

Science and Technology Group Annual Report FY2023

Eugene Khaskin

1 Introduction

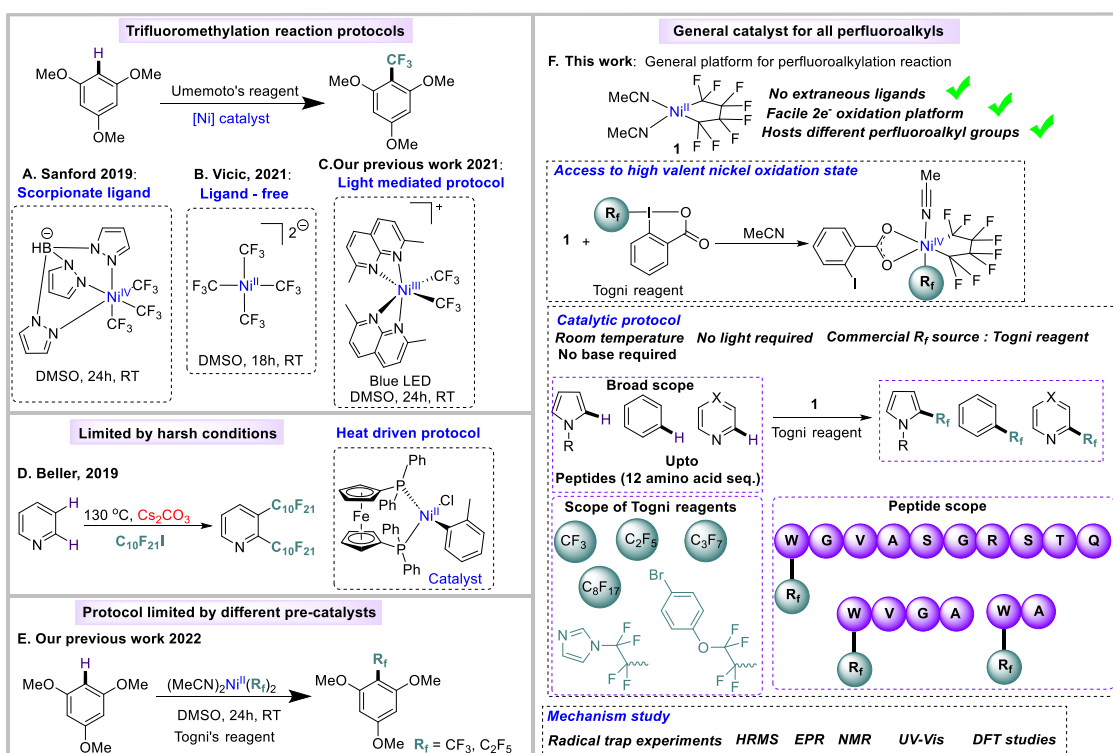
During FY2023, as my main research output I published an article on a general catalyst that that can introduce any fluoroalkyl group onto an electron rich heterocycle or peptides. ¹ This work is based on a paper from the pervious fiscal year, where we used a Ni pentafluoroethyl catalyst to introduce the pentafluoroethyl group onto heterocycles. The new nickel catalyst has a bidentate fluoroalkyl backbone, which kinetically prevents it from coming off, and the only fluoroalkyl group that can come off it is the one that was introduced by the fluorination reagent. Thus, many different fluorination reagents can be used. We applied for a patent on this catalyst in this fiscal year. We found that the new catalyst is more active for all fluoroalkyl groups besides CF₃, which required several equivalents of fluorinating reagent to reach the same effectiveness as other systems, which is not a problem due to the CF₃ fluorinating reagent being cheap. We were also able to use some rare fluorinating reagent that effectively gave coupling products between two heterocycles, joined by a C₂F₄ bridge.

The fluorocarbon group changes the properties of the molecule and can result in metabolism/activity differences, as well as helps the molecules to transit the blood-brain barrier.

