



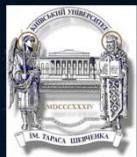
Флуоровмісні амінокислоти, аміни та діазоалкани: синтез та застосування в медичній хімії і агрономії

Подано

на Премію Президента України

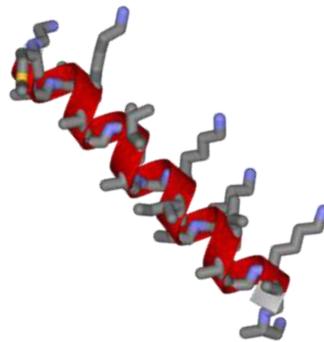
к.х.н. Павло К. Михайлюк

2017

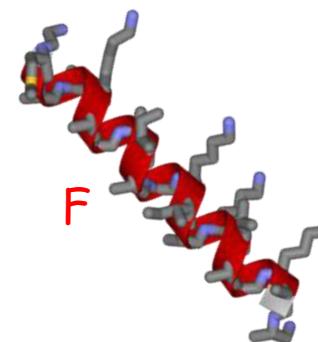


Дослідження протимікробних пептидів твердотільним ^{19}F -ЯМР

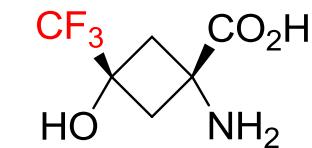
Природний пептид



Синтез F-аналогу

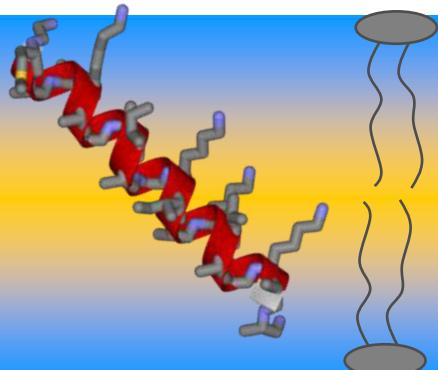


Синтез F-міток

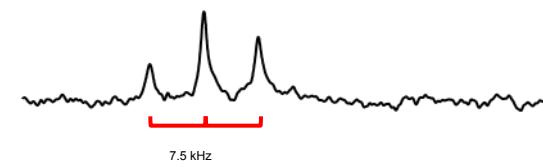


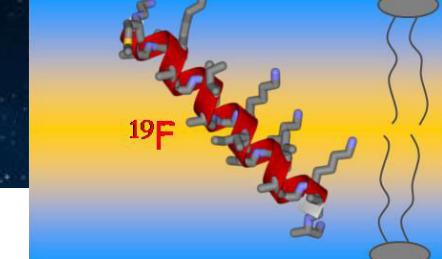
конформаційно
утруднені

Розрахунок структури



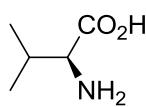
Твердотільний ^{19}F -ЯМР



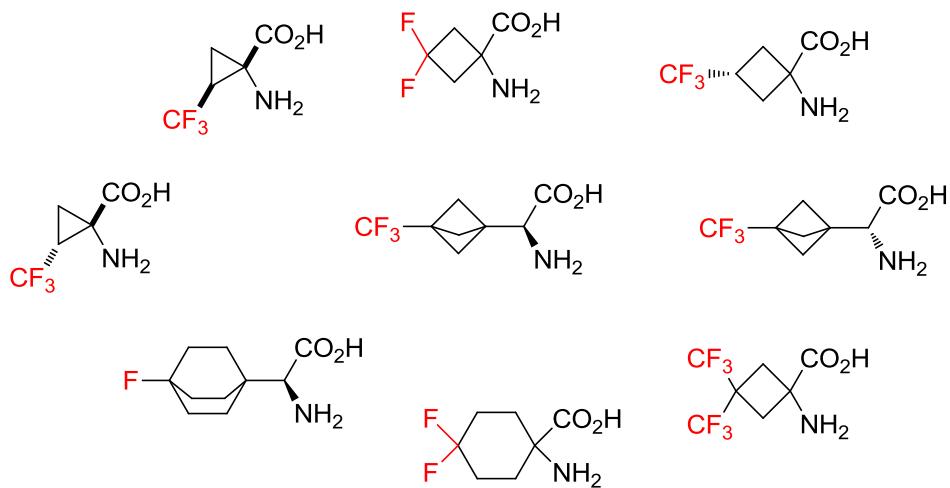
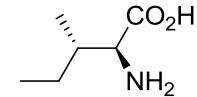
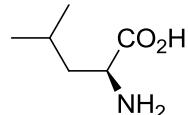


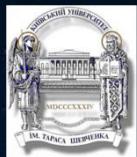
Нові ^{19}F -мітки для аліфатичних амінокислот:

Валін

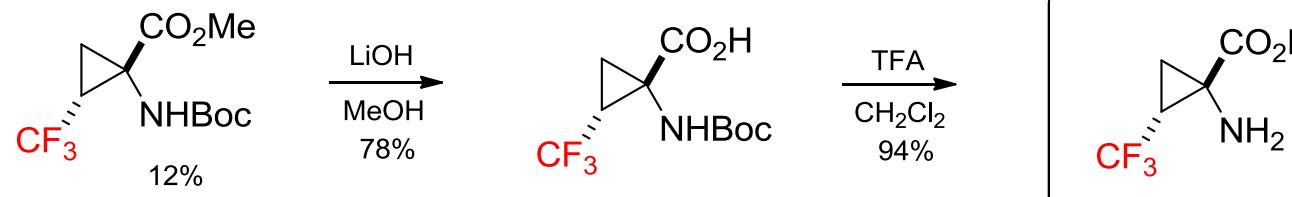
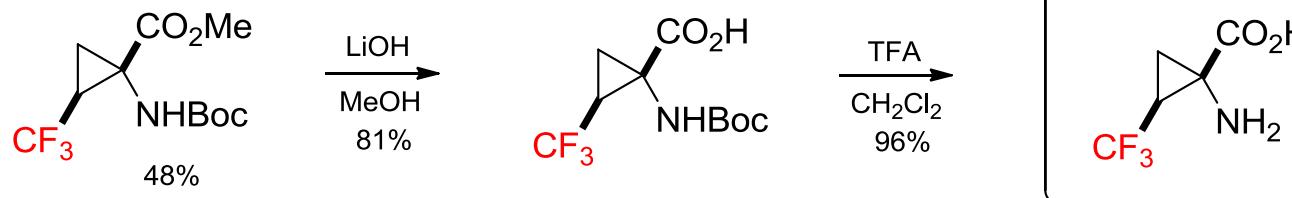
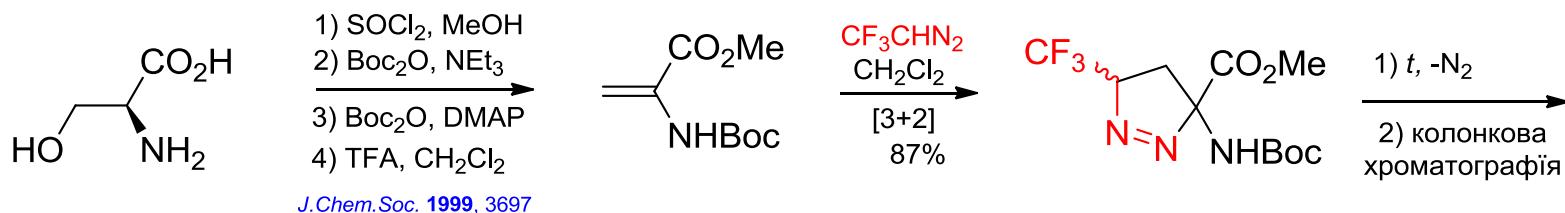


