Final report on Design of novel methods for the functionalization of heterocyclic molecules (Project NKFIH-OTKA K130458)

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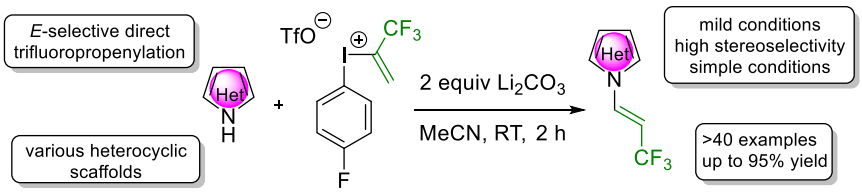
1. Synthesis of trifluoropropenylated heterocyclic molecules with iodonium reagent

Enamine type moieties are important building blocks for synthetic chemistry. Perfluorinated olefins react readily with almost any kind of nucleophiles. They can be turned easily into the proper perfluorinated enamine derivative through nucleophilic substitution with high regio- and stereoselectivity due to their electronic properties. However, the synthesis of moderately fluorinated olefins (so called hydrofluoroolefins) based enamine structures, more likely (trifluoromethyl)vinyl group, and even heterocycle containing ones are underrepresented in the recent literature. The only described C2-CF3 synthesis equivalents are (trifluoromethyl)acetylene, 2-bromo-3,3,3-trifluoropropene and the sulfonium salt derived from the bromide through harsh condition and using diarlyl iodonium species. Utilization of the proper acetylene derivative needs the handling of the gas phase reagent. We can find patents for the building of this group on heterocycles through C1-CF3 synthesis equivalent by Claisen condensation of 2-(*N*)-acetic acid derivatives with the inexpensive trifluoroacetic anhydride. The formation of double bound needs multistep reactions and harsh conditions. All these procedures lack of the broad applicability, each of them with narrow substrate scope. For this purpose, we planned to use the proper (3,3,3-trifluoroisopropenyl)iodonium salt, designed by our research group for the synthesis of N-substituted 2-(trifluoromethyl)aziridines.

At the beginning of the project, we used benzotriazole as model substrate for our optimization studies. We dissolved/suspended the starting material in dichloromethane (10 mL/1 mmol substrate), then 2.0 equivalent of sodium carbonate was added, followed by the careful addition of 1.2 equivalent of iodonium salt. We successfully isolated the main product and identified it by MS and NMR studies as the chain ending *N*-(3,3,3-trifluoropropen-1-yl)benzotriazole. Other side products couldn't be isolated, but were detectable by GC-MS in the sample taken from reaction mixture. We reoptimized the reaction conditions regarding the solvent, the base and its necessity, and the amount of iodonium salt. As inorganic bases, we examined alkalic carbonates (except rubidium), NaH, NaOH and K_3PO_4. As organic bases, 2,4,6-collidine and *N,N*-diisopropylethylamine were tested. All of them gave >90% overall conversion, but the ratio of the same main product altered from 60% to 88%. We best results were obtained in case of lithium carbonate (83%) and collidine (85%). Using these two bases, we refined the solvent, investigating toluene, diethyl ether, ethyl acetate, DMF and acetonitrile. Lithium carbonate (79- 93% conversion) proved to be superior to collidine (66-83%), the higher was in case of Li_2CO_3/MeCN combination with 93% conversion for main product. We chose for further refining base-solvent pairs regarding the isolated yield: in THF and MeCN, where we experienced the best solubility and are easily removed under reduced pressure, with Li_2CO_3, Na_2CO_3 and K_3PO_4, because in preliminary experiments in tetrahydrofuran, it showed promising results. We could isolate the main product after processing it by evaporation onto Celite, then purified by column chromatography. With 2.0 equivalent of lithium carbonate in THF we reached 76% and from acetonitrile in 90% isolated yield. 2.0 Equivalent of sodium carbonate resulted 73% and 76%, 2.0 equivalent of potassium phosphate in 44% and 55% respectively. The necessity of base was also tested. Without any base, we were able to isolate the main product in 56% yield. We stirred the reaction mixture at room temperature for 2 hours, and added 2.0 equivalents of lithium carbonate for 5 minutes, then processed as usual, to give an improved 86% yield. According to these results we chose lithium carbonate as a base in acetonitrile as a solvent. The utility of distilled acetonitrile showed to be irrelevant, so later we used it as received without any purification. When we used the concentrated aqueous solution of lithium carbonate, the yield dropped to 79%. As a last step in optimization, we investigated the necessary amount of iodonium salt. Above 1.1 equivalent we couldn't improve the 95% yield, but using 1.0