My work with OIST collaborators this year included co-corresponding authorship in a review on ligands originally designed by me, that were subsequently used in an ongoing collaborative research project with the Khusnutdinova group, ² as well as a number of works where I measured and solved crystal structures, helped with writing of parts of the papers, and designing and carrying out some of the experiments. ³⁻⁷

2 Activities and Findings

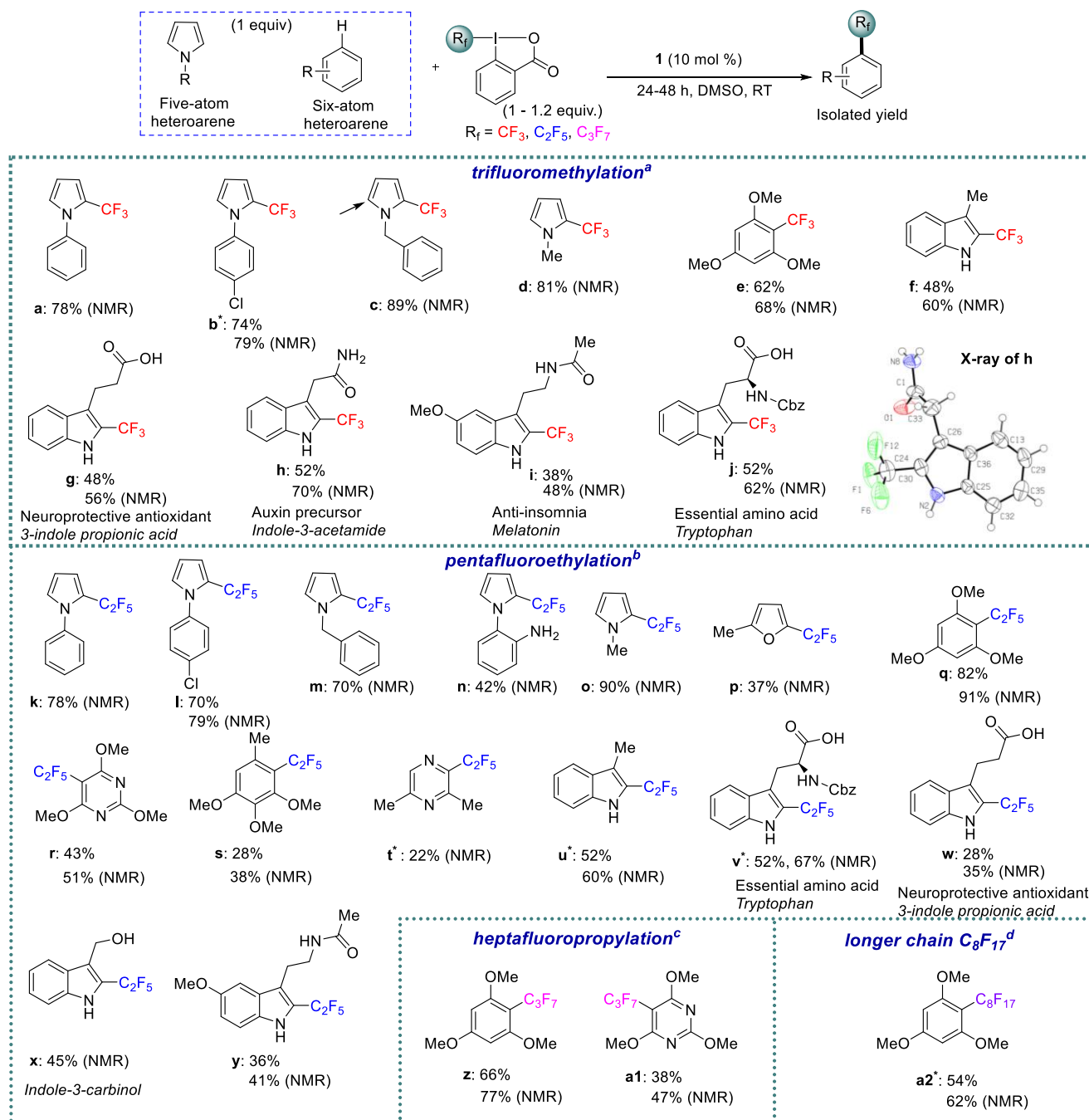
Due to a lack of space to discuss findings, and the fact that the main work discussed above involves the catalytic modification of organic compounds, I will include general schemes and substrate/product figures, in lieu of a greater discussion that can be found in the papers themselves. Below is the general scheme introducing the paper:



Scheme 1: (A-E) Previously reported protocol for CH trifluoromethylation and perfluoroalkylation. (F) Common protocol for CH perfluoroalkylation of heteroarene and peptides.

Science and Technology Group Annual Report FY2023

Eugene Khaskin

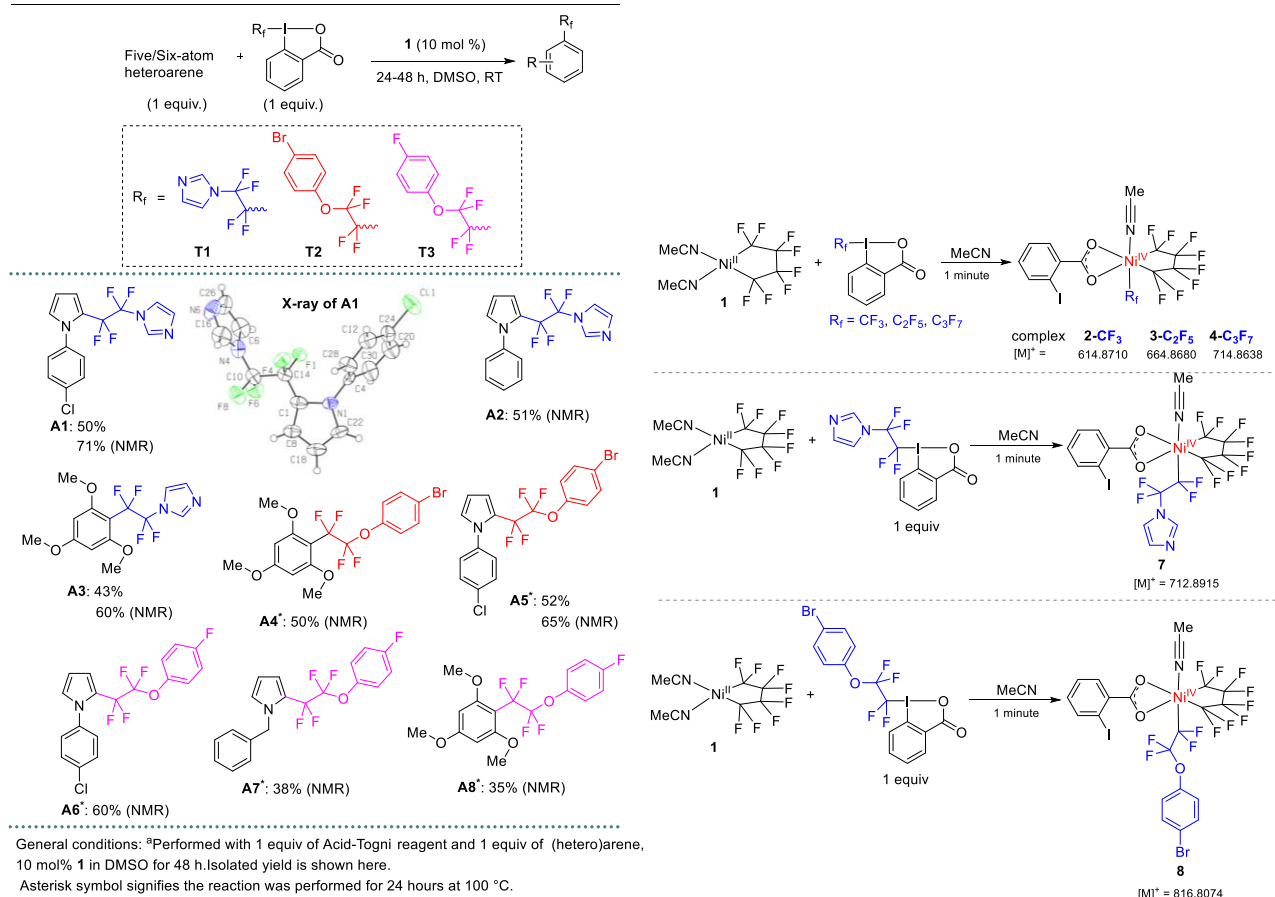


General conditions: ^aPerformed with 1.2 equiv of 1-trifluoromethyl-1,2-benziodaxol-3(1H)-one, ^bPerformed with 1 equiv of 1-pentafluoromethyl-1,2-benziodaxol-3(1H)-one, ^cPerformed with 1 equiv