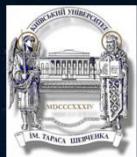
Лейцин



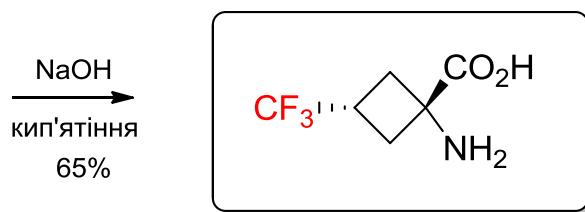
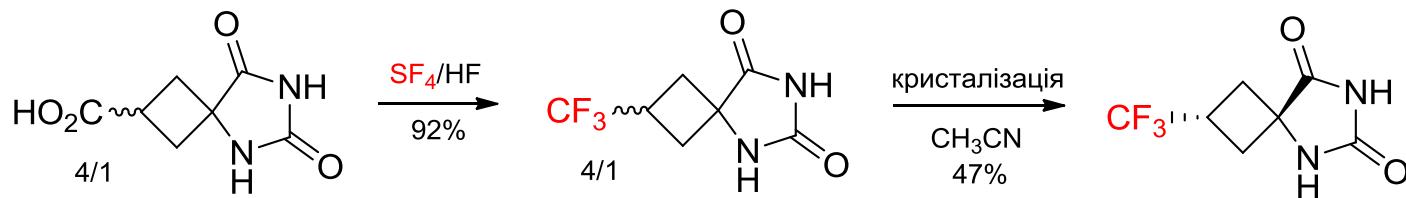
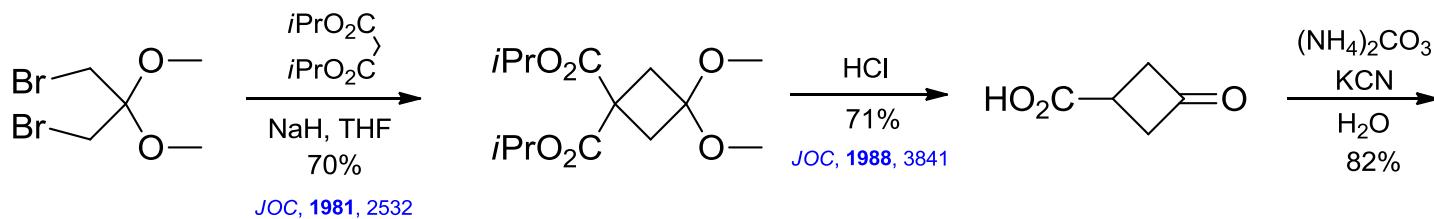


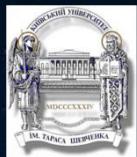
CF₃-аміноциклопропанкарбонова кислота



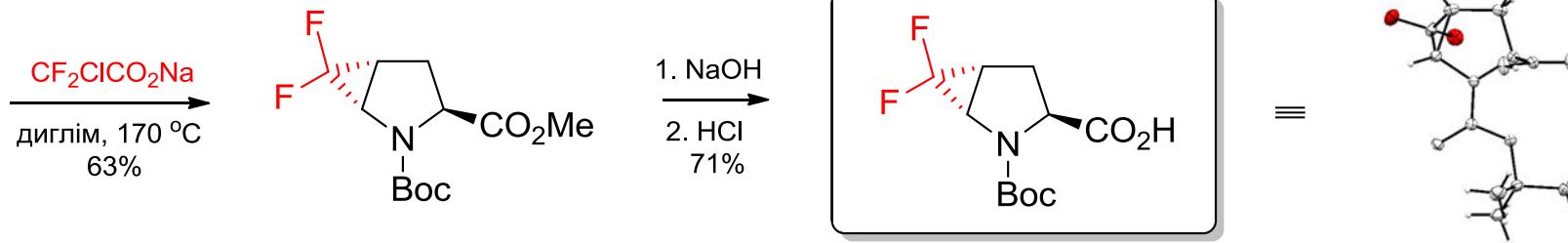
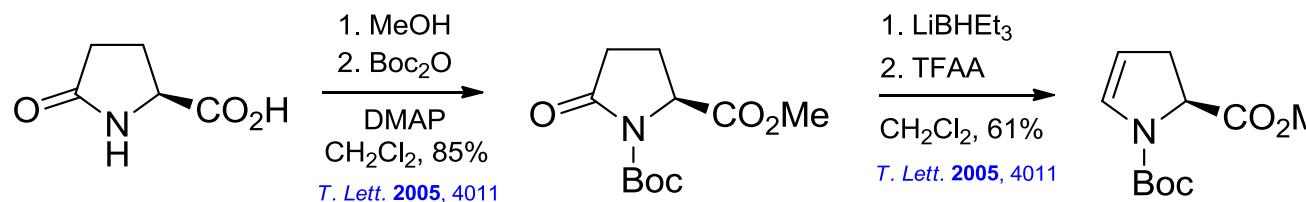


CF₃-аміноциклобутанкарбонова кислота

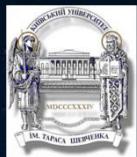




F₂-4,5-метанопролін (F₂-Pro)

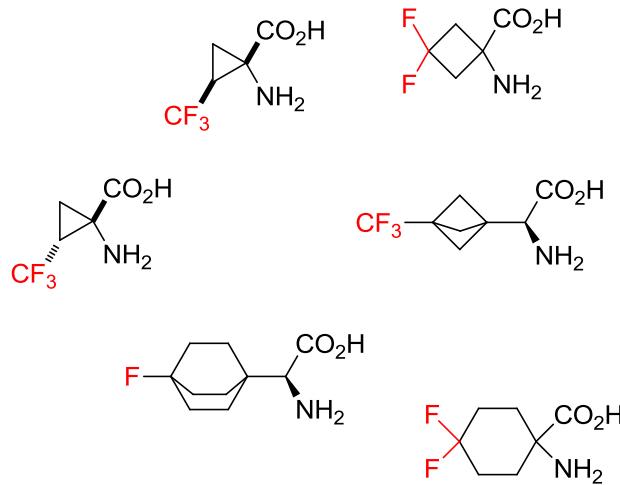


- V. Kubyshkin et al. *J. Fluorine Chem.* 2015, 73.
V. Kubyshkin et al. *J. Fluorine Chem.* 2013, 136.
V. Kubyshkin et al. *Org. Lett.* 2012, 5254.

