

Rearrangements of fluorinated cyclopropylamines as a novel approach towards fluoroalkene-based peptidomimetics

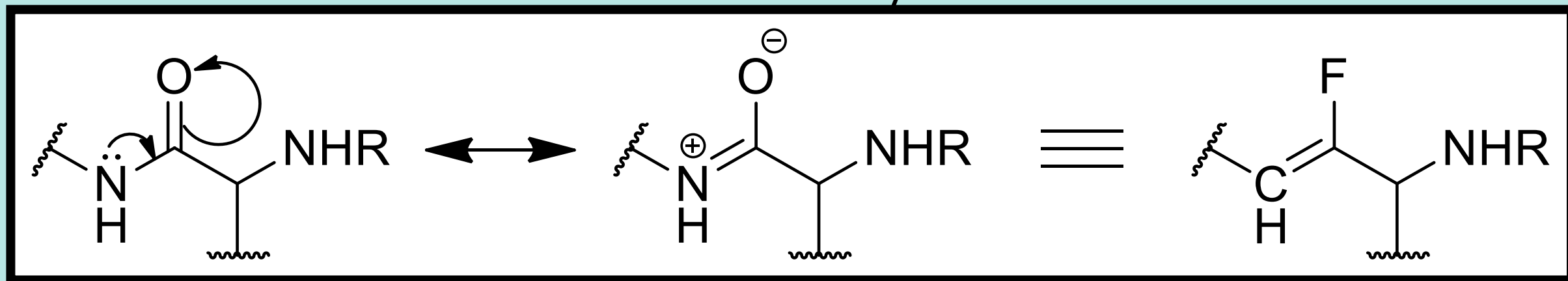


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Moscow South-Eastern School named after V.I. Chuikov
(former Moscow Chemical Lyceum)

Supervisor: Dr. Maxim Novikov
N.D. Zelinsky Institute of Organic Chemistry

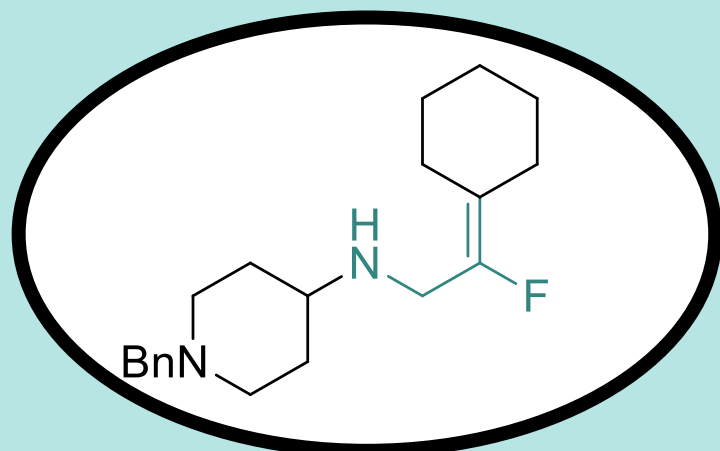


Actuality

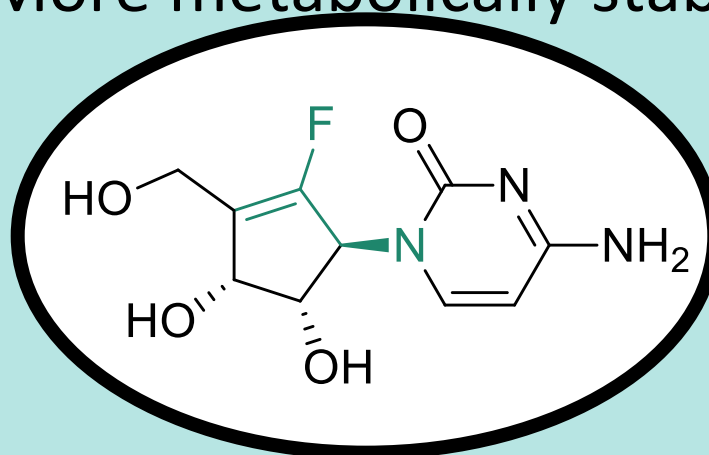


Advantages of fluoroalkene-based peptidomimetics:

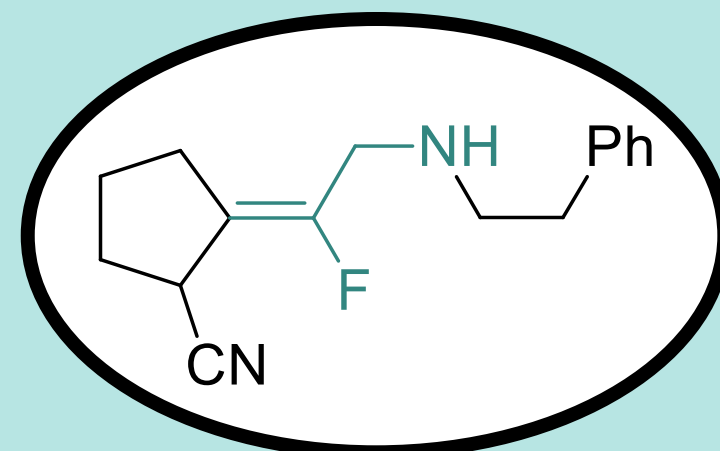
- ❖ Increased lipophilicity
- ❖ Strict conformation
- ❖ More metabolically stable