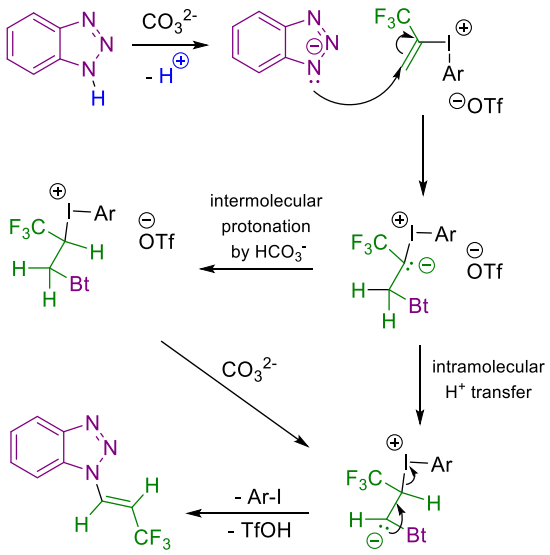
equivalent resulted 86% yield. With these optimized conditions in our hand, we explored the scope and limitations of our reaction.

First, starting from benzotriazole, we used its 4- and 5-nitro derivatives. In these cases, the formation of the other 2 isomers was more ponderous, lowering the yield for main product to 56-60%. In case of 4-nitroderivatives, the other two isomers could also be isolated, their NMR studies are in progress. Pyrazoles, as substrates were also tested. 3,5- and 3,4,5-symmetrically substituted derivatives gave one product, the E-stereoisomer exclusively in 50-90% yield. If position 5 wasn't occupied, we were able to isolate only one regio- and stereoisomer only. 3,5-Nonsymmetrically substituted pyrazoles gave mixture of regioisomers. The electronic properties of aryl substituents were less important than their steric ones, which reflected in the ratio of regioisomers altering from 1:1 to 7:1 with more difference in the steric properties of substituents. Indazole were also trifluoropropenylated successfully. 5-Substituted indazoles reacted smoothly under our conditions, regardless of the substituent. Electron donating group containing derivatives were isolated in 66-88% yield, and 5-nitroindazole in 87%. If electron-withdrawing ethyl carboxylate was on the 5-membered ring, the two forming isomers could be separated in 77% overall yield. Imidazoles and benzimidazoles were also adequate substrate for the transformation. To our delight, we were able to detect and isolate one regio- and stereoisomer. Their volatility was the only difficulty in the isolation process. Thus, we couldn't isolate the imidazole derivative, only the substituted ones, from 50% to 95% yield, regarding the molecular weight and polarity of product. Benzimidazoles gave the proper products in 40-79% yield. Halogenated purine analogues also reacted to give the trifluoropropenylated moieties in 82-85% yield. Azaindoles, such as 5-bromo-7-azaindole and 2-chloro-3-methyl-7-azaindole showed reactivity towards our reagent, with 37% and 47% yield respectively. Not just heteroaromatic systems, but also acidic imides were trifluoropropenylated. Phthalimide and phenytoin reacted to give only one regioisomer in 75% and 93% yield. Overall, with aid of the reagent and with the use of the developed reaction conditions we successfully synthesized more than 40 new compounds in up to 95% isolated yield.



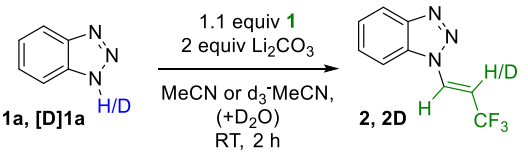
Scheme 1. *Synthesis of trifluoropropenylated heterocycles*

With experimental studies we supported our mechanistic proposal which could describe best the details of the transformation. The first step is the deprotonation of the *N*-heterocycle, which makes the heterocyclic anion more nucleophilic, and facilitates its attack to the terminal sp^2 carbon of the trifluoropropenyl moiety in a Michael addition reaction. The formed benzotriazolyl iodonium ylide undergoes intramolecular proton transfer resulting the corresponding anion. As an alternative route, the stabilized carbanion can be protonated by the base ion intermolecularly, providing the next intermediate. This species can be deprotonated by the base, and the formed anion undergoes *E*-selective elimination and provides the final product.



Scheme 2. *Proposed mechanistic steps*

In order to support the mechanistic hypothesis, we performed the reactions with both [1H] and [1D]-benzotriazole **1a** and **[D]1a**) in MeCN and d_3-MeCN, and measured the deuterium incorporation in the product. The [1*H*] substrate **1a** gave product **2** with 0% deuterium incorporation both in MeCN and d_3-MeCN (isolated yields 95% and 87%). Trifluoropropenylation of **[D]1a** in MeCN resulted 19% deuterium incorporation, while in d_3-MeCN the same reaction provided the product with 24% deuterium incorporation. In the presence of 1 equivalent of D_2O, the deuterium incorporation increased about 15-20% independently from the substrate and the applied solvent, showing the possibility of intermolecular protonation. These results support that both H-atoms of trifluoropropenyl group of the product are dominantly derived from the reagent 1 through intramolecular proton transfer, but intermolecular base assisted proton transfer could also operate, beside some minor solvent effect on the proton transfer.