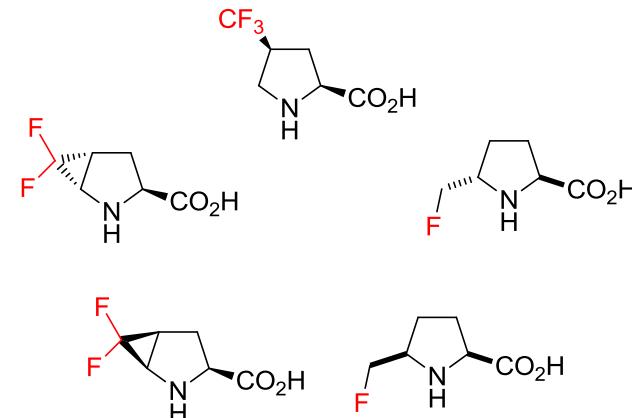


Синтезовані ^{19}F -мітки:

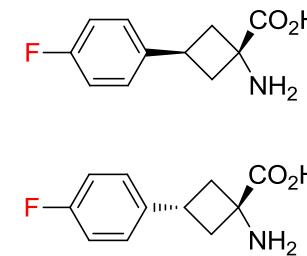
Лейцин, ізолейцин, валін, гліцин



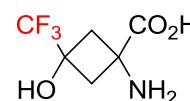
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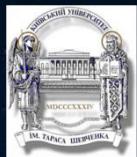
Фенілаланін



Серин



- D. Bandak et al. *OrgLett* **2015**, 226.
 V. Kubyshkin et al. *Org.Biomol.Chem.* **2015**, 3171.
 A. Tkachenko et al. *Eur. J. Org. Chem.* **2014**, 3584.
 A. Tkachenko et al. *Angew. Chem. Int. Ed.* **2013**, 1487.
 A. Kubyshkin et al. *J. Fluorine Chem.* **2013**, 136.
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 O. Grygorenko et al. *Tetrahedron* **2011**, 803.
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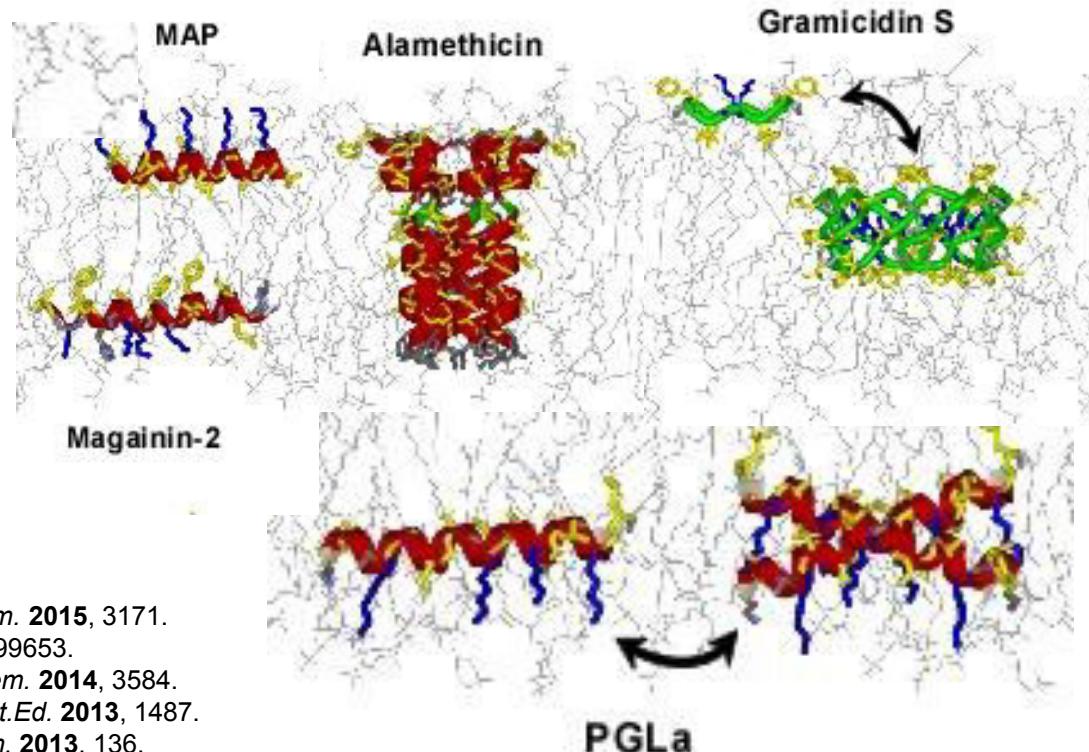


Визначена структура >10 пептидів



Співпраця з
проф. А. Ульрих
Німеччина

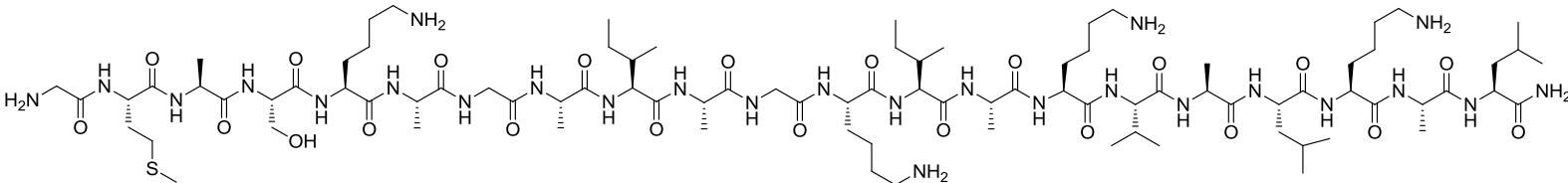
- Темпорин A
- Аламетицин
- Граміцидин S
- Магаїнін 2
- (KIGAKI)₃
- SAP
- **PGLa**
- VPE
- VPK
- Kalata B1
- Транспортан 10
- BP100



