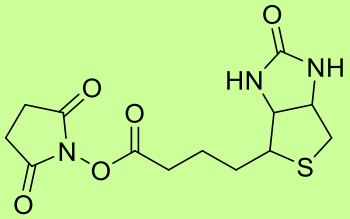


PCL022

CAS: 824426-32-6



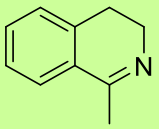
PCL023

CAS: 35013-72-0

Speciality chemicals

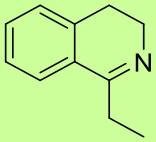
Dihydroisoquinolines

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*. Furthemore, 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.



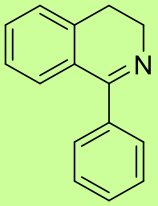
DHIQ001

CAS: 2412-58-0



DHIQ002

CAS: 41173-70-0



DHIQ003

CAS: 52250-50-7

DHIQ004

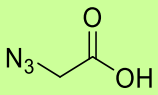
CAS: 26323-31-9

DHIQ005

CAS: 52250-51-8

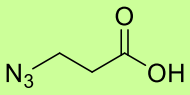
Azide building blocks

We offer a selection of azide building blocks for synthesis.



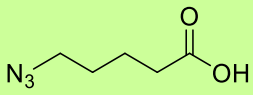
AZ001

CAS: 18523-48-3



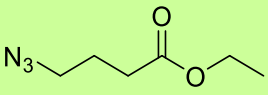
AZ002

CAS: 18523-47-2



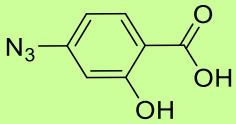
AZ003

CAS: 79583-98-5



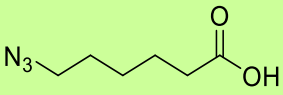
AZ005

CAS: 51453-79-3



AZ006

CAS: 66761-27-1



AZ007

CAS: 79598-53-1

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