DPP II inhibitor

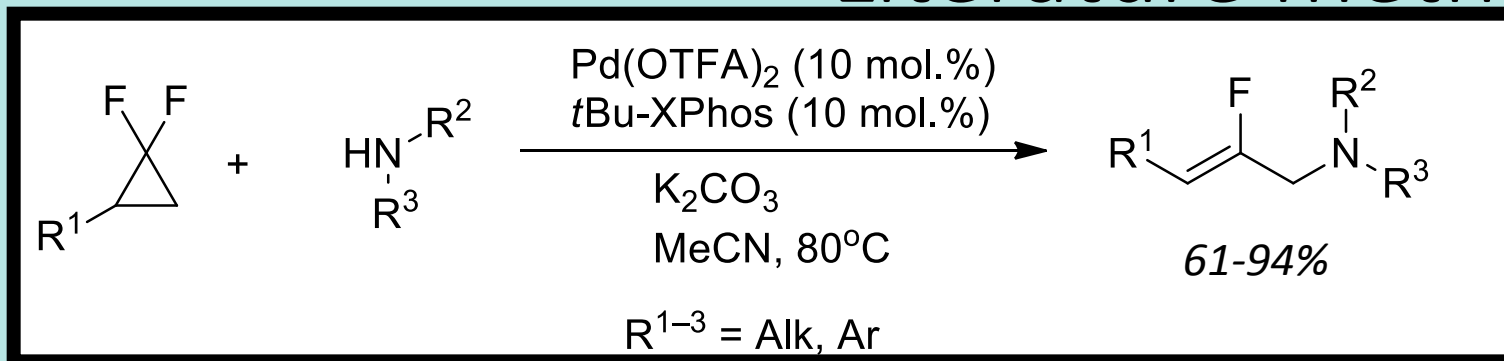


[F]-Neplanocin A

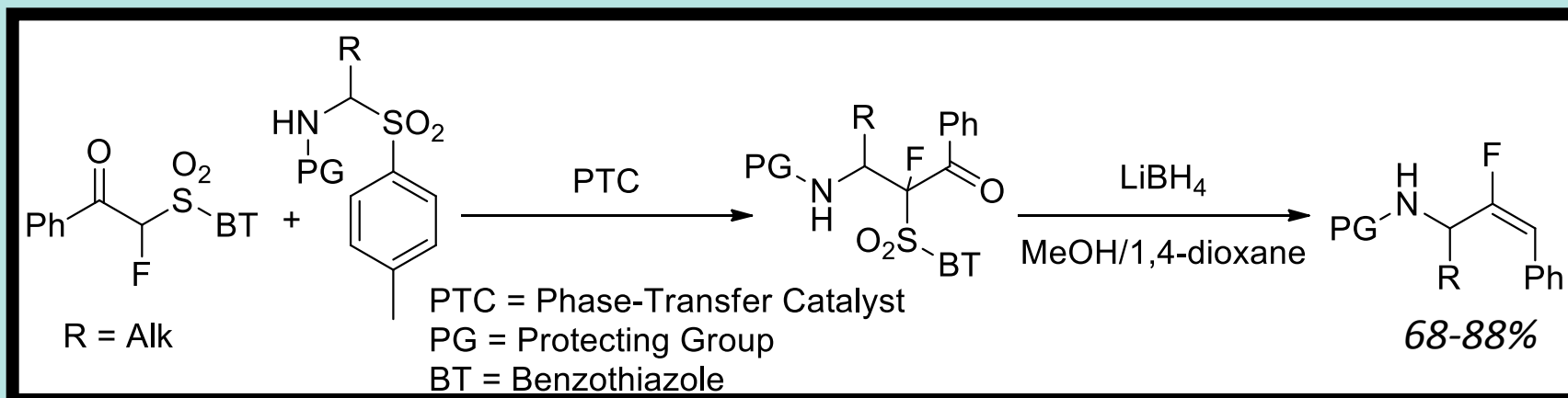


DPP IV inhibitor

Literature methods

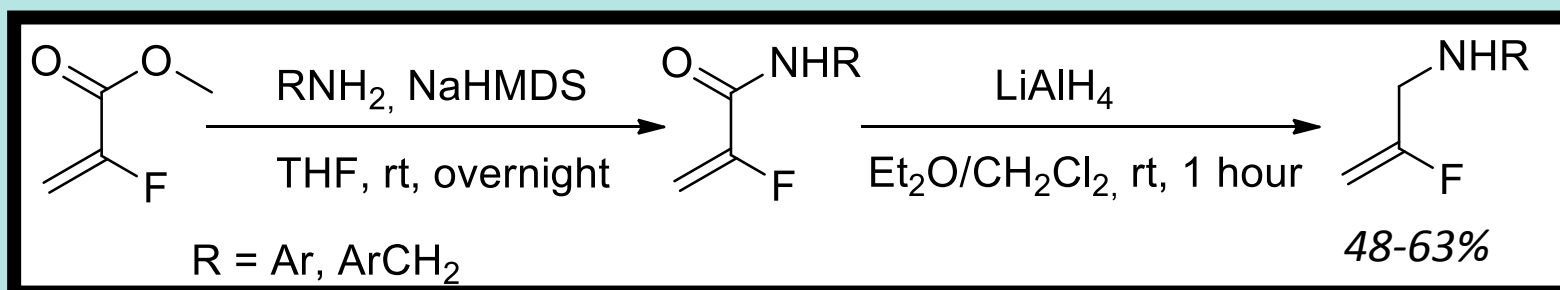


J. Xu, E.-A. Ahmed, B. Xiao, Q.-Q. Lu, Y.-L. Wang, C.-G. Yu, Y. Fu, *Angew. Chem.* **127** (2015) 8349–8353.



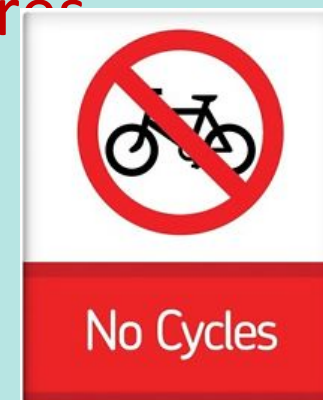
C. Calata, E. Pfund, T. Lequeux, *Tetrahedron* **67** (2011) 1398–1405.

C. B. Jacobsen, M. Nielsen, D. Worgull, T. Zweifel, E. Fisker, Jorgensen, *J. Am. Chem. Soc.* **133** (2011) 7398–7404.

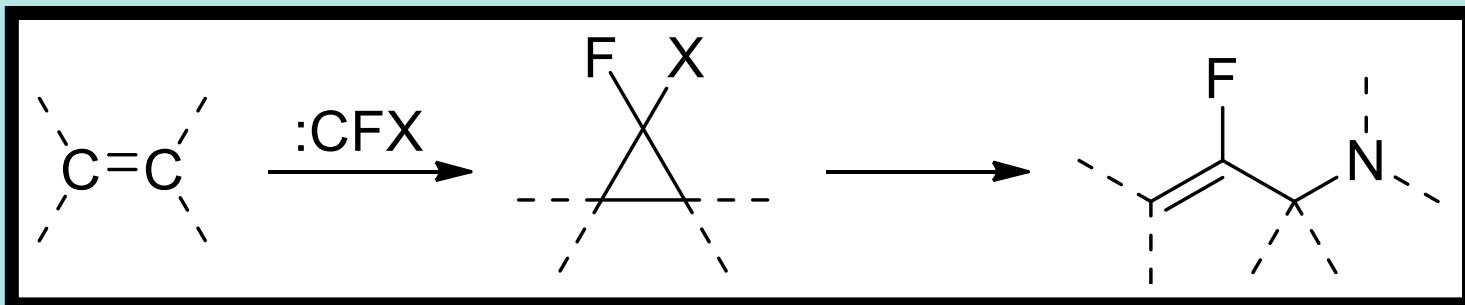


Y. Li, K. Li, Y. Wu, Q. Ma, X. Lei, *Tetrahedron* **72** (2016) 4845–4853.

- ❖ Expensive
- ❖ Produces a lot of waste
- ❖ Requires few stages
- ❖ Unable to synthesize cyclic structures



