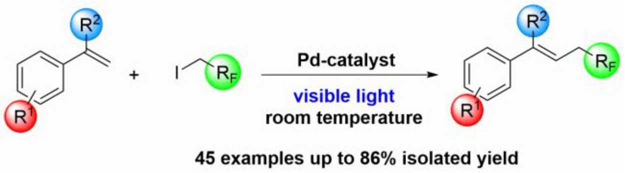
Final report on the NKFIH project K132077 entitled "Development of novel organic methods for the synthesis of fluorinated compounds"

1. Palladium catalyzed fluoroalkylation of alkenes

There are several different strategies to construct the trifluoroethylated styrene structure. It can be synthesized through several synthetic ways but the direct fluoroalkylation of C-C double bond in alkyl cross-coupling is a new approach. In our research project, we developed a new Heck type coupling method for introducing fluoroalkyl groups into the styrene moiety using palladium catalysis under photocatalytic conditions. We found that the coupling of trifluoroethyliodide and styrene derivatives works efficiently in presence of palladium(II) acetate, Xanthphos ligand and Cs_2CO_3 as base in benzene at 25°C using 440-445 nm LED for 18 hours. Altogether 23 different trifluoroethylated products were prepared in this transformation. The reactivity of different fluoroalkyl iodides was also investigated. We found that 1,1-difluoro-2-iodoethane is also capable of participating in the coupling reaction. This attracted our interest because the difluoromethyl moiety is a well-studied motif in medicinal chemistry. The difluoromethyl group is isosteric and isopolar with the OH and SH groups and can behave as a H-donor as well. With increased reaction time (24 hours) we could isolate the corresponding difluoroethylated styrene products, and with the slightly modified procedure 12 additional compounds were prepared. 1*H*,1*H*-pentafluoropropyl iodide also gave the corresponding coupled products in the standard reaction conditions. Three other fluoroalkyl iodides were also tested in this transformation and gave successfully the desired coupled products. In conclusion, we have successfully developed a palladium catalyzed Heck type coupling of styrenes and fluoroalkyl iodides induced by visible light. A series of styrene derivatives were subjected to the present reaction conditions and formed the corresponding fluoroalkyl derivatives with good yields. Five different fluoroalkyl iodide were tested in this transformation and found effective. This method offers a useful procedure to incorporate fluorine containing functional groups into styrene derivatives.



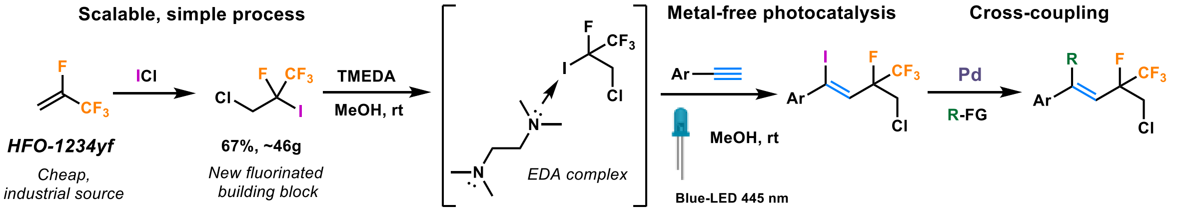
The results were published in Organic Letters: **Palladium-Catalyzed Fluoroalkylation of Styrene Derivatives**, Réka Adamik, Tamás Földesi, Zoltán Novák, *Org. Lett.* **2020**, *22*, 8091-8095. DOI: 10.1021/acs.orglett.0c03043.

2. Transformations of HFO gases

2.1. Utilization of HFO-1234yf-ICl adducts in radical addition reactions: synthesis of new fluorous building blocks and their Suzuki and Sonogashira coupling

The successful transformation of HFO-1234yf gas into iodinated species through the addition of iodine monochloride opens several possibilities for organic reactions. In the project we prepared novel fluoroalkyl iodide reagent and studied its reactivity toward alkynes under visible light induced photochemical additions. With the optimized reaction conditions, the addition product could be isolated in 92% chemical yield up to a 4 mmol scale. Increasing further the scale of the reaction (12-72 mmol) caused a slight reduction of the efficiency and the product was isolated in 78-80% yield. We explored the scope and limitation of the transformation, and successfully isolated different arylacetylene derivatives and 4 products from alkylacetylenes.

