Fluorinated diazoalkanes: synthesis and application

Pavel Mykhailiuk

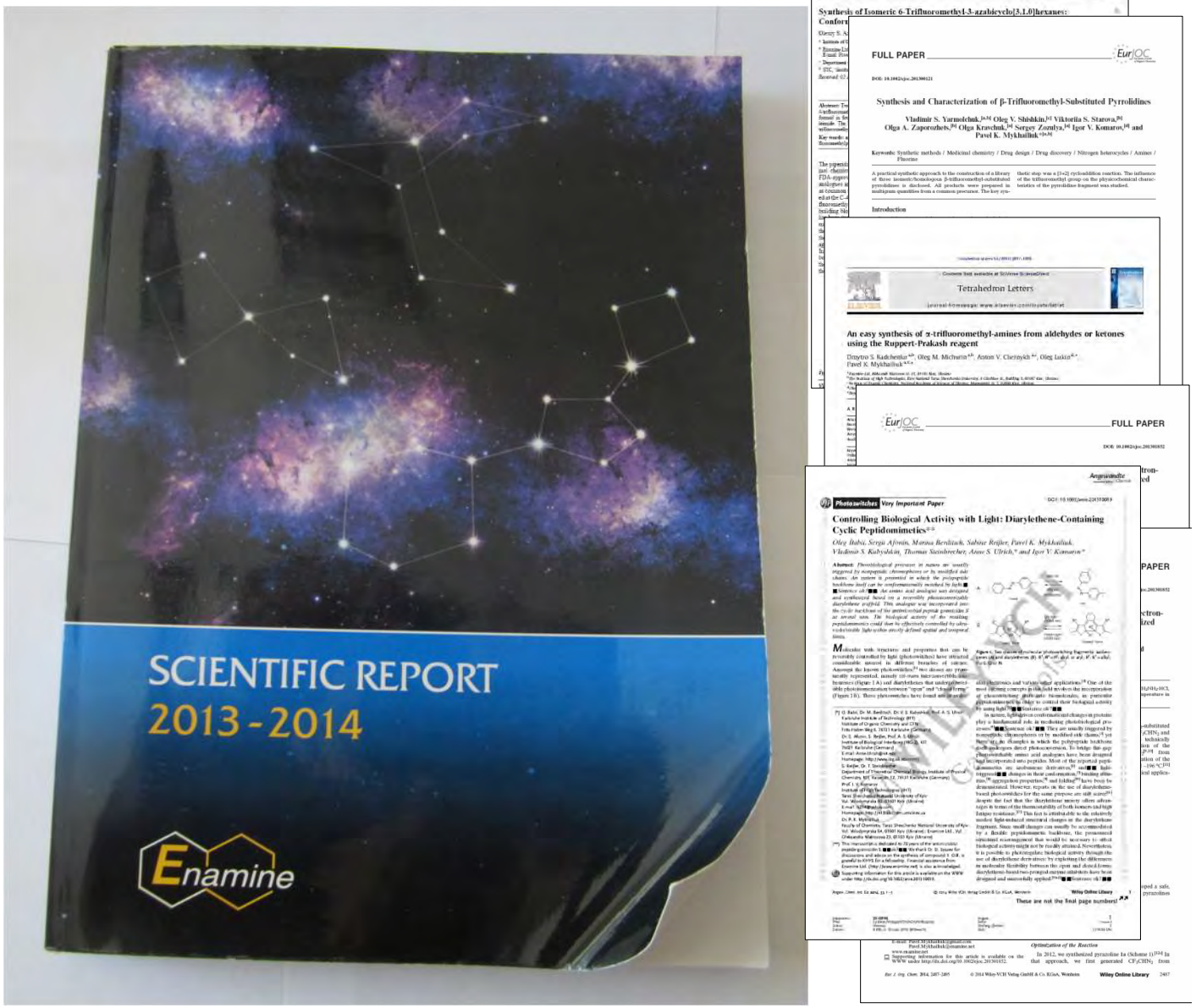
2016

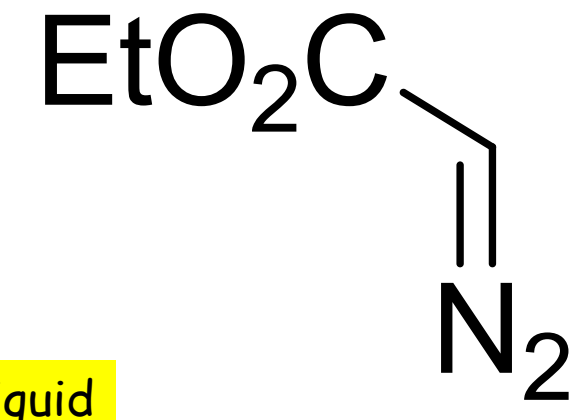
World's largest producer of building blocks

~100.000 compounds on stock
(gram-scale)

500 chemists
10 own buildings
private company

50 papers

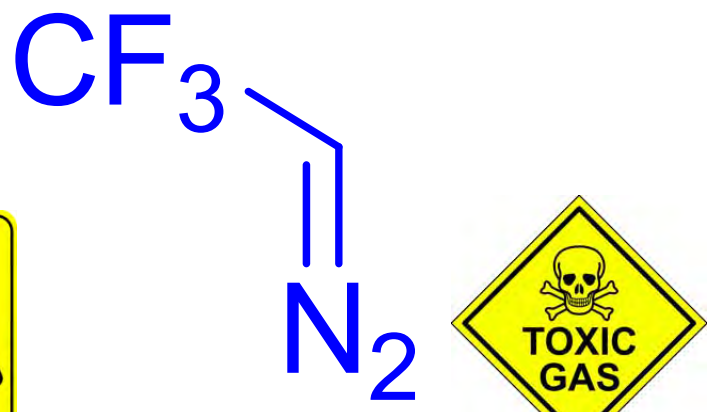

SCIENTIFIC REPORT
2013 - 2014
Enamine
FULL PAPER
Synthesis and Characterization of β-Trifluoromethyl-Substituted Pyrrolidines
Tetrahedron Letters
An easy synthesis of α-trifluoromethyl-amines from aldehydes or ketones using the Ruppert-Prakash reagent
FULL PAPER
Photoswitches Very Important Paper
Controlling Biological Activity with Light: Diarylethene-Containing Cyclic Peptidomimetics



Liquid

Ethyl diazoacetate is
extremely popular (> 100 reactions).

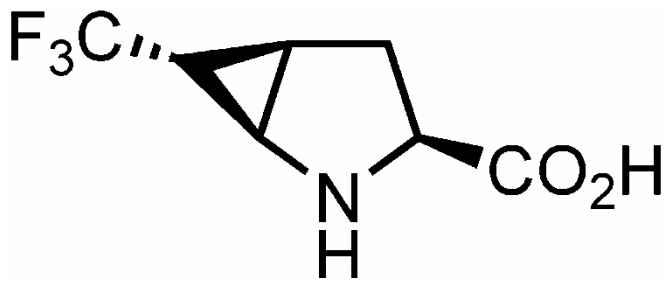
T. Curtius *Chem. Ber.* **1883**, 2230.



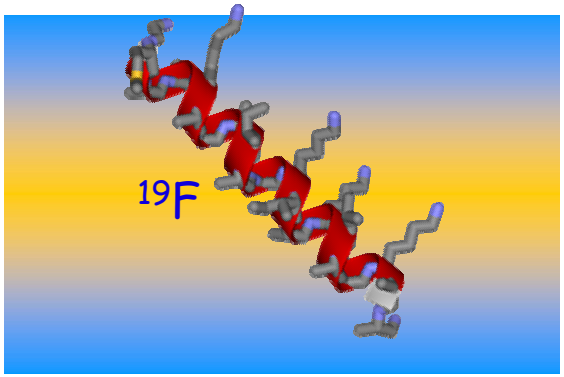
Until 2006 CF_3CHN_2
was rarely used in chemistry.