of 1-heptafluoropropyl-1,2-benziodaxol-3(1H)-one, ^dPerformed with 1 equiv of 3,3-Dimethyl-1-(perfluorooctyl)-1,3-dihydro-1λ³-benzo[d][1,2]iodaoxole and 1 equiv of (hetero)arene, 10 mol % **1** in DMSO for 24 h. Isolated yield is shown here. Asterisk symbol signifies the reaction was performed for 48 hours. Arrow signifies the site of minor isomer.

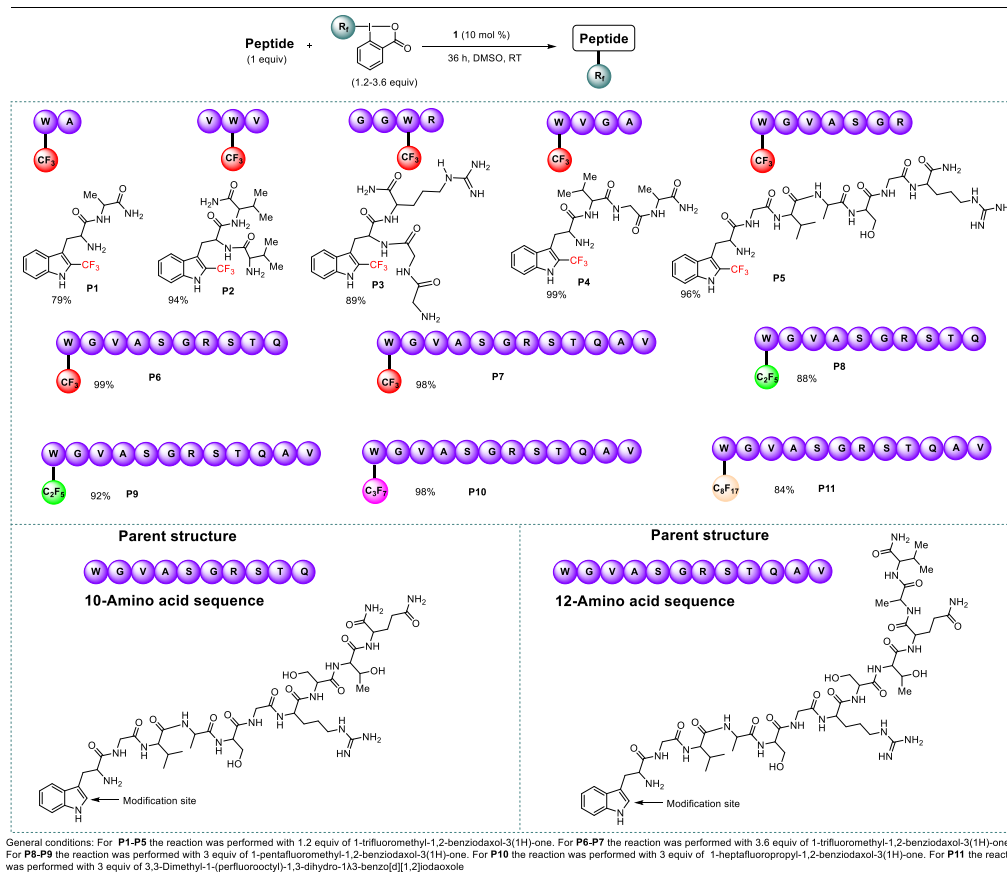
Scheme 2: Scope evaluation of perfluoroalkylation of heteroarenes mediated by **1**.