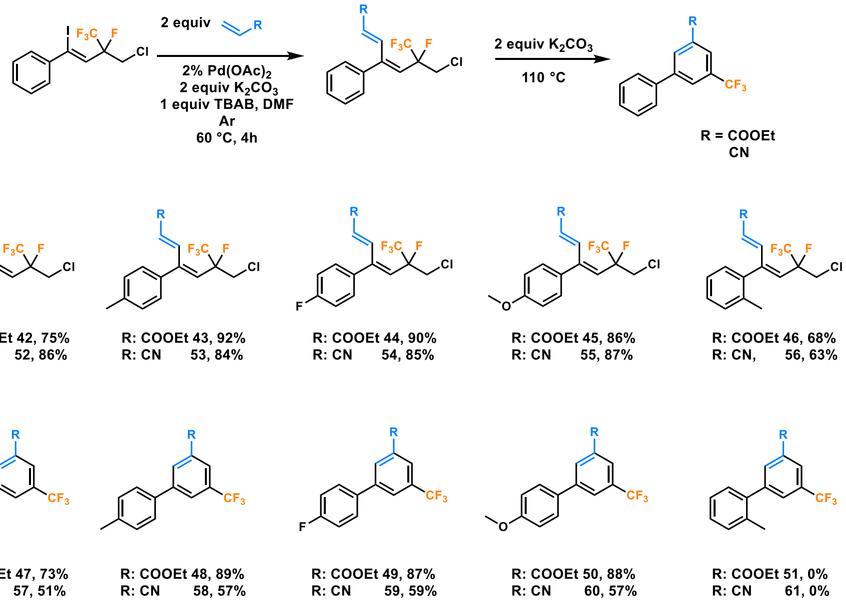
As the products contain the reactive vinyliodide function, we explored their synthetic potential to obtain new conjugated diarylalkene and enyne systems bearing the new fluoroalkyl group. The synthesis of a novel high fluorine containing reagent, starting from cheap industrial materials was described, and its use in an atom transfer radical addition reaction. After illustrating the use of the transformation, we extended the scope of the reaction by preparing multiple derivatives.



The results were summarized and published in Organic Letters (**Synthesis and Photochemical Application of Hydrofluoroolefin (HFO) Based Fluoroalkyl Building Block**, Bálint Varga, Balázs L. Tóth, Ferenc Béke, János T. Csenki, András Kotschy, Zoltán Novák, *Org. Lett.* **2021**, *23*, 4925–4929. DOI: 10.1021/acs.orglett.1c01709 .)

2.2. Diene synthesis and cyclization studies of the HFO derived viyl iodides

As an extension of the previously described work, we used the vinyl-iodides prepared from HFO-1234yf as starting materials for palladium catalyzed Heck reaction, and we observed an interesting transformation under the Heck conditions. Reaction with electron-deficient olefins (for example ethyl acrylate) did not stop at the Heck coupling stage and the diene product underwent halogen elimination followed by cyclization producing trifluoromethyl-biphenyls. Using elevated temperatures (110 °C) with Pd(OAc)$_2$ as a catalyst we observed by-product formation in GC-MS besides the desired diene product. After analysis this turned out to be a trifluoromethylated biphenyl derivative formed from the Heck-coupled product. After some optimization we managed to separate the coupling and the cyclization step with a simple temperature adjustment.