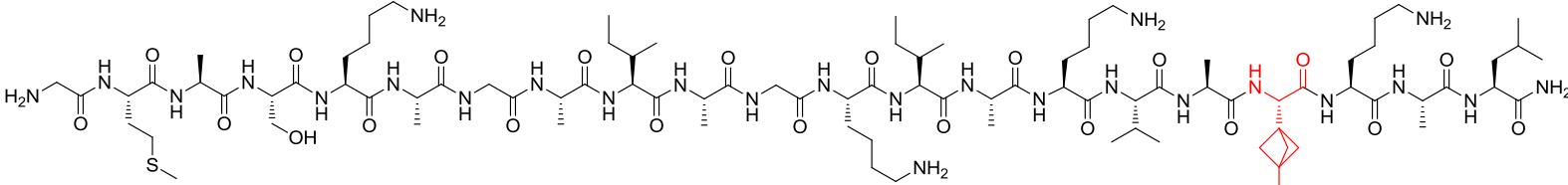
- V. Kubyshkin et al. *Org. Biomol. Chem.* **2015**, 3171.
S. Fanghaenel et al. *PLOS* **2014**, e99653.
A. Tkachenko et al. *Eur. J. Org. Chem.* **2014**, 3584.
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V. Kubyshkin et al. *J. Fluorine Chem.* **2013**, 136.
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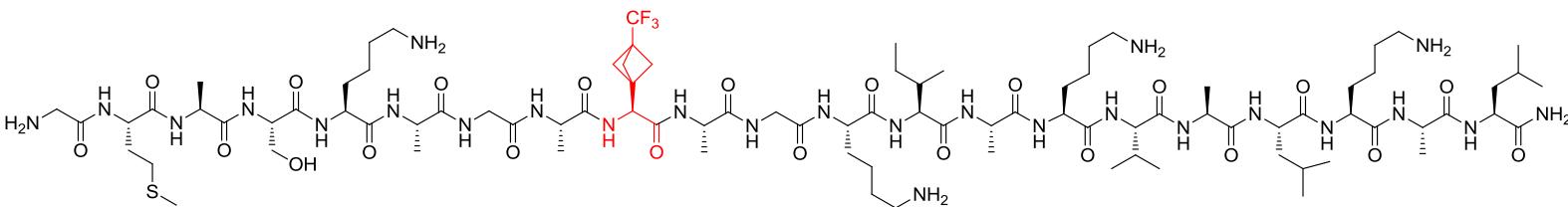
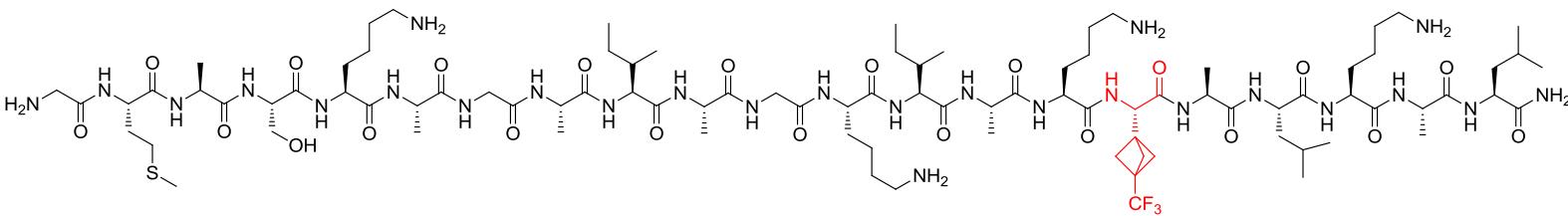
Протимікробний пептид PGLa

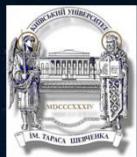


Синтез CF_3 -пептидів

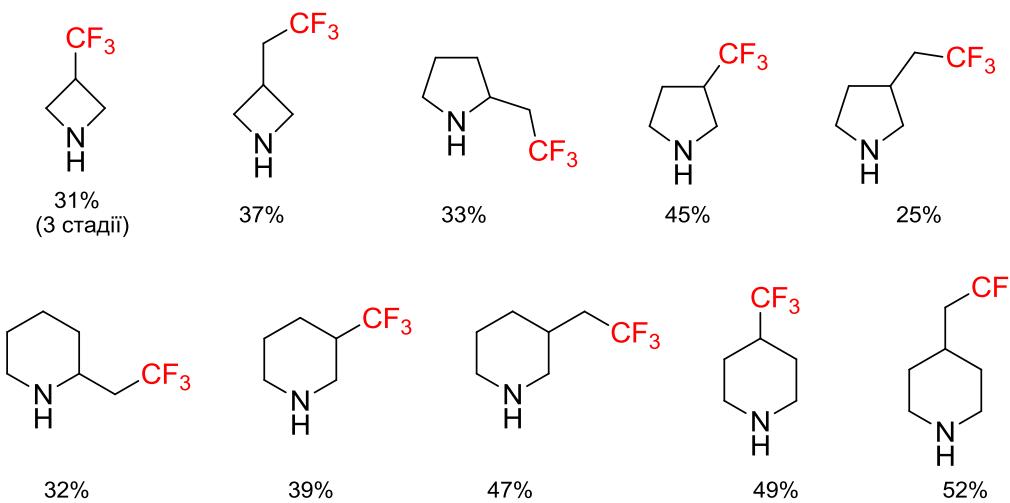
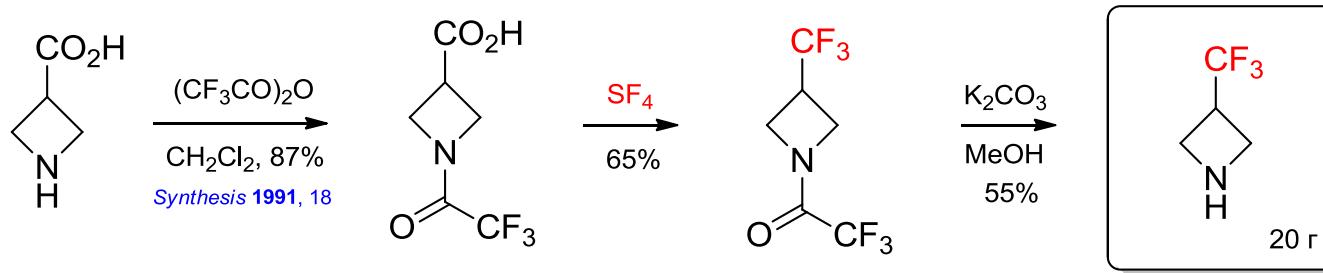