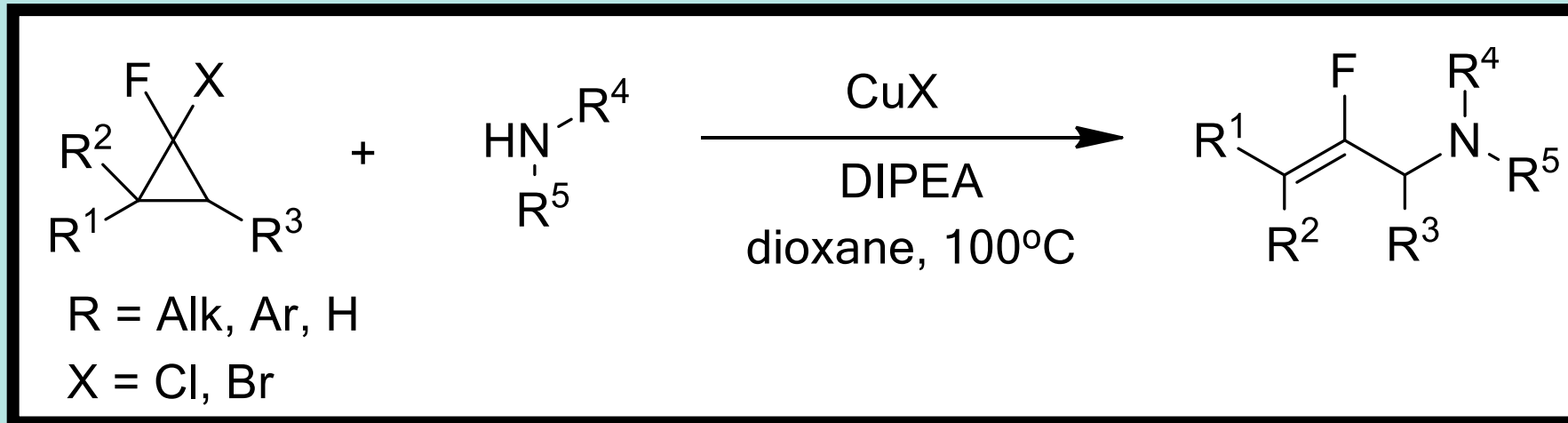
Methodology



Advantages over literature methods:

- ❖ Ability to synthesize cyclic fluoroalkenes
- ❖ Short synthesis from readily available substrates

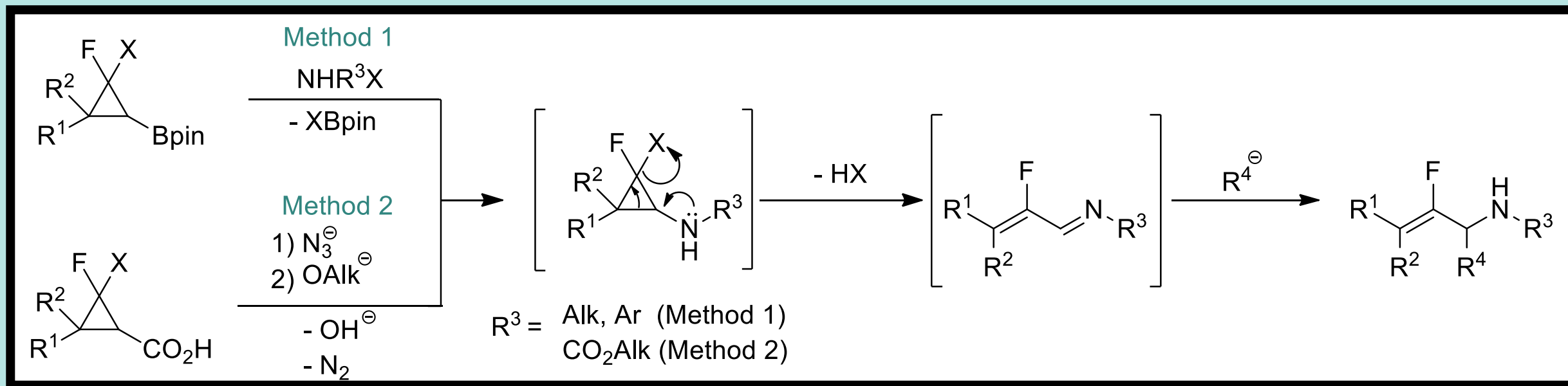
Earlier in our laboratory



- ❖ Up to 2 substituents in cyclopropane
- ❖ Less steps

M. A. Novikov, Y. A. Ibatov, N. V. Volchkov, M. B. Lipkind, S. E. Semenov, O. M. Nefedov, *J. Fluorine Chem.* **194** (2017) 58–72