H. Gilman, R. G. Jones *JACS*, **1943**, 1458.

2008

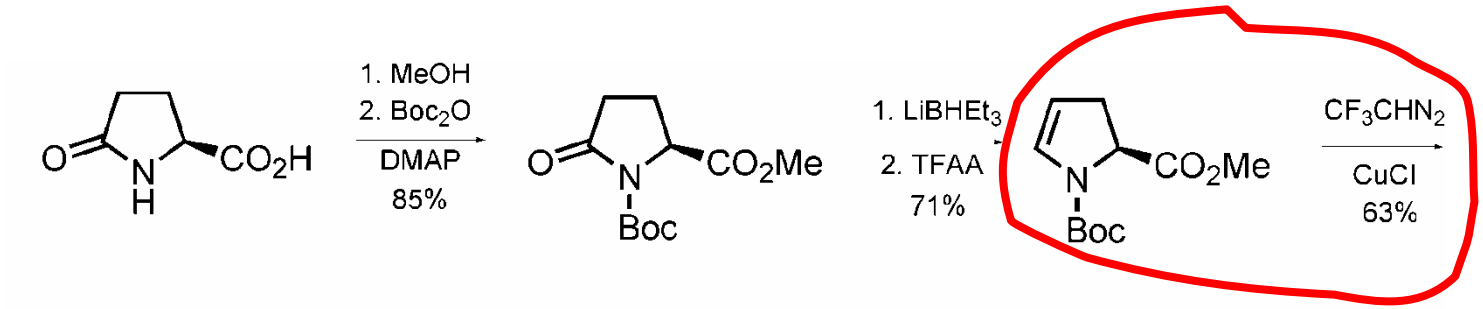


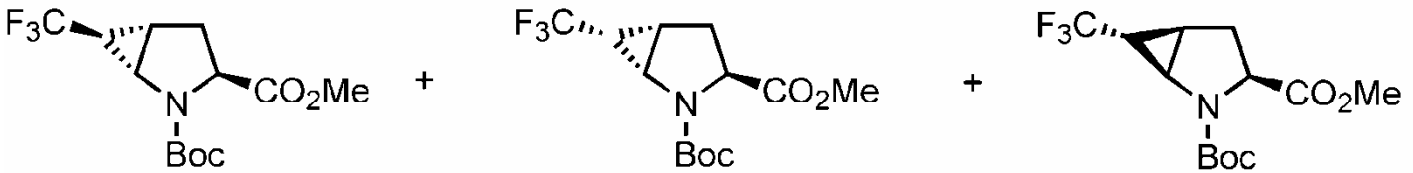
^{19}F-label for Proline

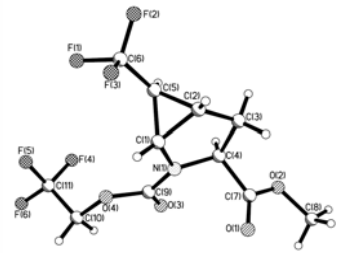


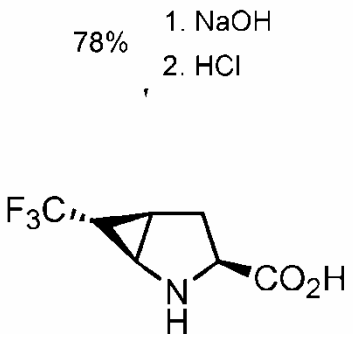
P. Mykhailiuk et al. *Angew. Chem. Int. Ed.* **2008**, 5765.