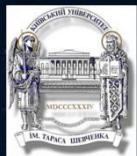
Fmoc



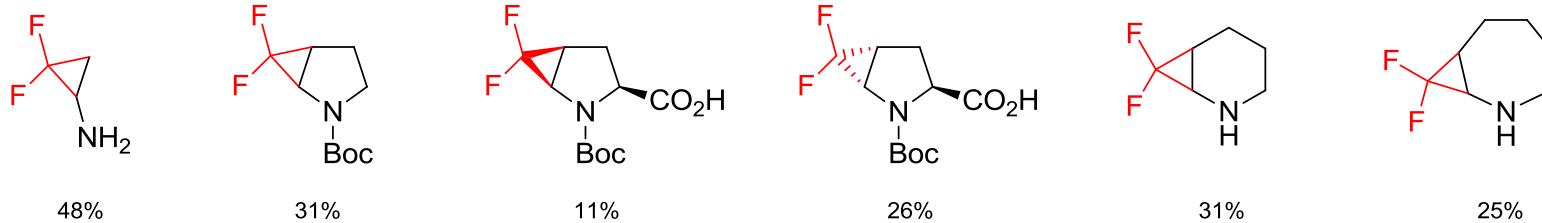
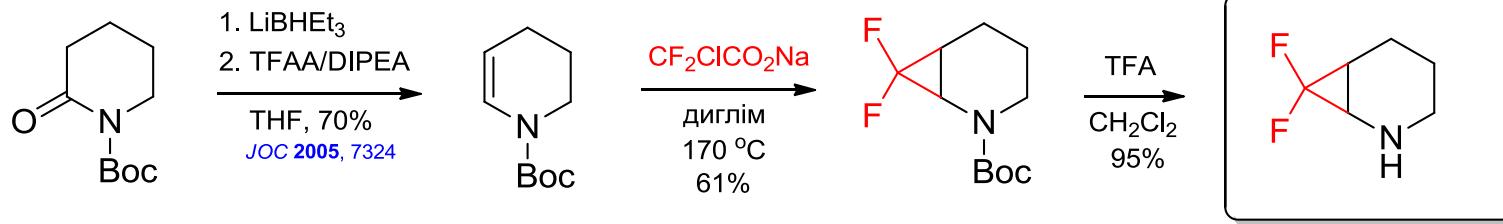


CF₃-аміни з амінокислот





CF₂-біциклічні аміни



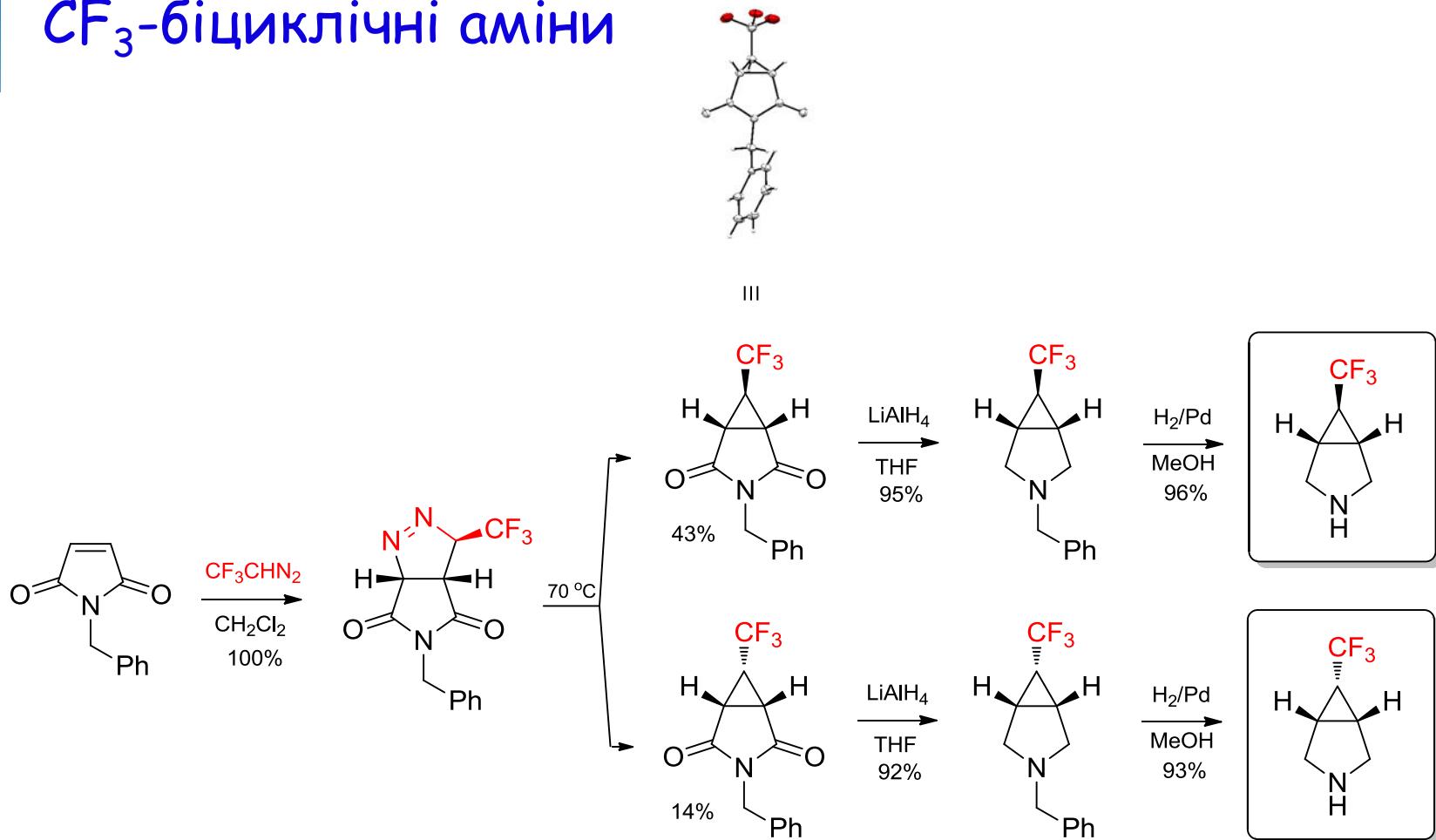
V. Kubyshkin et al. *J. Fluorine Chem.* **2015**, 73.