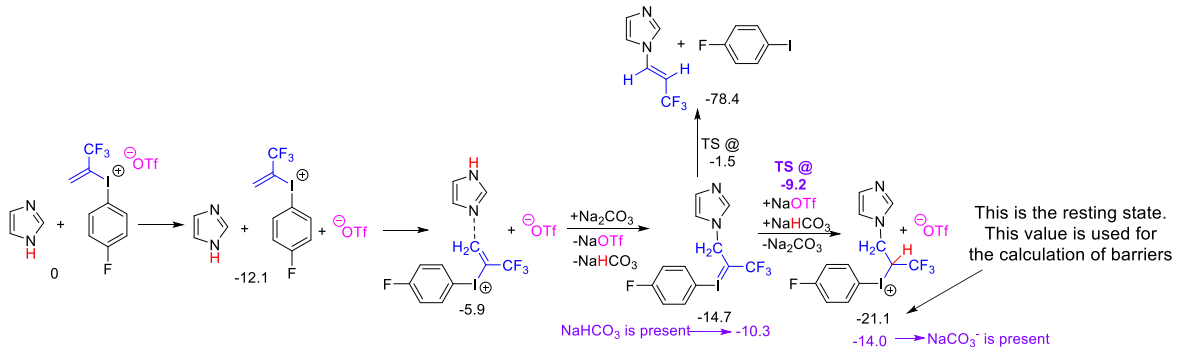


Substrate	Solvent	D_2O	Yield of 2+2D	2D %
1a	MeCN	0	95%	0%
1a	d_3-MeCN	0	87%	0%
[D]1a	MeCN	0	93%	19%
[D]1a	d_3-MeCN	0	92%	24%
1a	MeCN	1 equiv	95%	25%
[D]1a	MeCN	1 equiv	90%	53%
[D]1a	d_3-MeCN	1 equiv	81%	40%

Scheme 3. *Mechanistic studies*

The results were summarized and published in *Chemistry A European Journal*, **2021**, http://dx.doi.org/10.1002/chem.202102840. (Impact factor: 5.236)

We also investigated quantum-chemical calculations to analyze the possible reaction mechanisms. Energetics of several mechanistic paths were calculated and compared and we find correlation between the results of the theoretic and the experimental investigations. We found that the intramolecular proton transfer path is the most favorable among the others (Scheme 4).

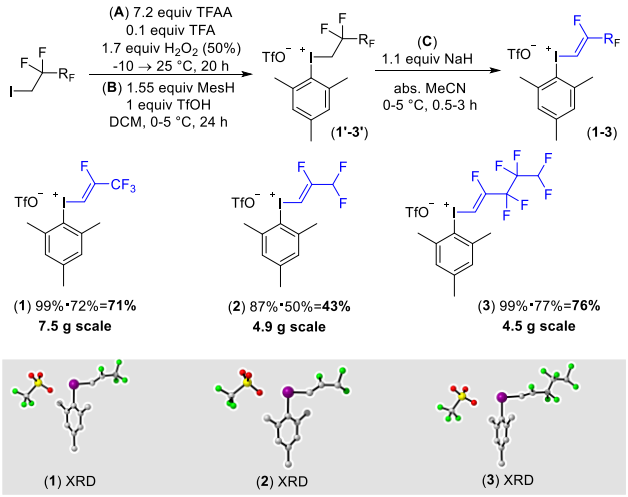


Scheme 4. *The most favorable reaction path*

Other ways and reactions with other substrates were also studied with the theoretical method and energy values were calculated. The calculations are finished and discussed in different manuscript, and the theoretical work will be submitted after the end of the project period.

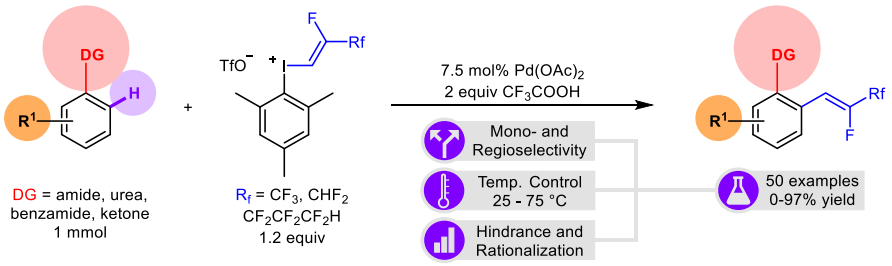
2. Palladium catalyzed alkenylation of heterocycles and aromatic systems