Synthesis of ^{19}F-label for Proline

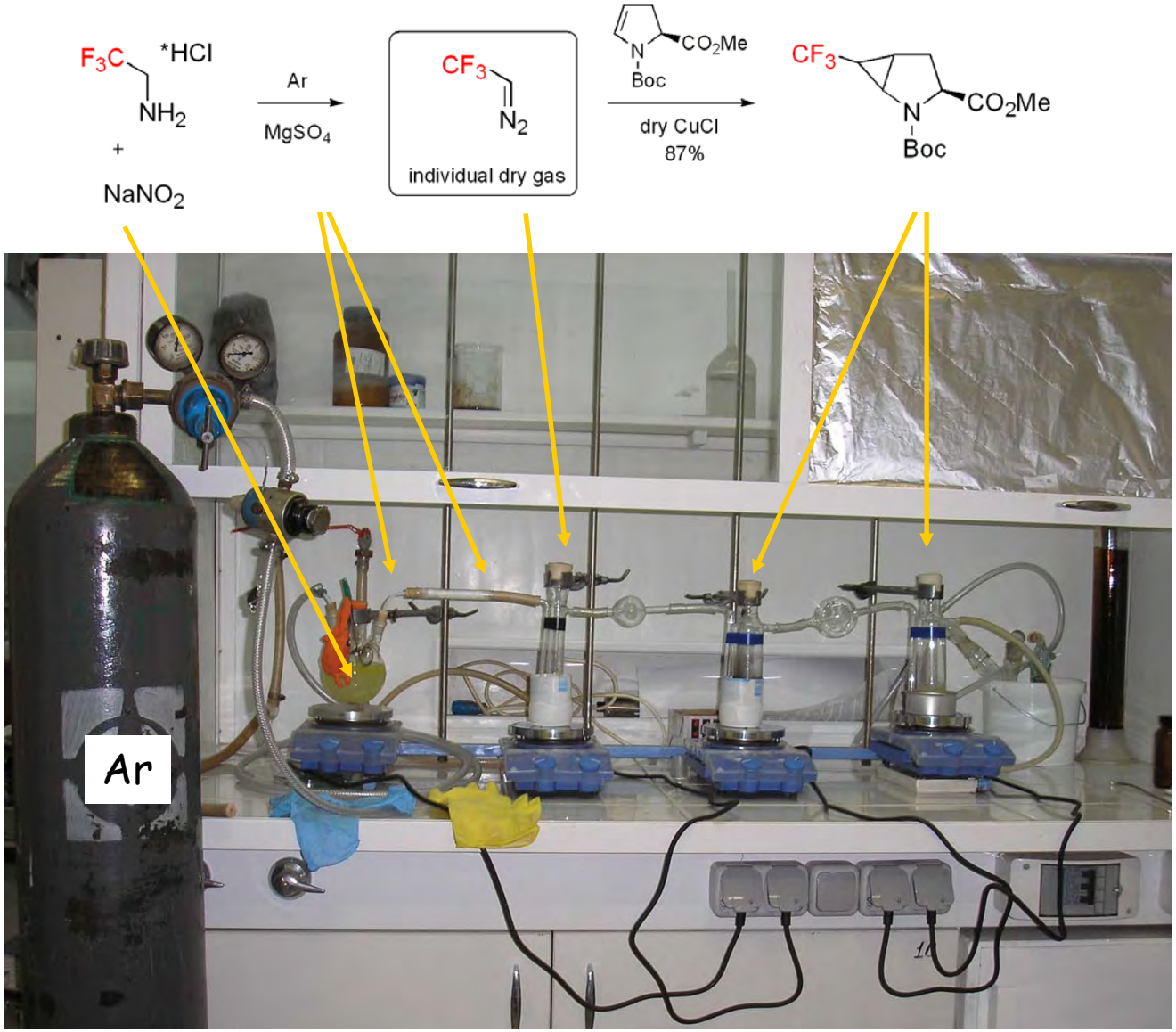


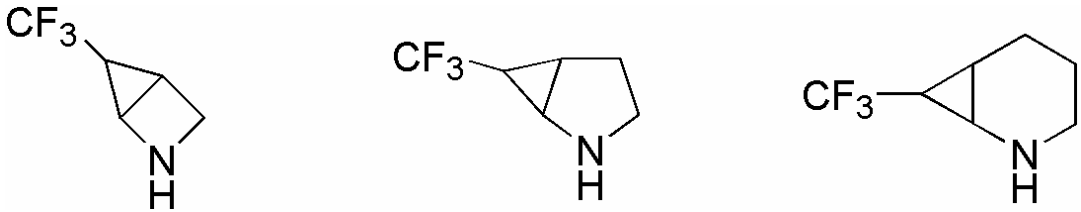






P. Mykhailiuk et al. *Angew. Chem. Int. Ed.* **2008**, 5765.

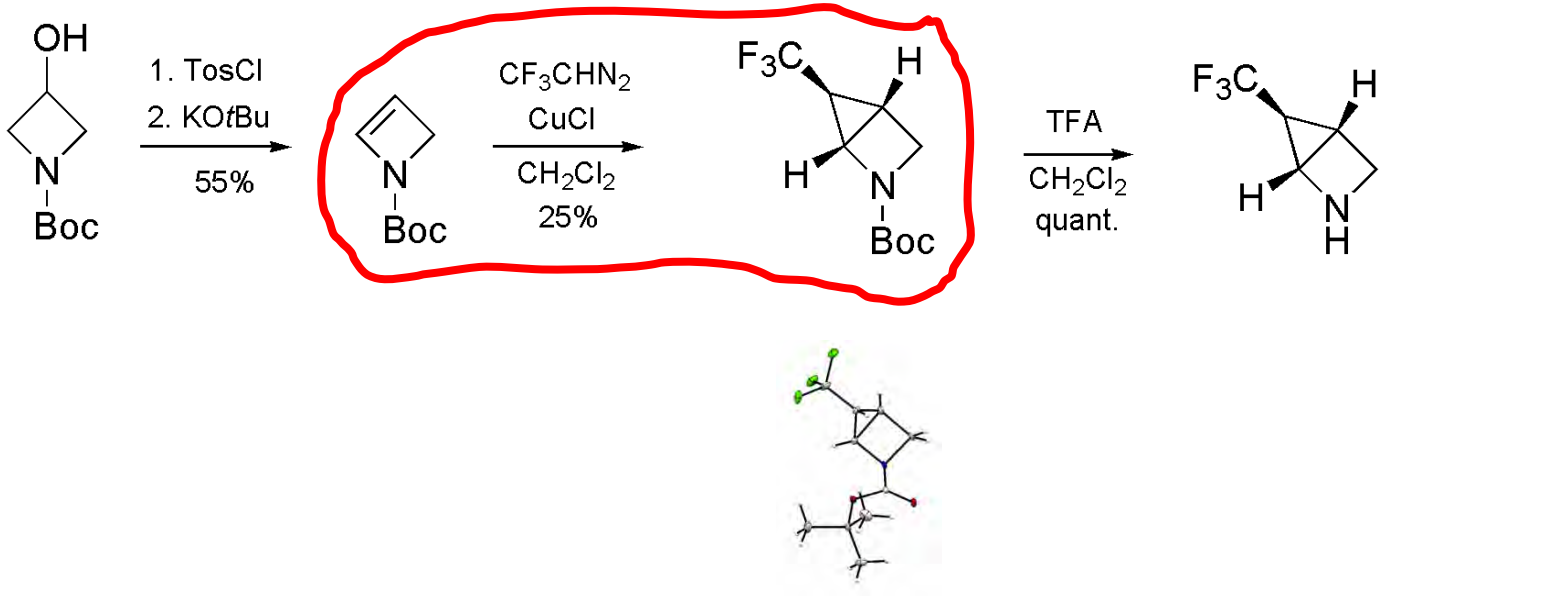

F3C *HCl
NH2
+
NaNO2
Ar
MgSO4
CF3
N2
individual dry gas
CO2Me
N
Boc
dry CuCl
87%
CF3
CO2Me
N
Boc
Ar

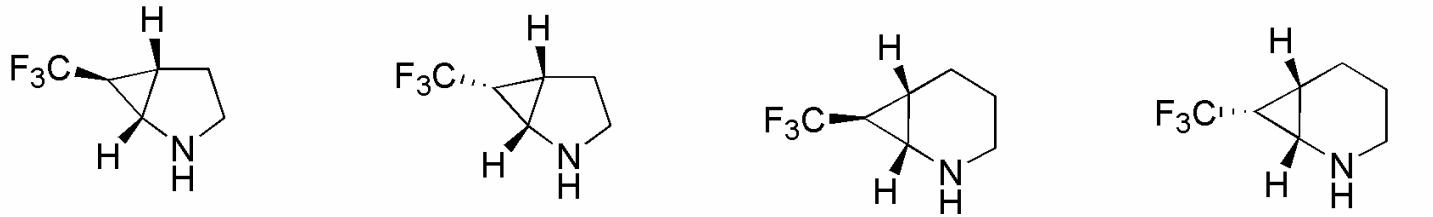


Advanced CF_3-amines for drug discovery

O. Artamonov et al. *EurJOC* **2014**, 3592.

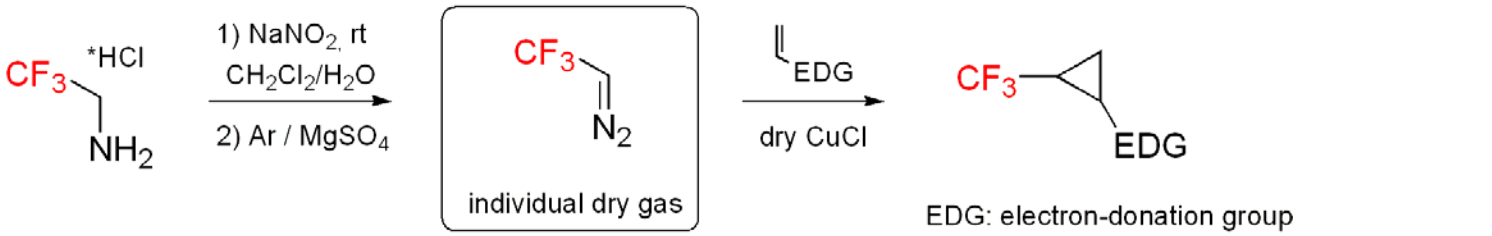
Synthesis of CF_3-amines

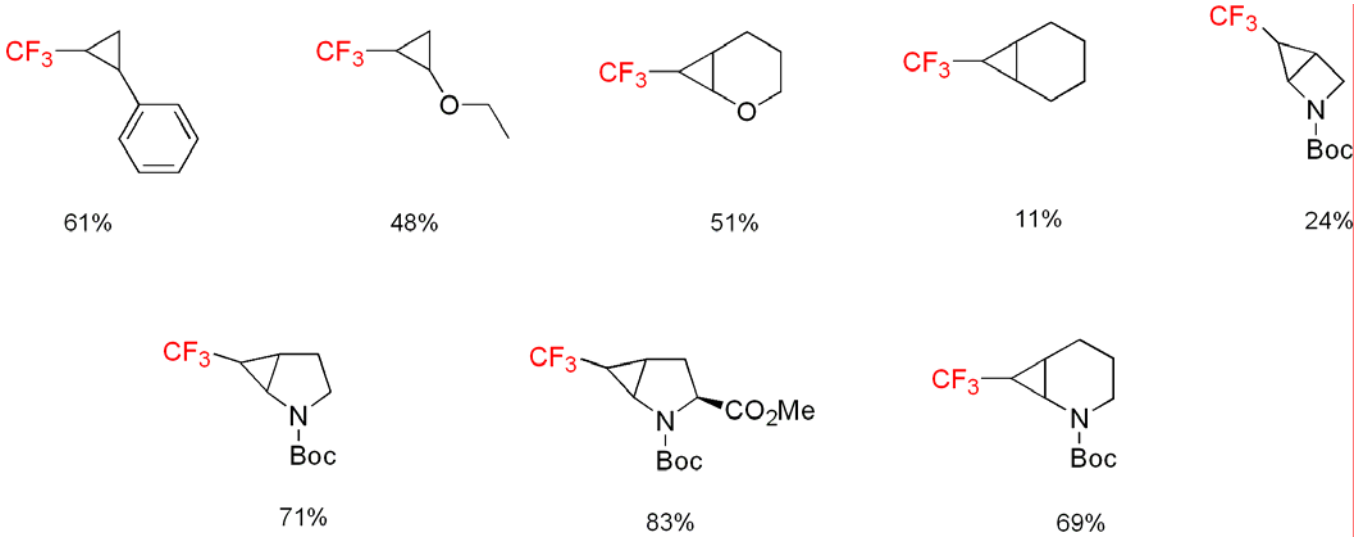




O. Artamonov et al. *EurJOC* **2014**, 3592.

CF_3-cyclopropanation of alkenes



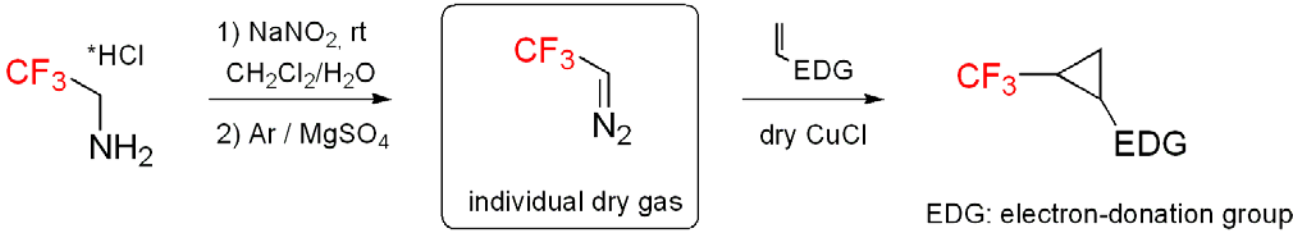


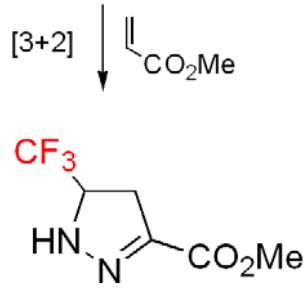
O. Artamonov et al. *EurJOC* **2014**, 3592.

P. Mykhailiuk et al. *Synthesis* **2008**, 1741.

P. Mykhailiuk et al. *ACIE* **2008**, 5765.

CF_3-cyclopropanation of alkenes



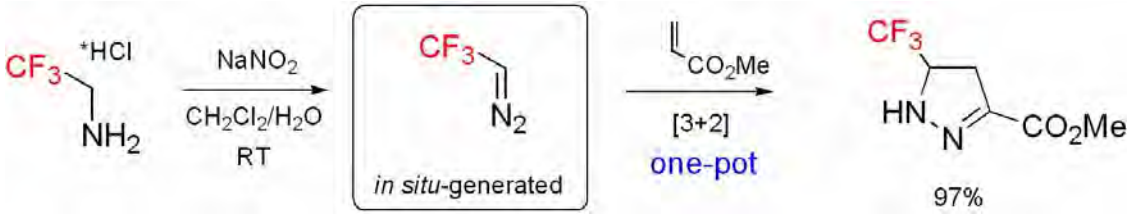


Do we need **dry** CF_3CHN_2 here?