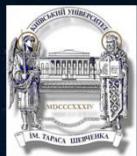
V. Kubyshkin et al. *J. Fluorine Chem.* **2013**, 136.

V. Kubyshkin et al. *Org. Lett.* **2012**, 5254.

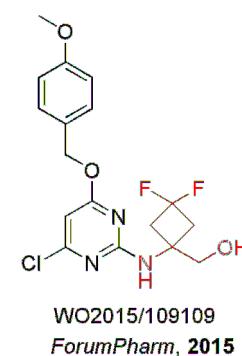
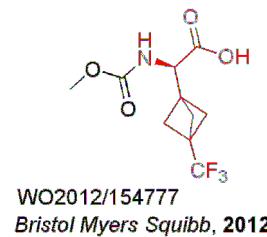
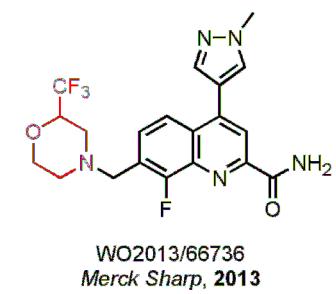
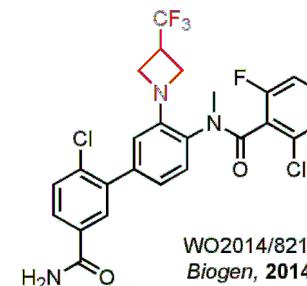
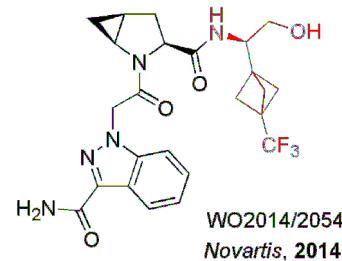
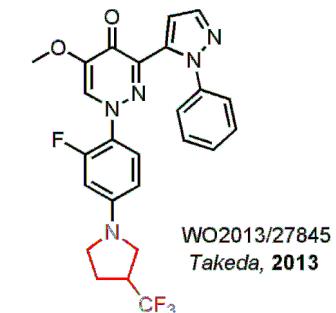
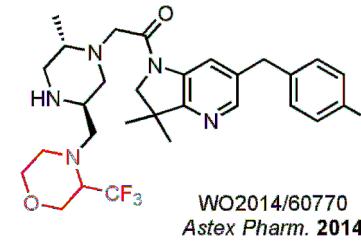
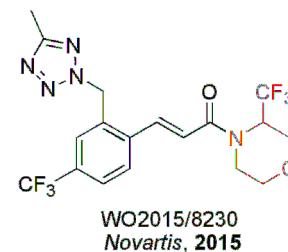
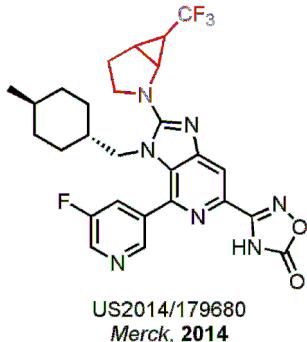


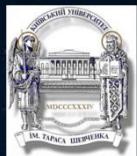
CF₃-біциклічні аміни



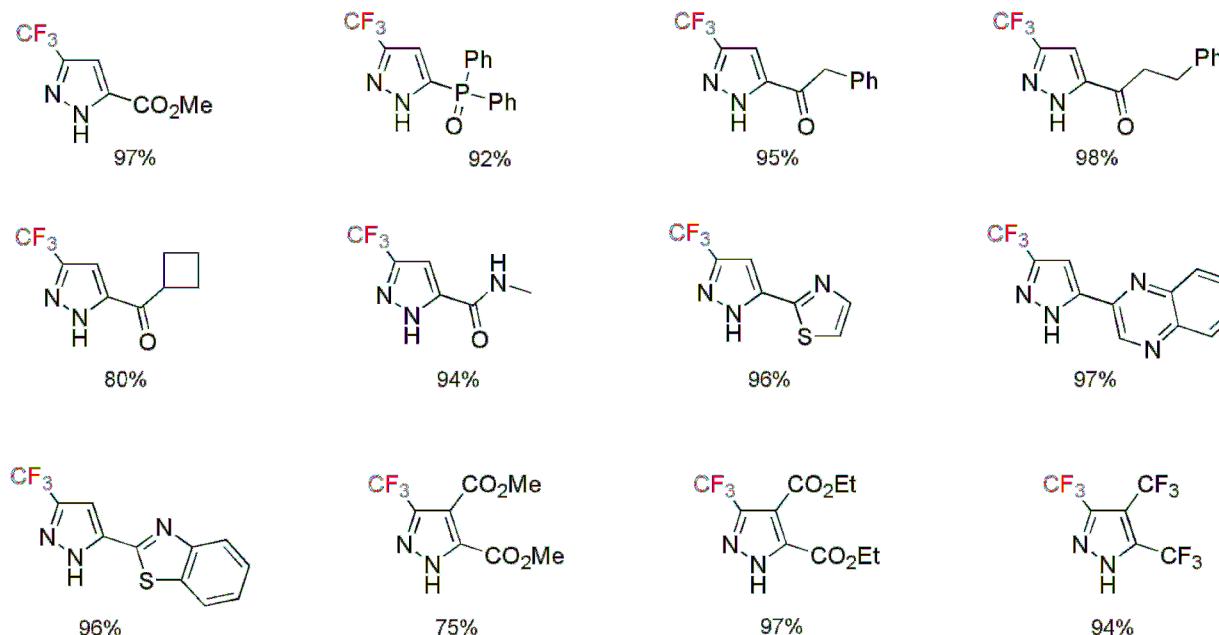
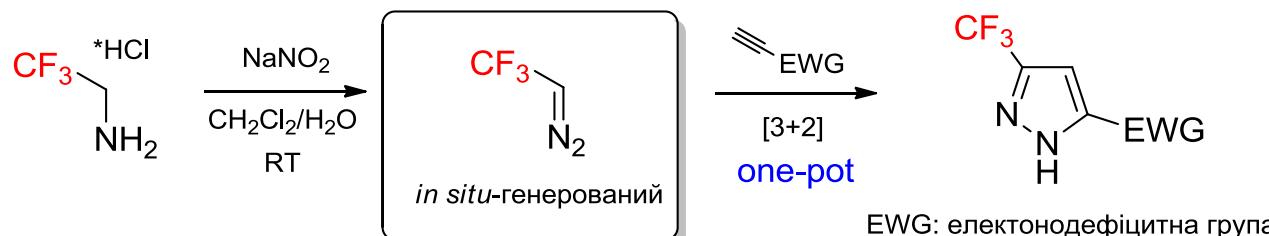