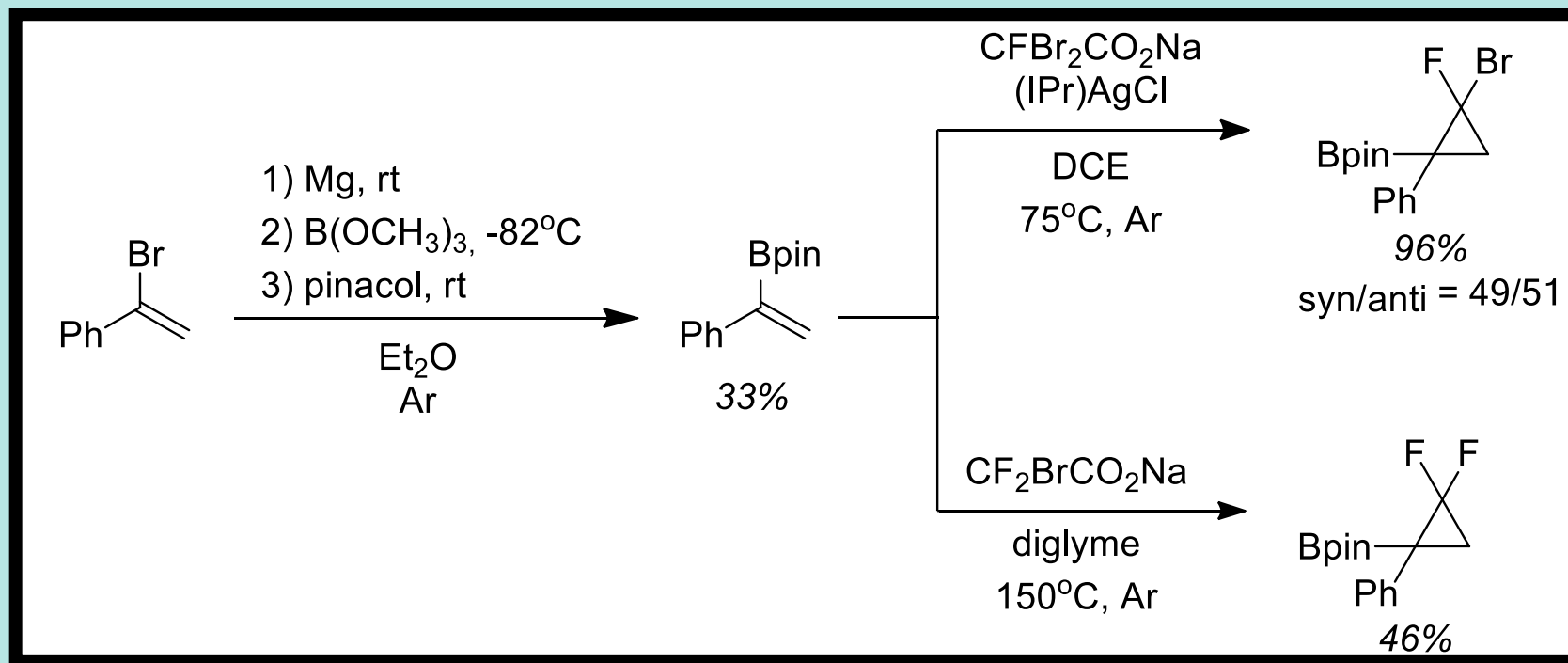
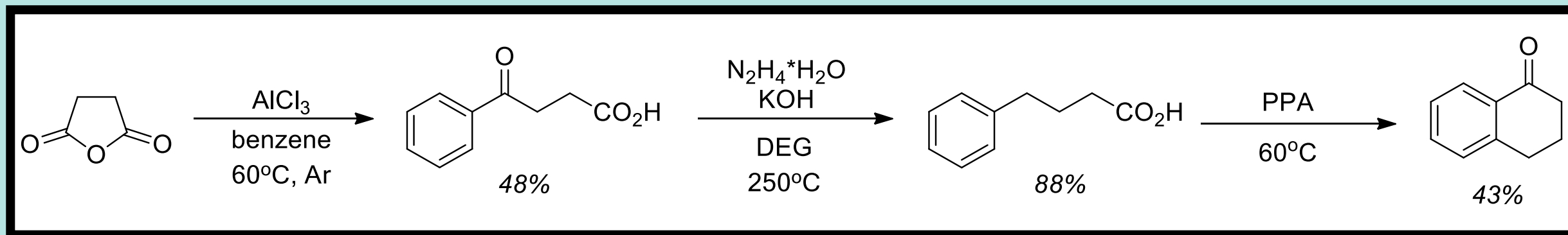
New idea



Advantages

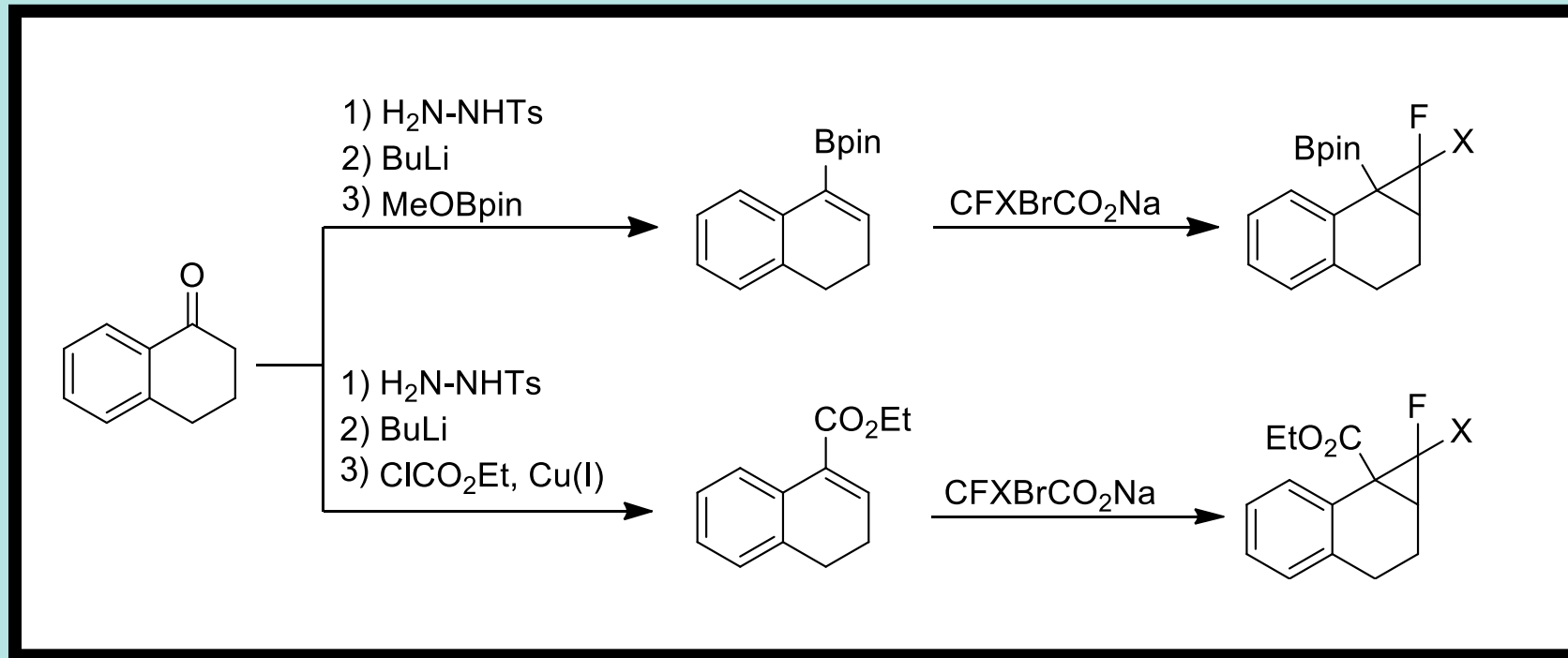
- ❖ Rearrangement occurs without heating (functional groups tolerance)
- ❖ Possibility to synthesize R⁴ separately (convergent synthesis)