Do we need to isolate it then?

[3+2]-cycloaddition with alkenes

[3+2]-cycloaddition with alkenes



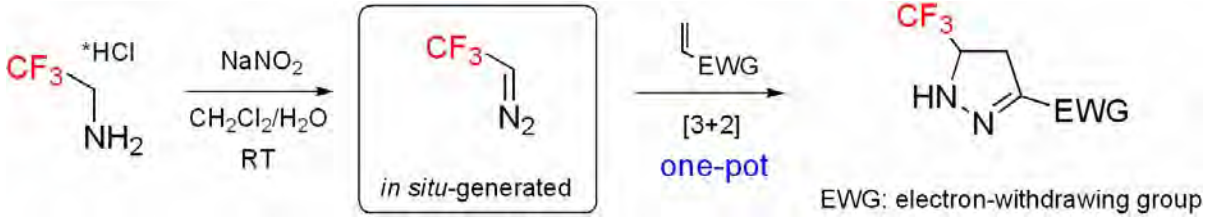
No purification

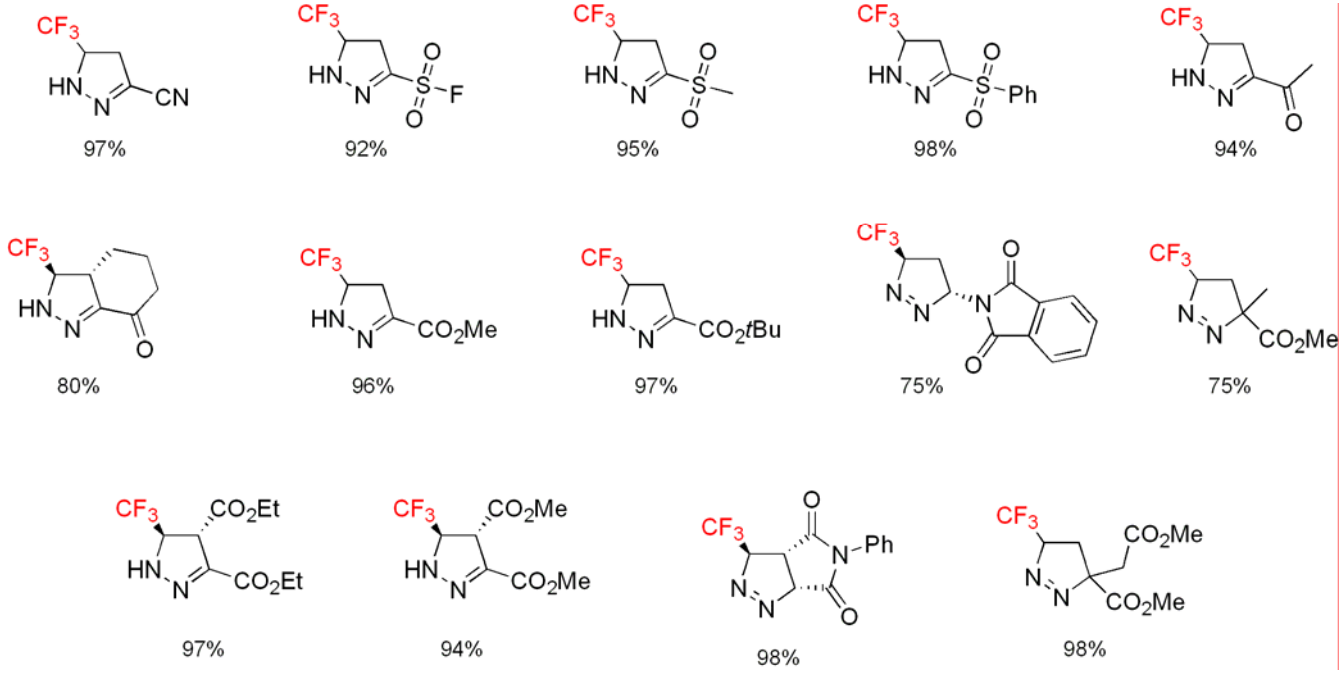
Scalable (500 g)

one-pot,
RT,
no inert atmosphere,
no catalysts,
common solvents,
no gaseous reagents,
no side products,
97% yield

E. Slobodyanyuk et al. *EurJOC* **2014**, 2487.

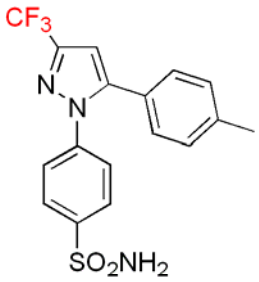
CF_3-pyrazolines



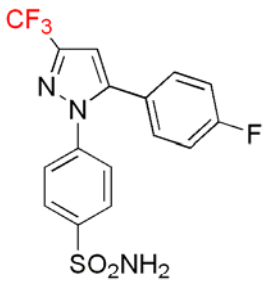


E. Slobodyanyuk et al. *EurJOC* **2014**, 2487.

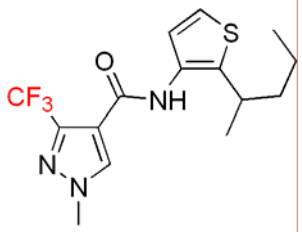
Bioaktive CF_3-pyrazoles



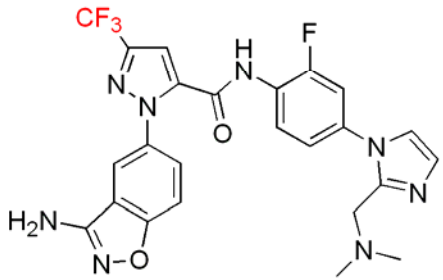
Celecoxib



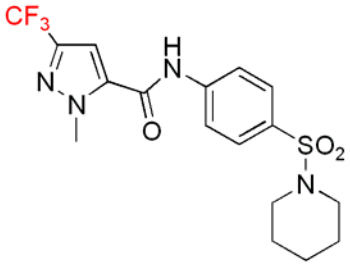
Mavacoxib



Penthiopyrad

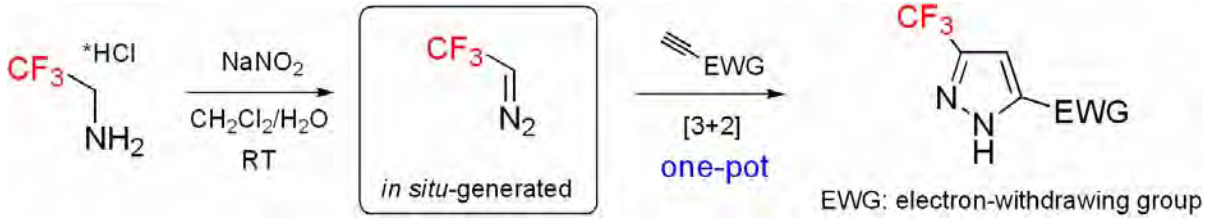


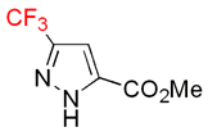
Razaxaban



AS-136A

CF_3-pyrazoles





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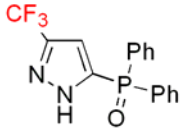

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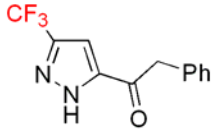

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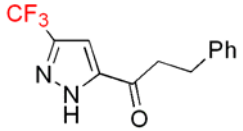

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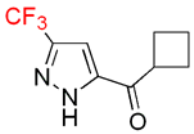

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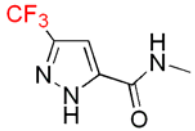

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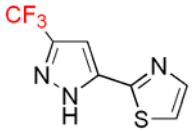

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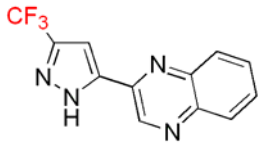

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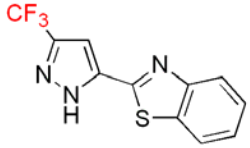

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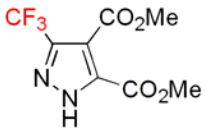

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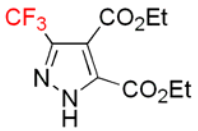