The direct and catalytic incorporation of fluorinated alkenyl molecular motifs into organic compounds resulting high-value added chemicals represents a rapidly evolving part of synthetic methodologies, thus this area is in the focus of pharmaceutical and agrochemical research. n our projectn we developed a stereoselective procedure for direct fluorovinylation of aromatic and heteroaromatic scaffolds. This methodology development has been realized by palladium-catalyzed ortho C-H activation reaction of aniline derivatives featuring the regioselectivity via directing groups such as secondary of tertiary amides, ureas or ketones. First, we designed and synthesized novel alkenyliodonium species starting from the corresponding alkyl-iodide, via the deprotonation-elimination of the alkyliodonium intermediate. We determined the structure of the novel species with various spectroscopic measurements including NMR and X-ray.



Scheme 5. *Synthesis and characterization of novel alkenyliodonium reagents*

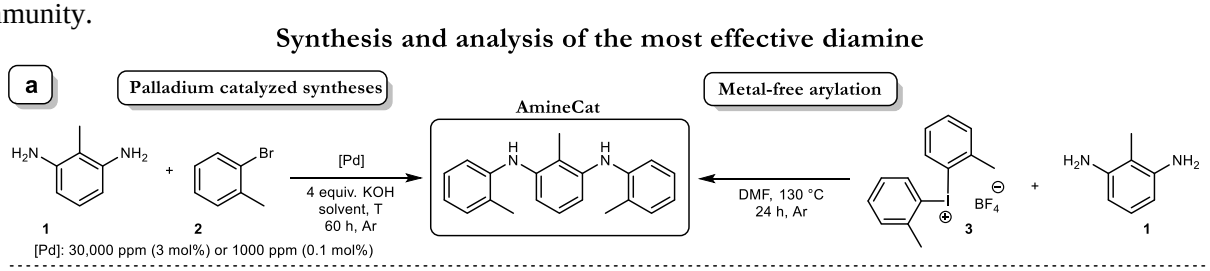
We demonstrated the application of these non-symmetrical aryl(fluoroalkenyl)-iodonium salts as fluoroalkenylating agents under mild reaction conditions. The scope and limitations have been thoroughly investigated and the feasibility has been demonstrated by more than 50 examples (Scheme 6). The manuscript can be accepted for publication in *Advanced Synthesis and Catalysis* (Impact factor: 5.837) after the first evaluation of the work, and the revised version of the manuscript currently is under consideration.



Scheme 6. *Synthetic applicability novel alkenyliodonium reagents for the alkenylation of aromatic and heterocyclic substrates*

3. Utilization of iodonium reagents for the study of metal free cross-coupling reactions

Cross-coupling reactions are one of the most frequently used chemical transformations in modern organic chemistry. These reactions generally use palladium or nickel catalysts for the construction of new carbon-carbon or carbon-heteroatom bonds. Some of the new synthetic developments focus to the development of metal free versions of transition metal catalyzed reactions, which is rather challenging. These developments should face with several experimental and mechanistic difficulties. The most important issue is the complete exclusion of metal impurities from the reaction mixtures. Recently and amine catalyzed Suzuki reaction was developed.[1] However, the amine catalyst was made through palladium catalyzed reaction, followed by purification and removal of any palladium traces. However, we supposed that the sensitivity of the Suzuki coupling reaction toward ppb level of palladium impurities might be responsible for the efficient transformation. In order to study this effect, the key is the metal-free synthesis of the amine catalyst. We found that with the aid of diaryliodonium salts this target compound can be prepared, and we obtained a completely metal free version of the amine catalyst. The metal content of the catalyst was determined by ICP-MS analysis, and the absence of palladium was verified. In a very detailed and accurate study we explored the sensitivity of the Suzuki reaction to palladium impurities, which served important information for synthetic and pharmaceutical community.



Scheme 7. *Synthesis of Amine-organocatalyst (AmineCat) via palladium catalyzed and metal free conditions with the utilization of iodonium salts*

The metal-free synthesis of the AmineCat on the basis of the utilization of iodonium species together was summarized in two manuscripts. The complete work was deposited first in a preprint server (10.26434/chemrxiv.14071247.v1) and it is accepted for publication to *Nature Catalysis* (NATCATAL-21035204A), and the paper will be published in due course.

[1] Xu, L.; Liu, F.-Y.; Zhang, Q.; Chang, W.-J.; Liu, Z.-L.; Lv; Y., Yu, H.-Z.; Xu, J.; Dai, J.-J. & Xu, H.-J. The amine-catalysed Suzuki–Miyaura-type coupling of aryl halides and arylboronic acids. *Nat. Catal.* **4**, 71–78 (2021).