Starting compounds

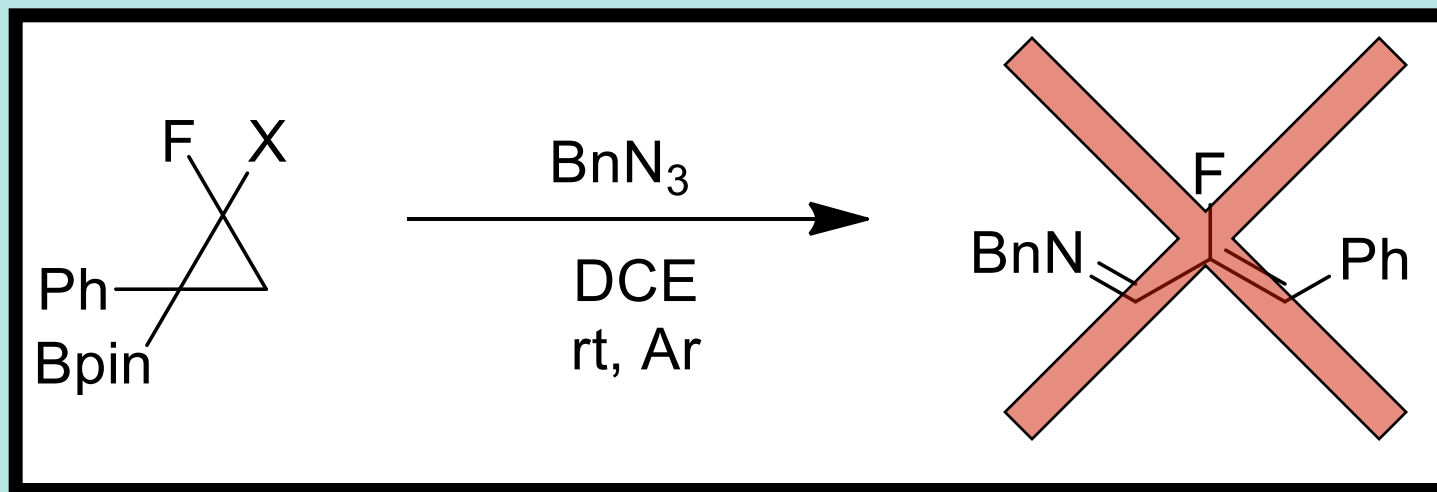


Structures of all obtained compounds were proved by ^1H NMR

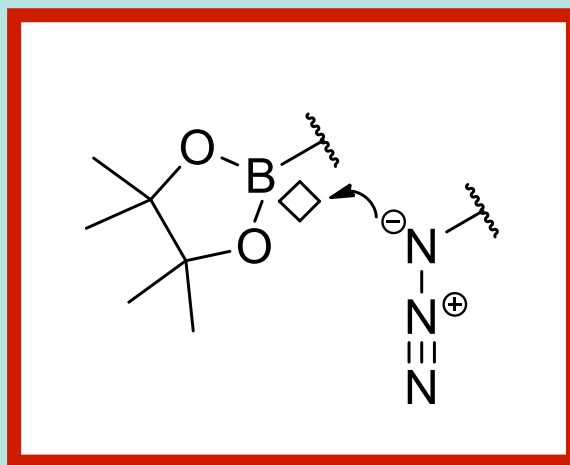
Starting compounds. Future plans



Method 1



**low boron
electrophilicity**

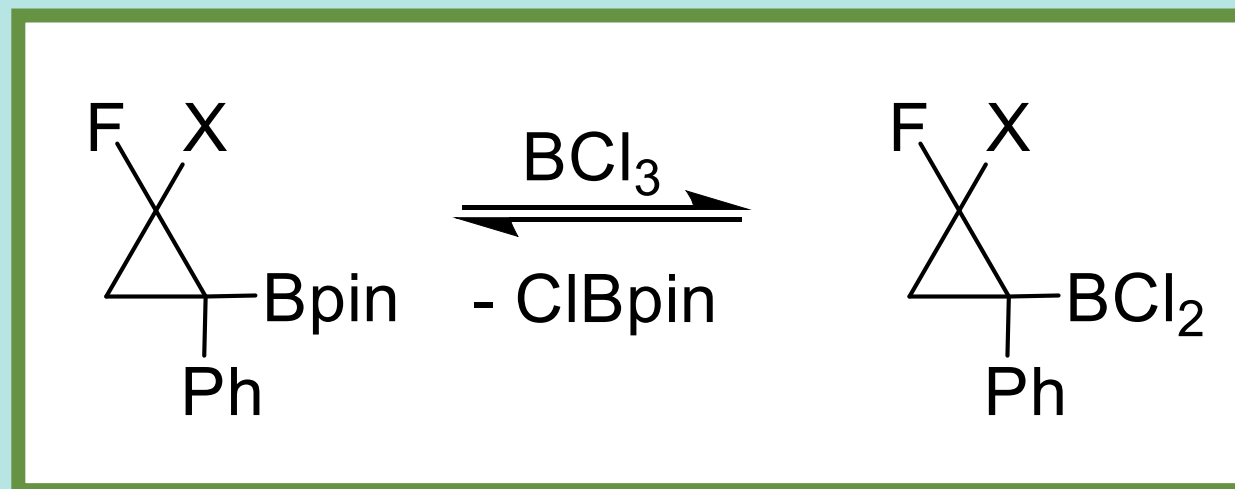


How to increase it?