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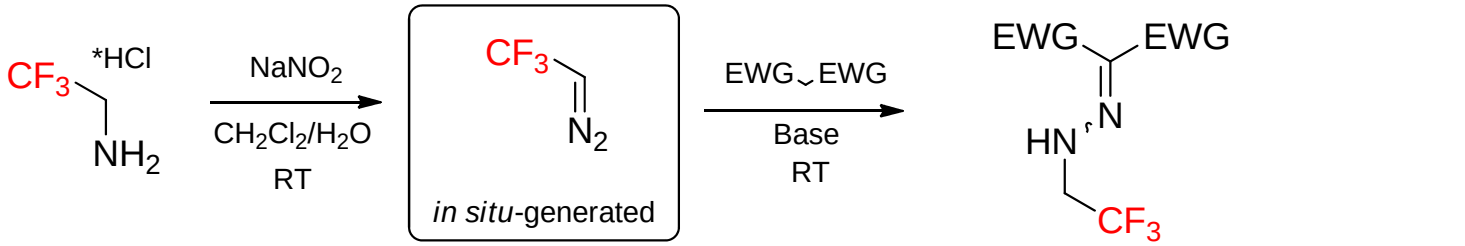
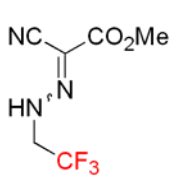
Japp-Klingemann reaction





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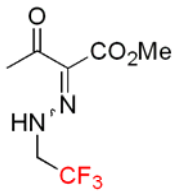

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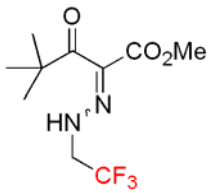

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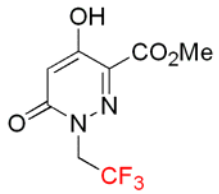

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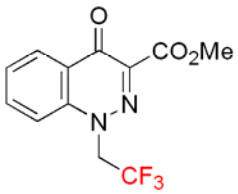

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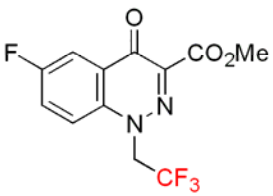

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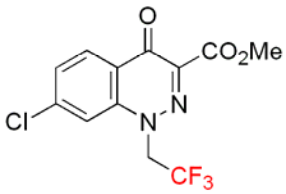

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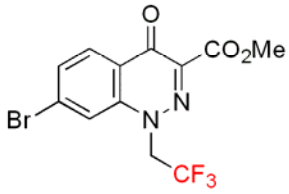

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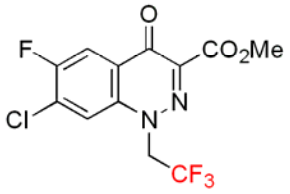

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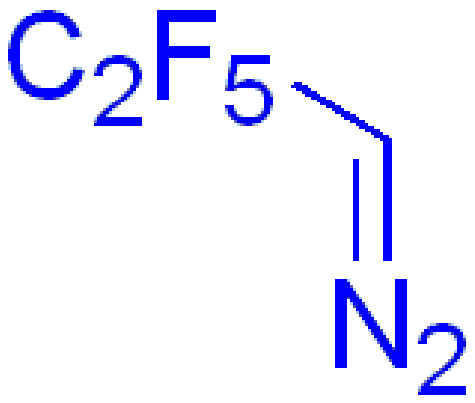
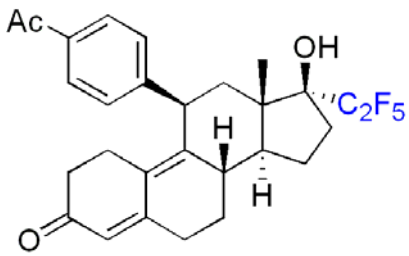
Unpublished results



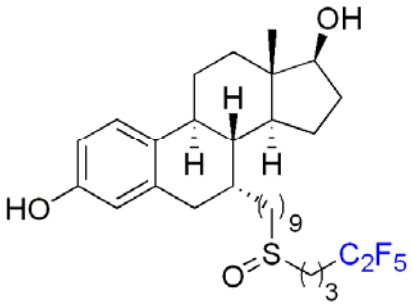
2014: unknown



Lonaprisan

anticancer

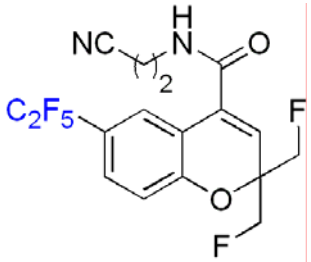
(Bayer HC; Phase II)



Fulvestrant

anticancer

(AstraZeneca; launched)

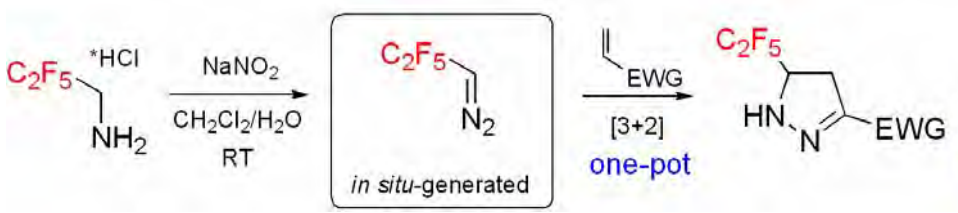


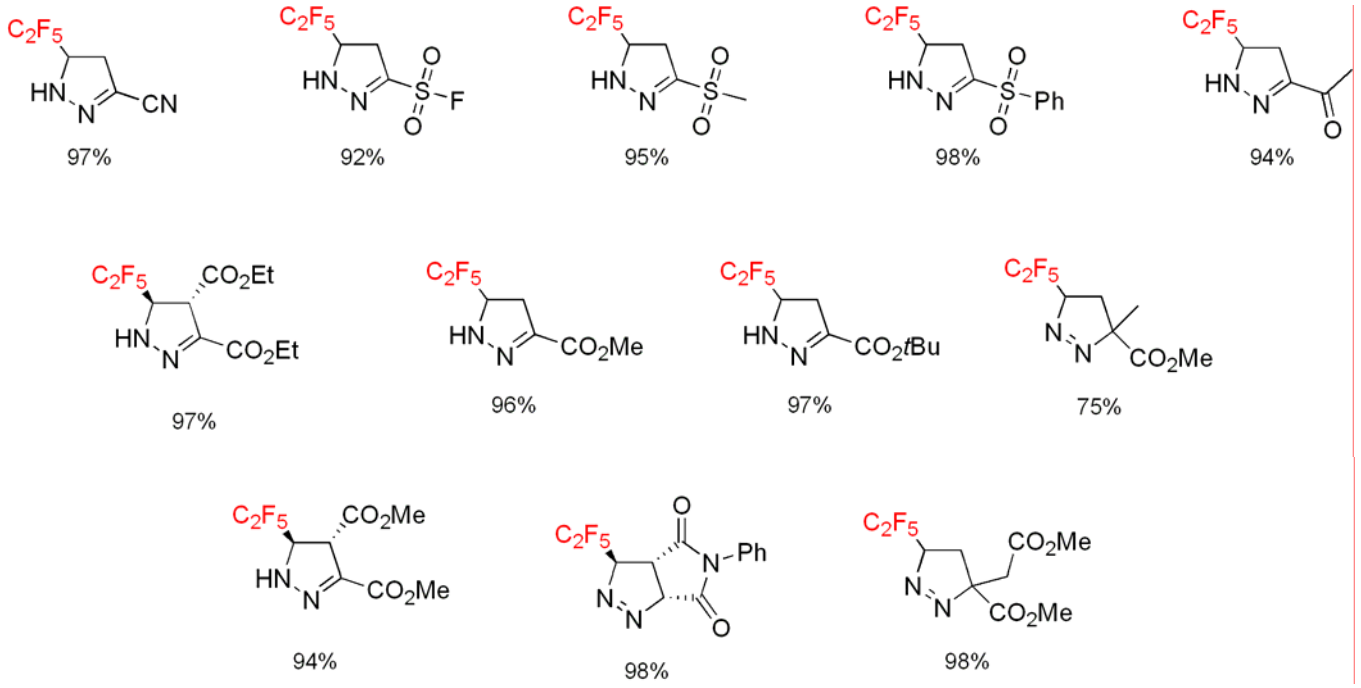
KC-515

antimigraine

(Chugai; preclinical)