R: COOEt 42, 75%
R: CN 52, 86%

R: COOEt 43, 92%
R: CN 53, 84%

R: COOEt 44, 90%
R: CN 54, 85%

R: COOEt 45, 86%
R: CN 55, 87%

R: COOEt 46, 68%
R: CN, 56, 63%

R: COOEt 47, 73%
R: CN 57, 51%

R: COOEt 48, 89%
R: CN 58, 57%

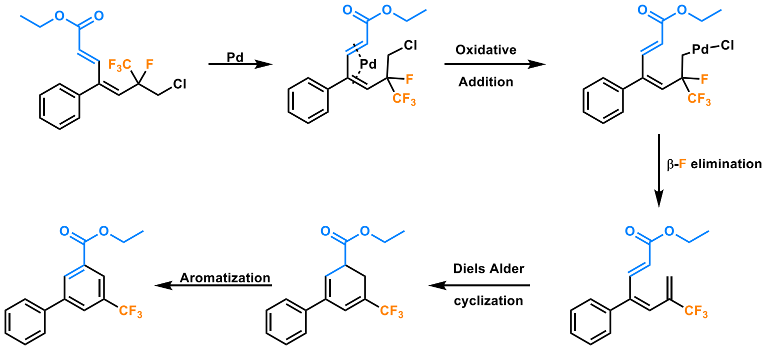
R: COOEt 49, 87%
R: CN 59, 59%

R: COOEt 50, 88%
R: CN 60, 57%

R: COOEt 51, 0%
R: CN 61, 0%

At 60 °C only the coupling occurred while elevating the temperature to 110 °C the biphenyl formation took place. Another interesting observation was when we tried to perform the reaction with ortho-methyl substituted derivative, the coupling proceeded smoothly, but after rising the reaction mixture to 110 °C no cyclization occurred.

With these result in mind, we propose the following mechanism for the transformation. First there is an oxidative addition into the C-Cl bond followed by a quick β-F elimination which produces our isolated triene. Then there is an electrocyclization followed by the aromatization which also can be assisted by palladium.

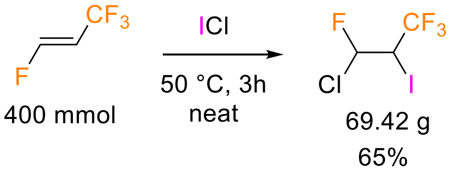


To gain deeper understanding of the underlying processes we extensively studied the reaction. As a result, we managed to separate the coupling and the cyclization into two separate steps. Proved that the overall reaction is palladium dependent and isolated a reaction intermediate. The role of different palladium sources, ligands and reducing agents were examined. With the use of ^{19}F NMR techniques and parallel GC-MS analysis we aimed to support our mechanistic hypothesis. Additionally, the mechanism has being analyzed by theoretical computations.

After the completion of the mechanistic studies the research results will be summarized in a manuscript which will be submitted after the closing of the project.

2.3. Utilization of HFO-1234ze-ICl adducts in radical addition reactions: synthesis of new fluorous building blocks and their Suzuki and Sonogashira coupling

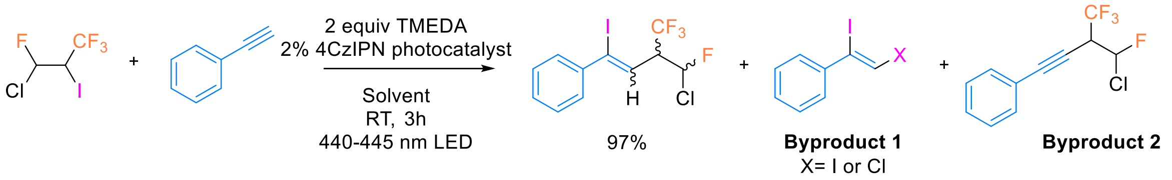
In continuation of this work, we extended the previously described transformation to HFO-1234ze gas, and as the result we prepared the corresponding ICl adduct of the gas. The first step was the synthesis of the ICl adduct reagent as a convenient source of a highly fluorinated C2 building block. For this we applied the procedure developed previously. Condensing the refrigerant gas into a pre-cooled pressure proof flask offered a convenient method for handling a gaseous reagent. After simple addition of the necessary amount of iodine-monochloride (ICl) and heating for 3 hours the addition reaction proceeded smoothly providing liquid derivative of the HFO as a single regioisomer. Simple washing (with sat. Na_2SO_3) and drying proved to be ample work up making the whole process organic solvent free.