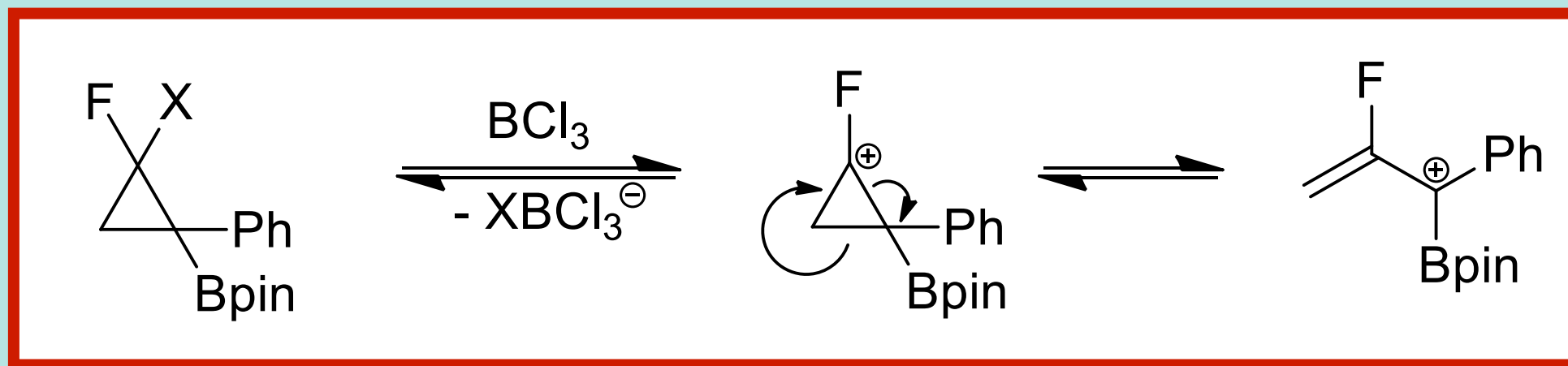


Method 1

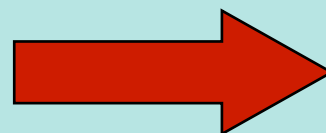
BCl_3 addition



Standard way to increase electrophilicity of boron



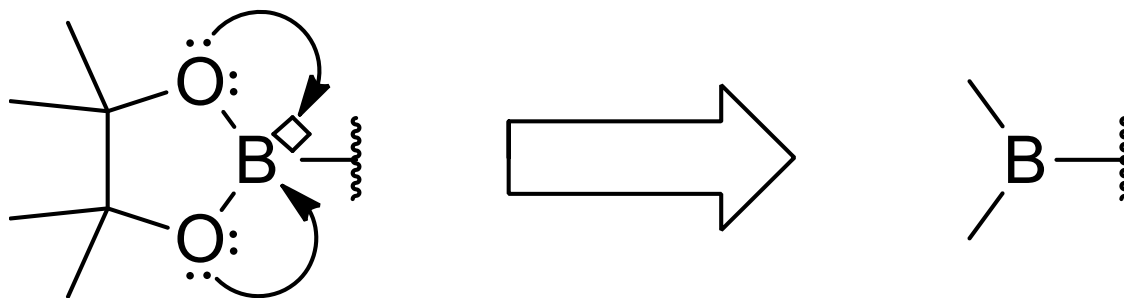
Rearrangement



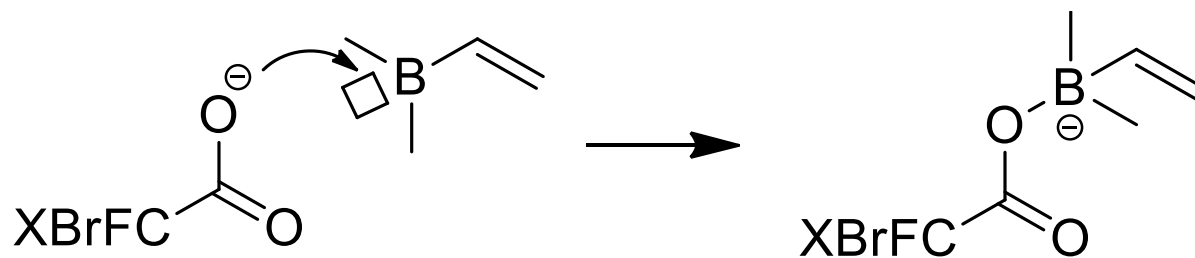
Complex mixture of products

Method 1. Future plans

Use alkyls
instead of
pinacol

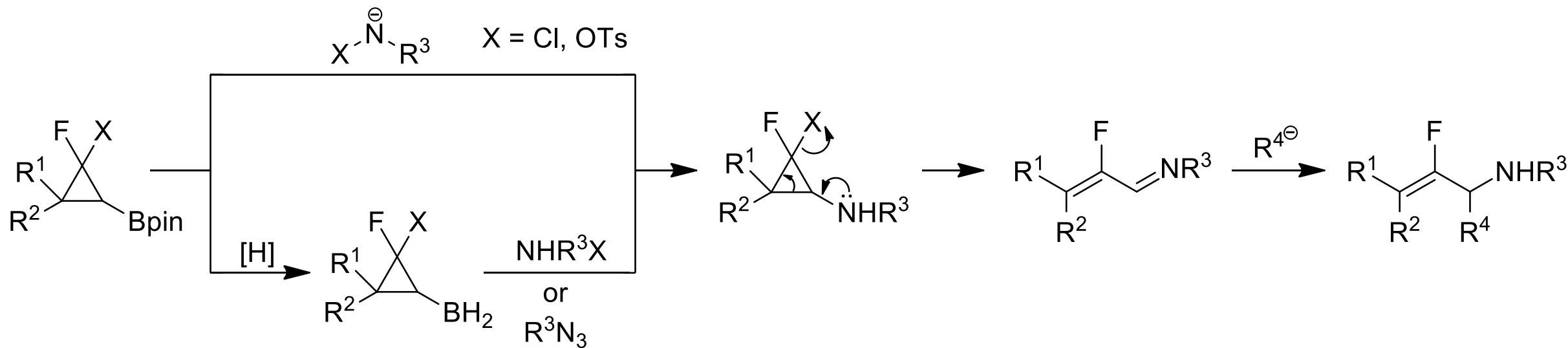


No conjugation,
more active

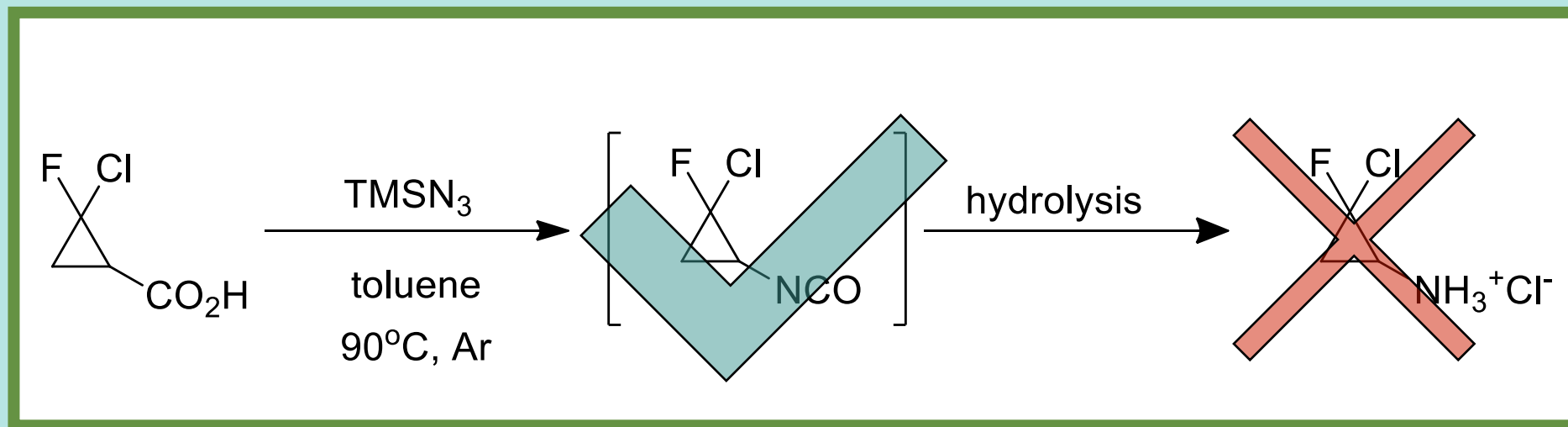


**Too active, hard to
cyclopropanate**

Method 1. Future plans



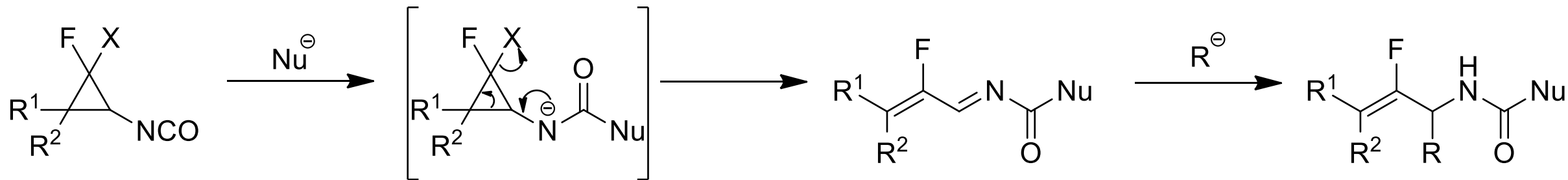
Method 2



detected by mass
spectrometry
and
gas chromatography

failed to
obtain

Method 2. Future plans



solution in
toluene

nucleophile-
mediated
ring opening

Results

- ❖ We suggested new way to the synthesis of fluoroalkene-based peptidomimetics
- ❖ We revealed that electrophilicity of Bpin group is not big enough to react with azide
- ❖ We detected the formation of isocyanate in the reaction of acid with TMSN_3