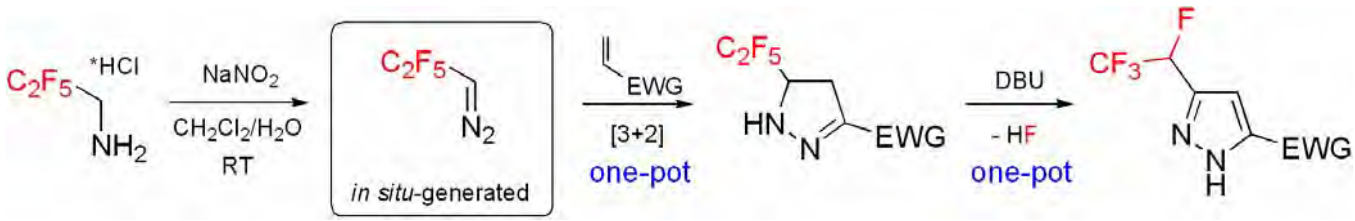
C_2F_5-pyrazolines

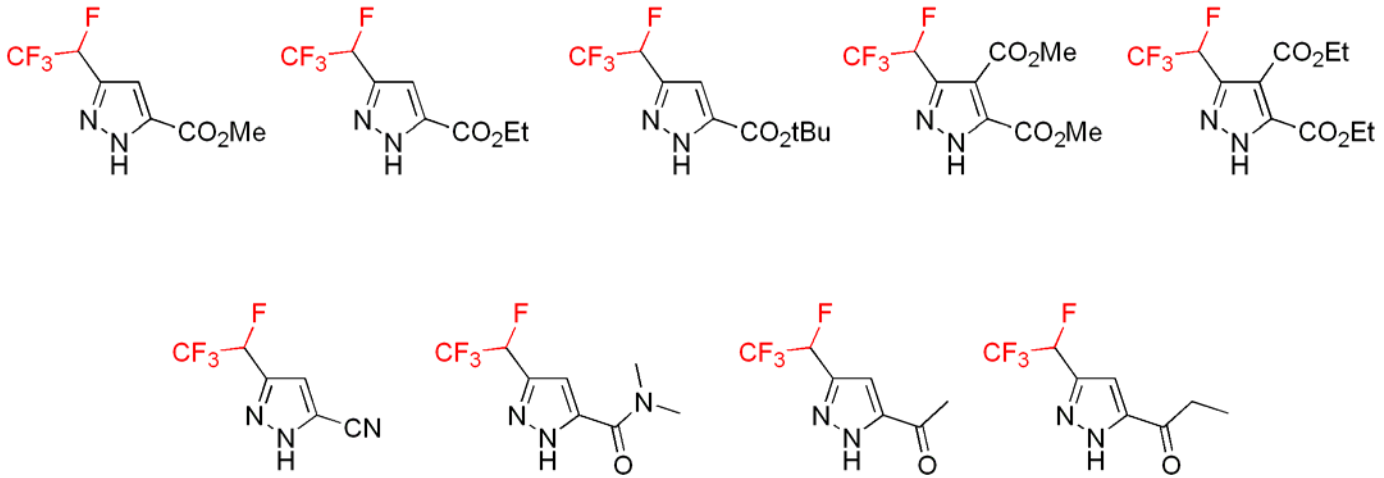




P. Mykhailiuk *Chem. Eur. J.* **2014**, 4942.
P. Mykhailiuk *Beilstein J. Org. Chem.* **2015**, 16.

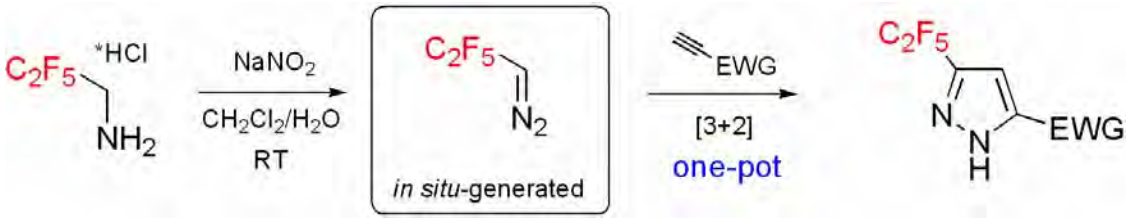
C_2F_4H-pyrazoles

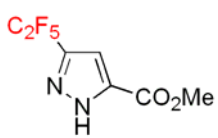




Unpublished results

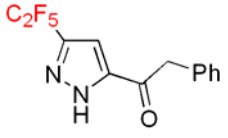
C_2F_5-pyrazoles





97%

92%



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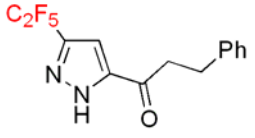

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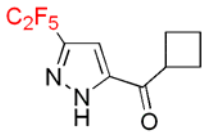

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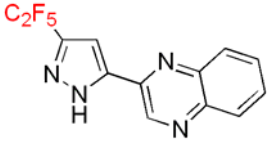

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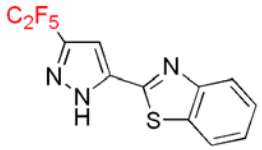

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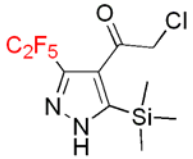

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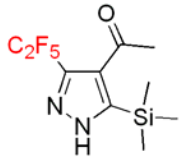

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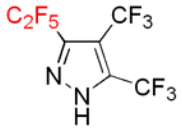

94%

P. Mykhailiuk *Chem. Eur. J.* **2014**, 4942; P. Mykhailiuk *Beilstein J. Org. Chem.* **2015**, 16; P. Mykhailiuk *Org. Biomol. Chem.* **2015**, 3438.

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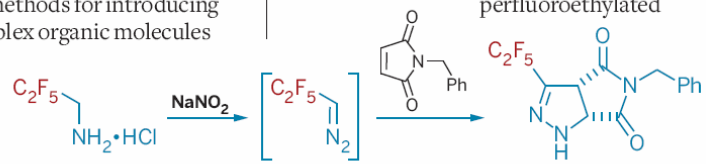
2014-20/17

DIAZOALKANE EXPANDS FLUORINE FOCUS ON ETHYL GROUPS

Developing new methods for introducing fluorine into complex organic molecules has been all the rage during the past few years. Researchers preparing drug candidates and crop protection chemicals typically seek to add a single fluorine atom or trifluoromethyl group and now have myriad ways to do so. But methods for adding longer, more lipophilic perfluoroalkyl groups such as pentafluoroethyl, $-C_2F_5$, to complex molecules



Ph = phenyl

Diazofluoroalkane

Pyrazoline

ly generates the fluorinated diazoalkane, $C_2F_5CH{=}N_2$, in situ from $C_2F_5CH_2NH_2{\bullet}HCl$ and $NaNO_2$. He demonstrated the utility of the reagent by using it in [3 + 2] cycloadditions with alkenes to prepare perfluoroethylated pyrazolines (one example shown) with better than 95% conversion rates. Mykhailiuk believes the diazofluoroalkane will also be as useful as other diazoalkanes for cyclopropanations, carbene insertions, and alkyne cycloadditions.—SR

A new fluorinated reagent ...

... discovered by scientists at Enamine Ltd., that is, $C_2F_5CHN_2$, is generated in situ from $C_2F_5CH_2NH_2{\cdot}HCl$ and sodium nitrite. The stars correspond to the atoms in the molecule. For more details see the Full Paper by P. K. Mykhailiuk on page 4942 ff.

Supported by ACES

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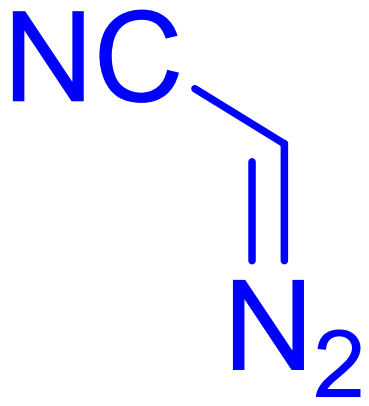

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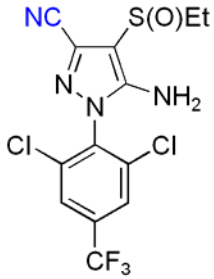
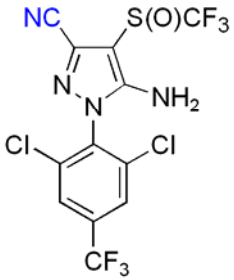
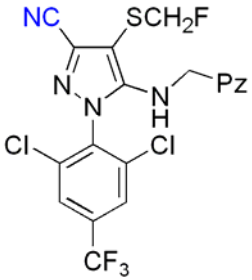


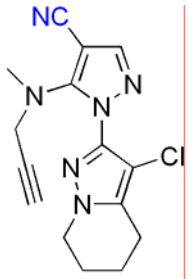
Ethiprole
insecticide
BASF



Fipronil
insecticide
BASF



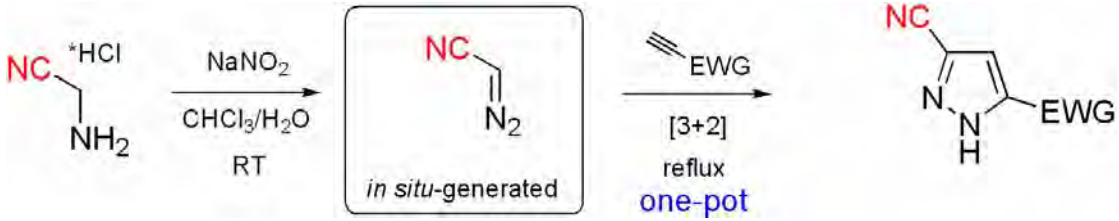
Pyrafluprole
insecticide
BASF

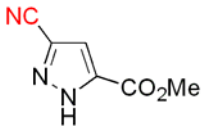


Pyrazlonil
herbicide
Hoechst Schering

T. Curtius *Chem. Ber.* **1898**, 2490.

CN-pyrazoles





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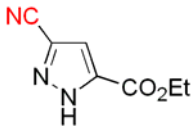

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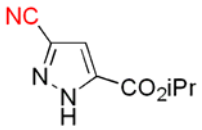

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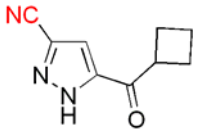

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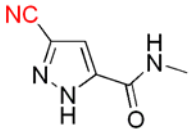

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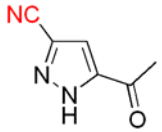

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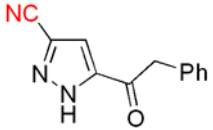

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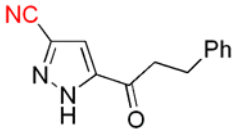

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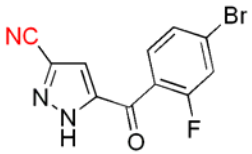

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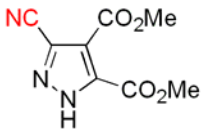

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P. Mykhailiuk *EurJOC* **2015**, 7235.