Science and Technology Group Annual Report FY2023

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Scheme 3: Left – scope for the coupling reaction with C_2F_4 spacer ; Right – experiments showing reaction proceeds via Ni^{IV}



Scheme 4: Scope for the modification of short peptide sequences.

Science and Technology Group

Annual Report FY2023

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3 Collaborations

I'm continuing my collaboration with the Khusnutdinova and Kuhn units, and trying to keep up with my foreign collaborations: Sydnes Group in Norway and Dmitry Gusev in Canada. Travel is still difficult due to the after-effects of the coronavirus pandemic.

4 Publications and other output

Author list, *Title*, Journal or other reference, volume information (year)

- (1) Deolka, S.; Govindarajan, R.; Gridneva, T.; Roy, M. C.; Vasylevskyi, S.; Vardhanapu, P. K.; Khusnutdinova, J. R.; Khaskin, E. General High-Valent Nickel Metallocycle Catalyst for the Perfluoroalkylation of Heteroarenes and Peptides. *ACS Catal.* **2023**, *13* (19), 13127-13139.
- (2) Pandey, D. K.; Khaskin, E.; Khusnutdinova, J. R. PNP-Pincer Ligands Armed With Methyls: New Tools To Control Sterics and Non-Innocence. *ChemCatChem* **2023**, *15* (20), e202300644.
- (3) Pandey, D. K.; Khaskin, E.; Pal, S.; Fayzullin, R. R.; Khusnutdinova, J. R. Efficient Fe-Catalyzed Terminal Alkyne Semihydrogenation by H₂: Selectivity Control via a Bulky PNP Pincer Ligand. *ACS Catal.* **2023**, *13* (1), 375-381.
- (4) Dinh, H. M.; He, Y.-T.; Fayzullin, R. R.; Vasylevskyi, S.; Khaskin, E.; Khusnutdinova, J. R. Synthesis of Aryl-Manganese(III) Fluoride Complexes via α -Fluorine Elimination from CF₃ and Difluorocarbene Generation. *Eur. J. Inorg. Chem.* **2023**, *26* (32), e202300460.
- (5) Dinh, H. M.; Govindarajan, R.; Deolka, S.; Fayzullin, R. R.; Vasylevskyi, S.; Khaskin, E.; Khusnutdinova, J. R. Photoinduced Perfluoroalkylation Mediated by Cobalt Complexes Supported by Naphthyridine Ligands. *Organometallics* **2023**, *42* (18), 2632-2643.
- (6) Deolka, S.; Govindarajan, R.; Khaskin, E.; Vasylevskyi, S.; Bahri, J.; Fayzullin, R. R.; Roy, M. C.; Khusnutdinova, J. R. Oxygen transfer reactivity mediated by nickel perfluoroalkyl complexes using molecular oxygen as a terminal oxidant. *Chem. Sci.* **2023**, *14* (25), 7026-7035.
- (7) Bahri, J.; Deolka, S.; Vardhanapu, P. K.; Khaskin, E.; Govindarajan, R.; Fayzullin, R. R.; Vasylevskyi, S.; Khusnutdinova, J. R. Photoinduced Carbon-Heteroatom Cross-Coupling Catalyzed by Nickel Naphthyridine Complexes. *ChemCatChem* **2023**, *15* (24), e202301142.