Acknowledgments

- ❖ Prof. S. E. Semenov – for giving us an opportunity to engage in the scientific work.
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Prof. S. E. Semenov



Dr. M. A. Novikov



Dr. R. A. Novikov

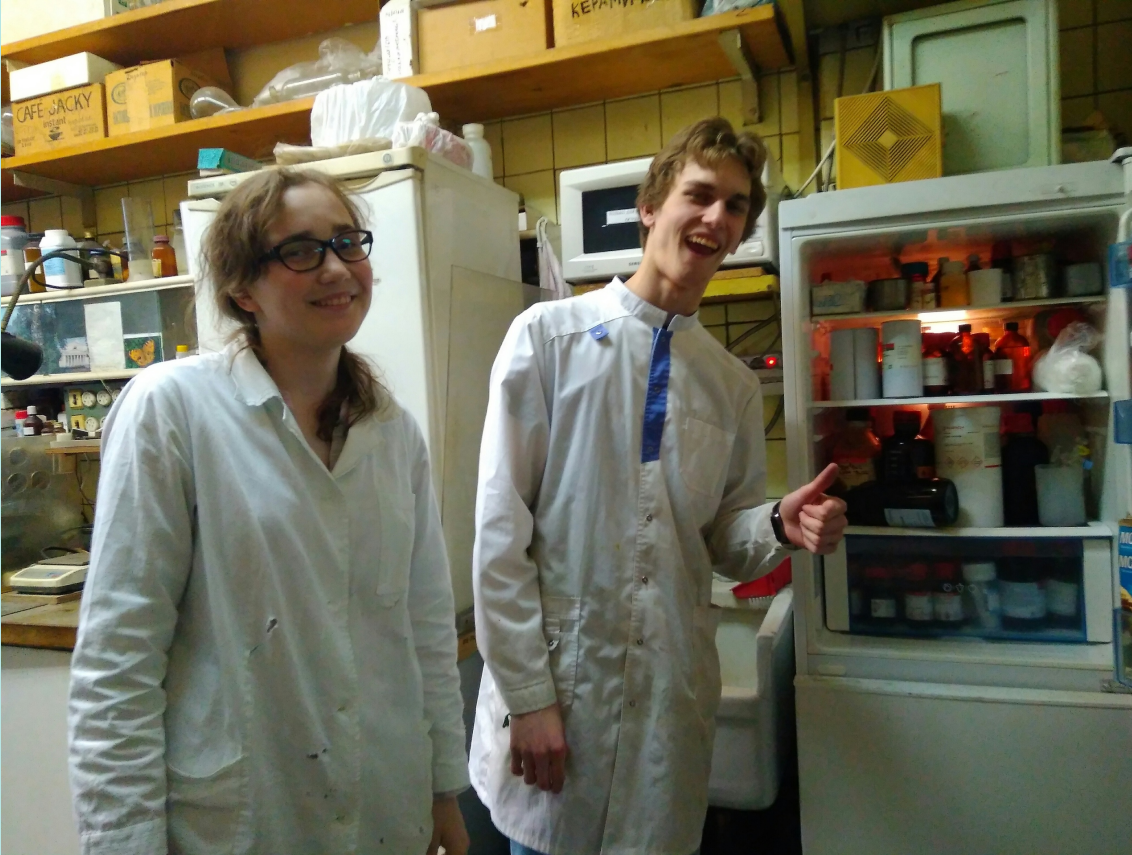


A. K. Zaytsev



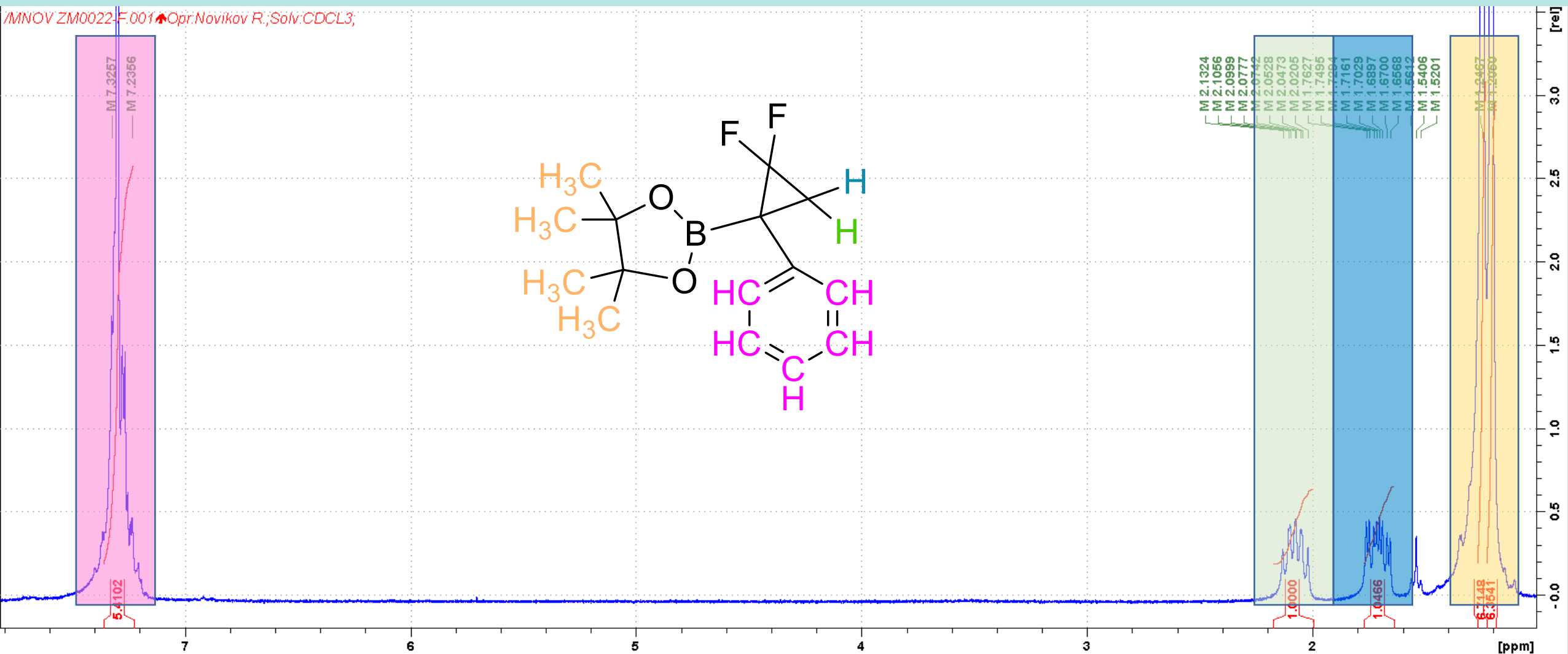
A. Y. Bobrova

Thank you for your attention!