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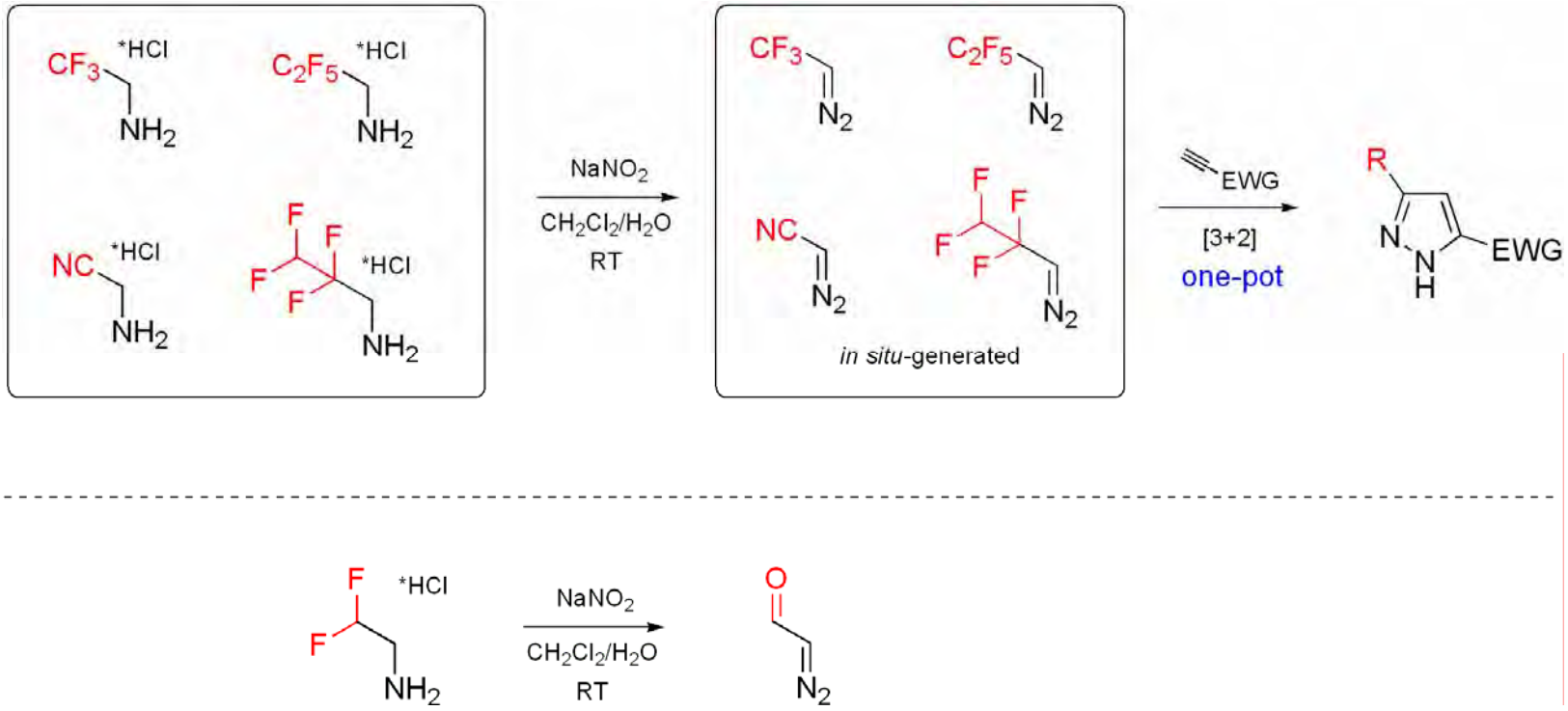
Scope



P. Mykhailiuk *Chem. Eur. J.* **2014**, 4942.
P. Mykhailiuk *Beilstein J. Org. Chem.* **2015**, 16.
P. Mykhailiuk *Org. Biomol. Chem.* **2015**, 3438.
P. Mykhailiuk *EurJOC* **2015**, 7235.
P. Mykhailiuk *Angew. Chem. Int. Ed.* **2015**, 6558.

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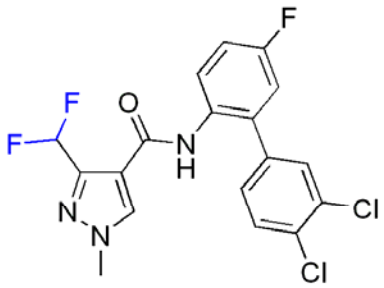
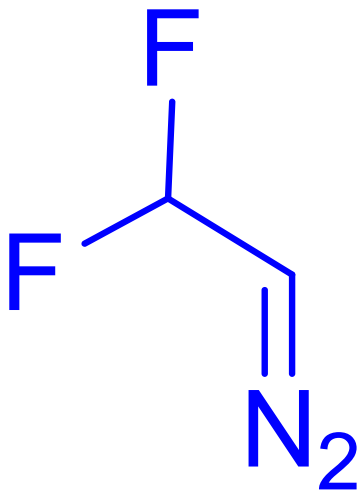
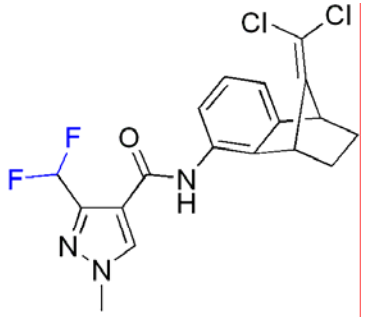
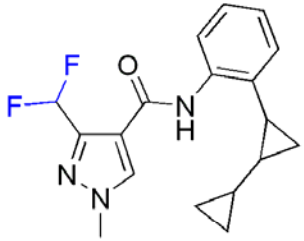