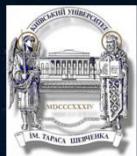
Наші F-аміни вже застосовуються в медичній хімії:





CF₃-піразоли





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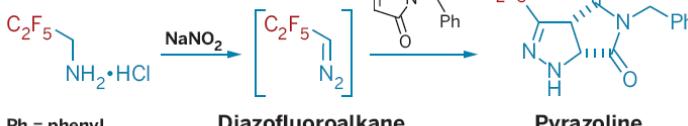
C&EN

CHEMICAL &

ING NEW

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, $-\text{C}_2\text{F}_5$, to complex molecules

ly generates the fluorinated diazoalkane, $\text{C}_2\text{F}_5\text{CH}=\text{N}_2$, *in situ* from $\text{C}_2\text{F}_5\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ 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

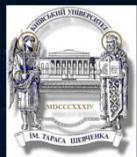
A new fluorinated reagent ...

discovered by scientists at Enamine Ltd., that is, $\text{C}_2\text{F}_5\text{CHN}_2$, is generated *in situ* from $\text{C}_2\text{F}_5\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ 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.



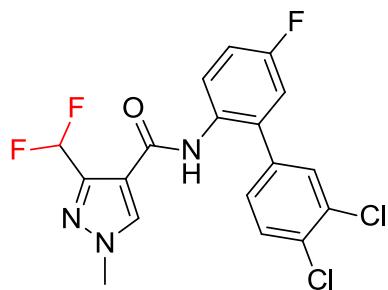
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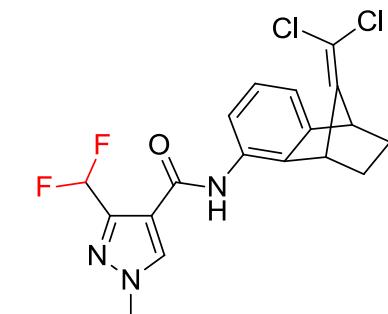
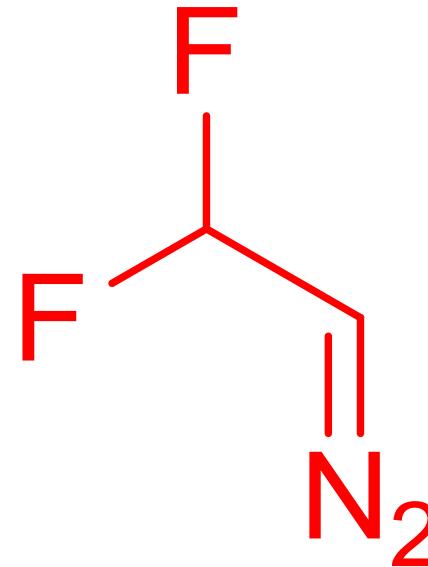


F

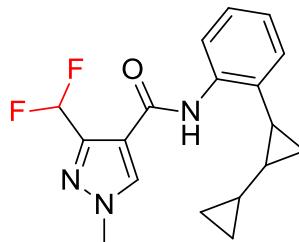
2015: невідомий



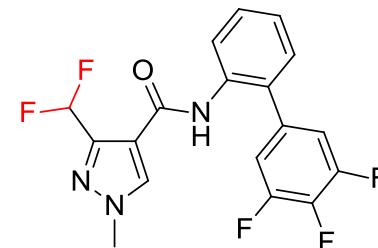
Bixafen
Bayer CS



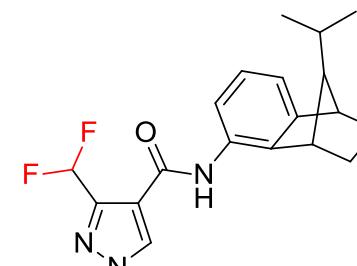
Benzovindiflupyr
Syngenta



Sedaxane
Syngenta



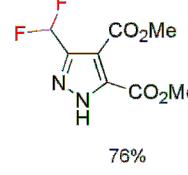
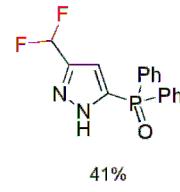
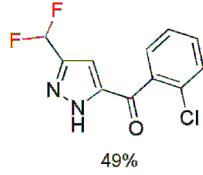
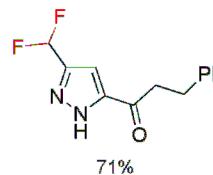
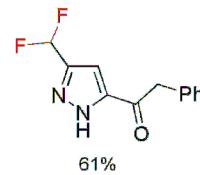
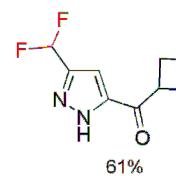
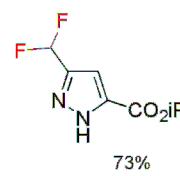
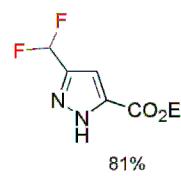
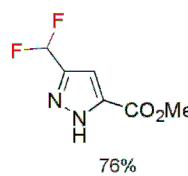
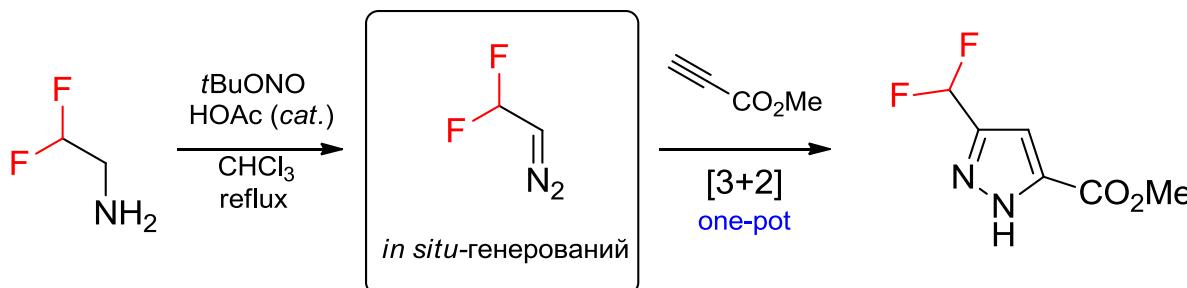
Fluxapyroxad
BASF