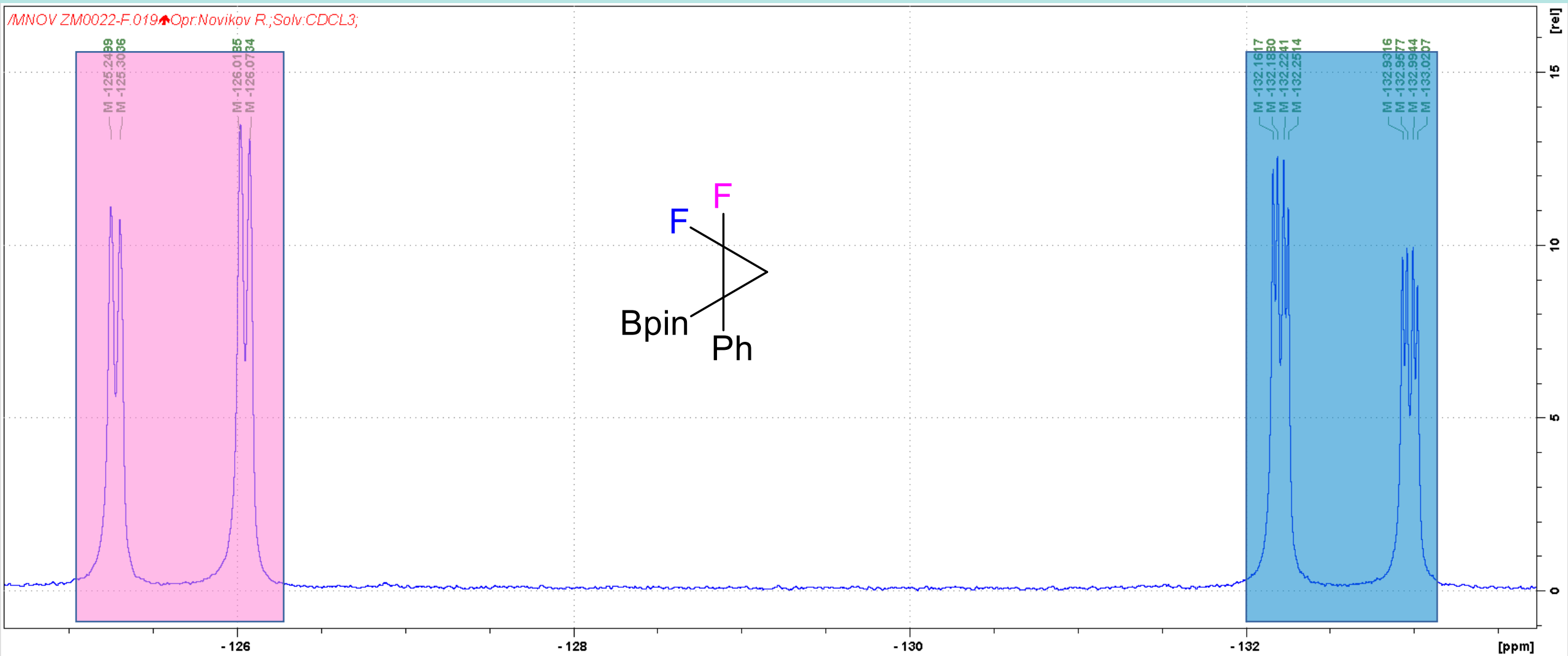


^1H NMR of difluorocyclopropane

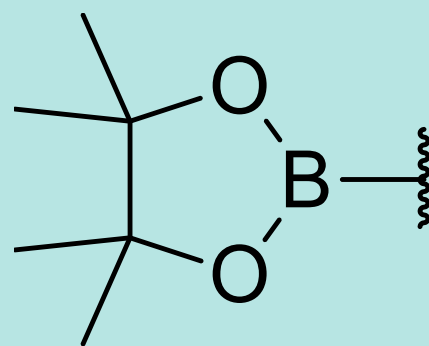
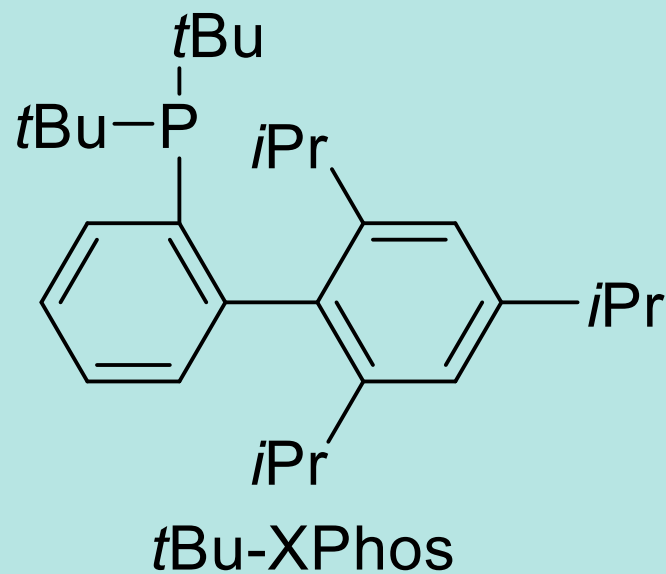
/MNOV ZM0022 F.001 Opr: Novikov R.; Solv: CDCL₃;



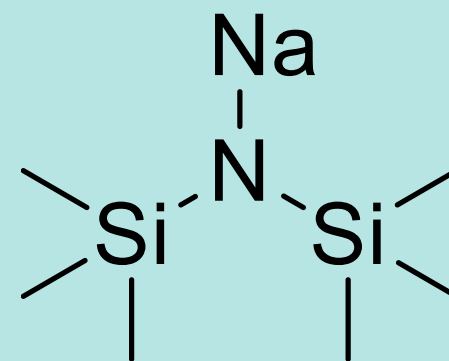
^{19}F NMR of difluorocyclopropane



Abbreviations



Bpin



NaHMDS