Bixafen
Bayer CS

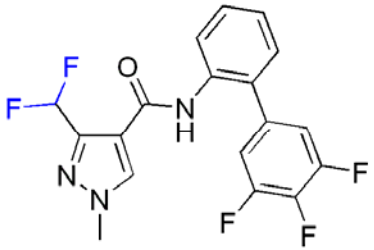




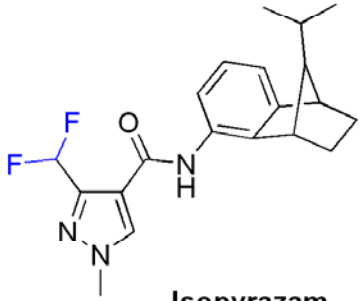
Benzovindiflupyr
Syngenta



Sedaxane
Syngenta

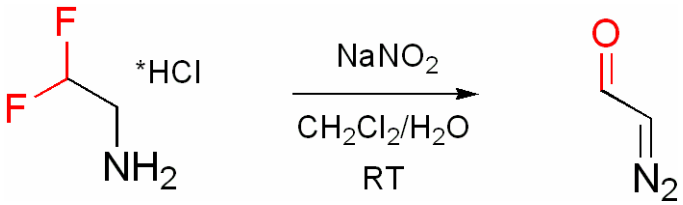


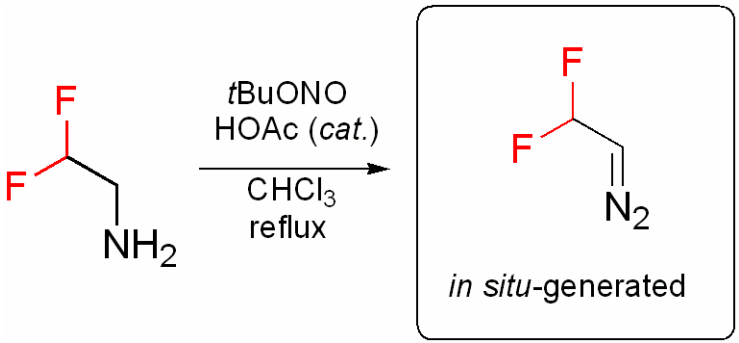
Fluxapyroxad
BASF



Isopyrazam
Syngenta

In-situ generation of CHF_2CHN_2

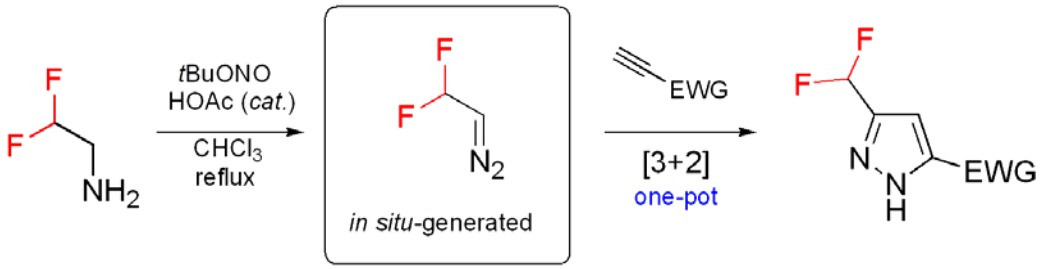


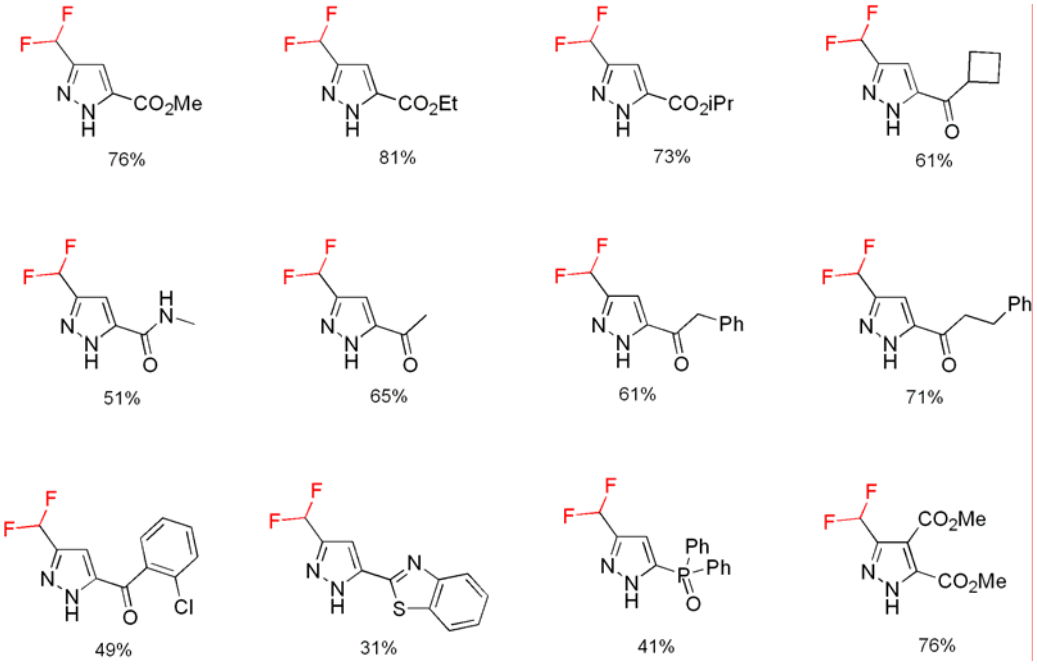


non-aqueous conditions?

P. Mykhailiuk *Angew. Chem. Int. Ed.* **2015**, 6558.

CHF_2-pyrazoles





P. Mykhailiuk *Angew. Chem. Int. Ed.* **2015**, 6558.

Enamine

In the Pipeline

May 13, 2015

More Fluorinated Fun

Posted by **Derek**

If you're an imaginative organic chemist, you how to generate it *in situ* without blo derivative. The key is to avoid aqueous ar Pavel Mykhailiuk of Enamine for making tl

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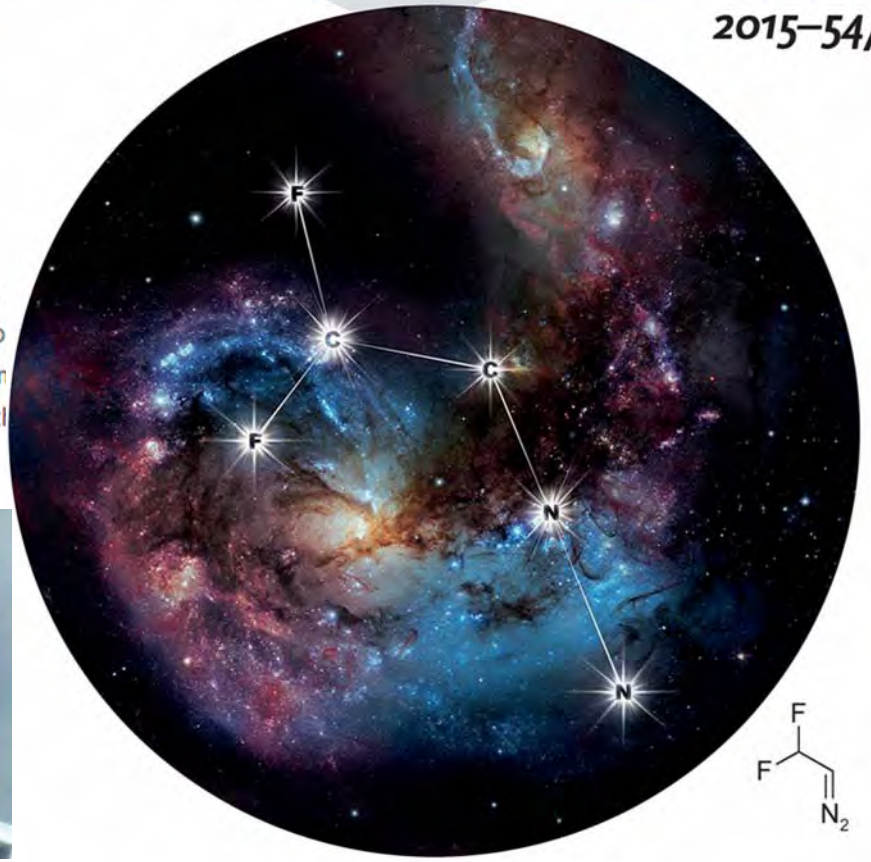

New Reagent Brings Fresh Approach To Fluorination

Stephen K. Ritter

To test its reactivity, **Mykhailiuk** trapped the reagent in a one-pot [3+2] cycloa disubstituted alkynes. **Mykhailiuk** selected the pyrazoles as a target because agrochemicals made by Syngenta, Bayer, and BASF.

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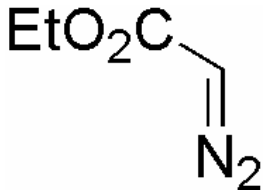
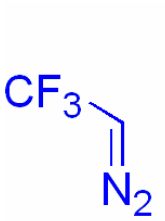
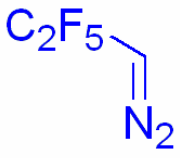


popular (> 4000 reactions)



>70 papers



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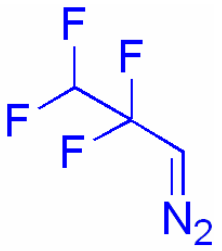

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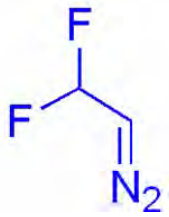

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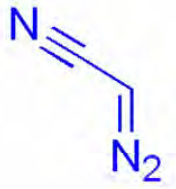

2015:

in situ-generated $RCHN_2$

Alekseenko A.
Artamonov O.
Artemenko A.
Andrushko O.
Arkhipov A.
Arkhipov V.
Bilenko V.
Chalyk B.
Datcenko O.
Denisenko O.
Dmitriv U.
Druzhenko T.
Granat D.
Gorulia O.
Garbuz P.
Gavrilenko K.
Gryshuk S.
Iminov R.
Komarov I.
Kokhan S.

500 chemists

Kondratov V.
Kubyshkin V.
Khutorianskii A.
Levchenko K.
Logvinenko V.
Martirosov R.
Moroz U.
Mituk A.
Mikhalchuk V.
Ostapchuk E.
Pasternak A.
Parhomenko L.
Pervak I.
Pustovit U.
Radchenko D.
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Trofimchuk S.
Tverdokhlebov A.
Tymtsunik A.
Volochnyuk D.
Yakovenko N.
Yarmolchuk V.
Yarmoluk D.

Thank you!

Enamine: world's largest supplier of building blocks

2016