Isopyrazam
Syngenta



CHF₂-піразоли



2015-54/22



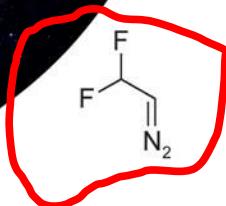
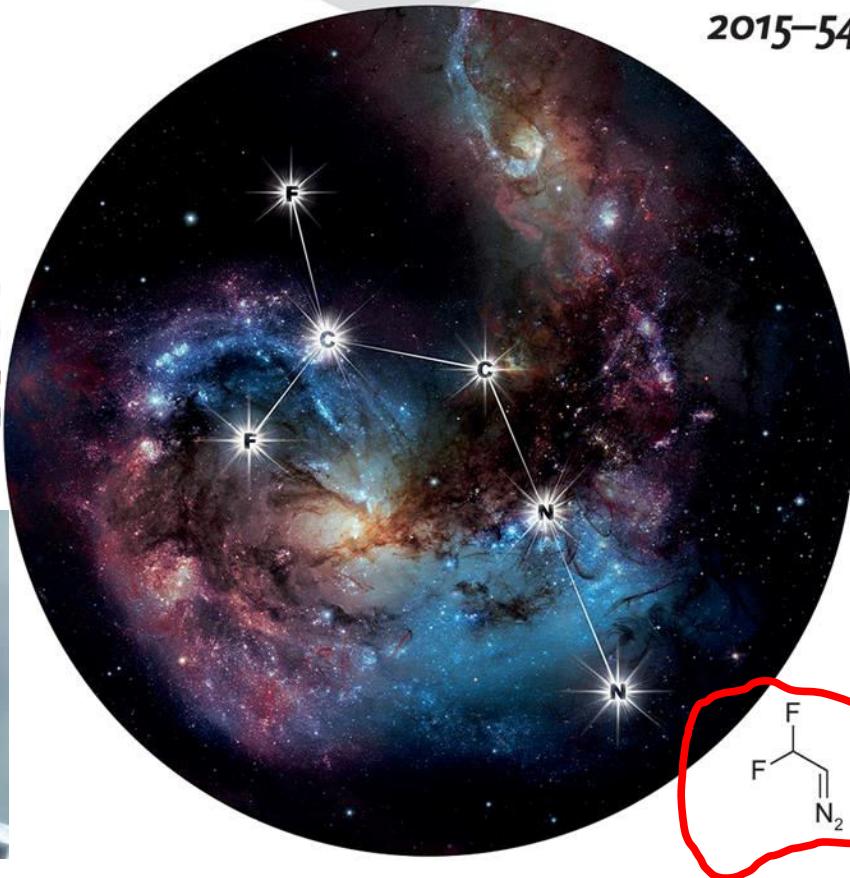
In the Pipeline

May 13, 2015

More Fluorinated Fun

Posted by **Derek**

If you're an imaginative organic chemist, you know how to generate it *in situ* without a derivative. The key is to avoid aqueous anhydrides. Pavel Mykhailiuk of Enamine for making trifluoromethylated alkenes.



APRIL 28, 2014



New Reagent Brings Fresh Approach To Fluorination

Stephen K. Ritter

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

Frustrated Lewis Pairs

Review by D. W. Stephan and G. Erker

Electrochemical Amination

Highlight by S. R. Waldvogel and S. Möhle

ACIEFS 54 (22) 6373–6652 (2015) · ISSN 1433–7851 · Vol. 54 · No. 22

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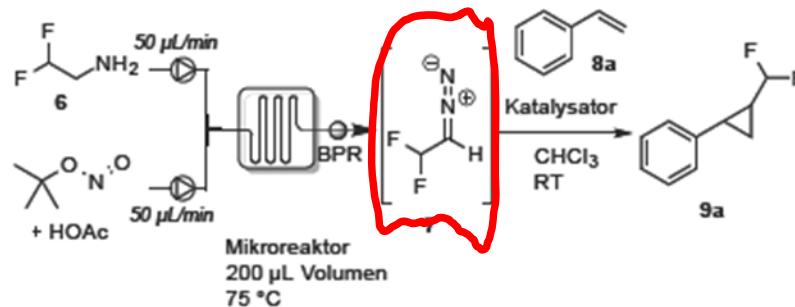
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Katharina J. Hock,^[+] Lucas Mertens,^[+] and Rene M. Koenigs^{*[a]}



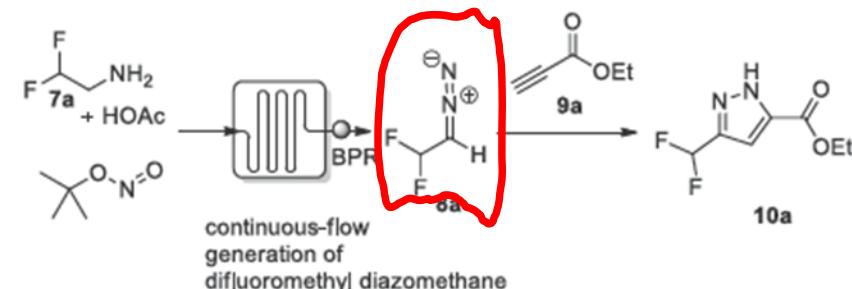
K. Hock et al. *Angew. Chem. Int. Ed.* **2016**, *in press*.

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Fluoroalkyl-substituted Diazomethanes and their Application in a General Synthesis of Pyrazoles and Pyrazolinones

Lucas Mertens,^[+] Katharina J. Hock,^[+] and Rene M. Koenigs^{*[a]}



K. Hock et al. *Chem. Eur. J.* **2016**, *9542*.

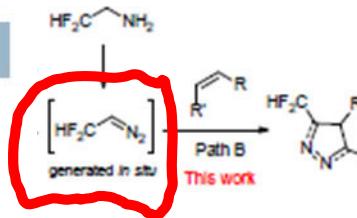
Organic Chemistry Frontiers

ARTICLE

[3+2] cycloaddition of electron-deficient alkenes and *in situ* generated CF_2HCHN_2 : an efficient strategy for synthesis of difluoromethylated pyrazolinest†

Xinling Yut, Jue Lit, Songyang Lv, Hailong Zhang, Li Hai, Su Fu* and Yong Wu*

Received 00th January 20xx,
Accepted 00th January 20xx
DOI: 10.1039/xxxxxxx

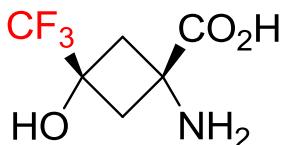


X. Yu et al. *Org. Front. Chem.* **2016**, *in press*.

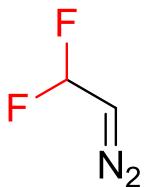


Висновки:

F-амінокислоти
для дослідження пептидів



F-діазоалкани
для органічного синтезу



F-аміни
для медичної хімії