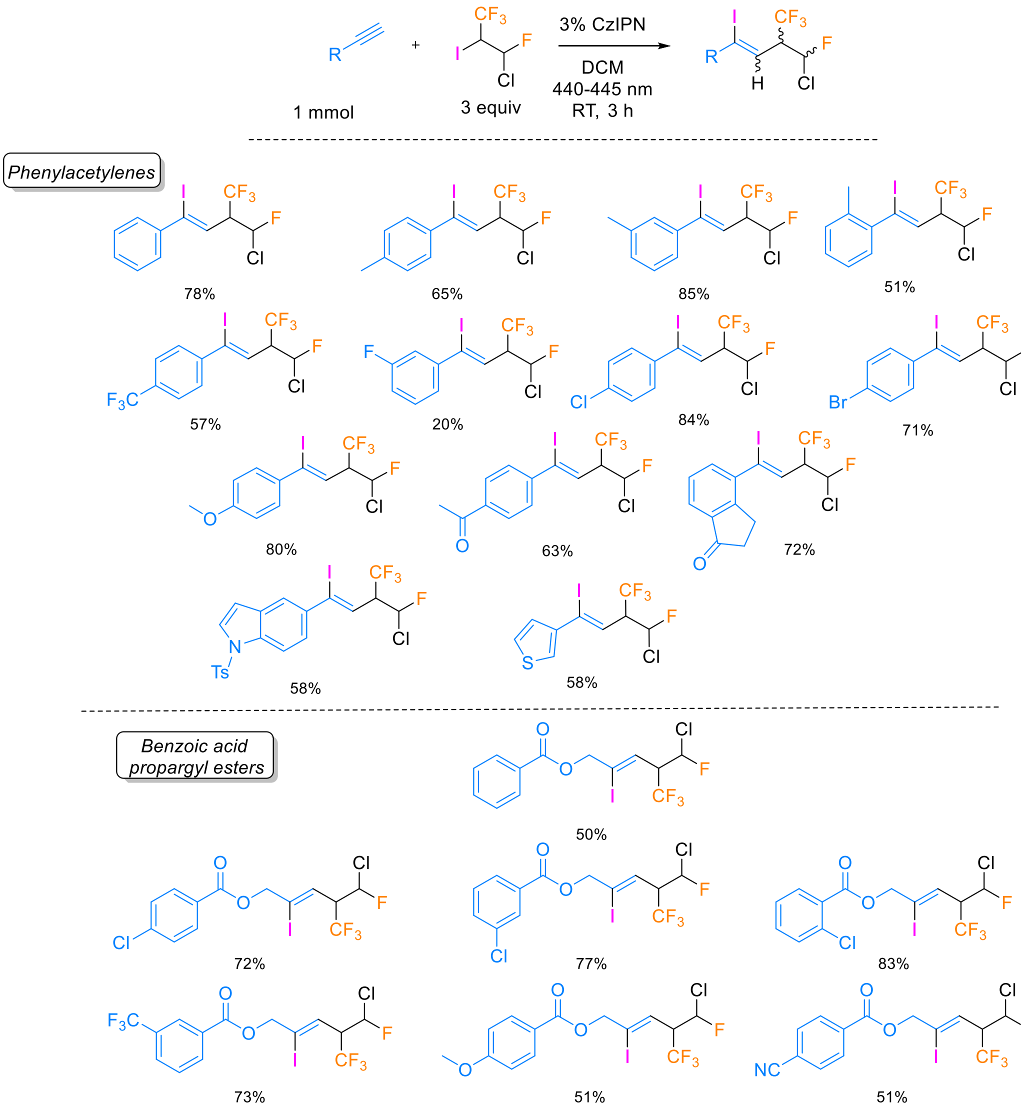
Multigram scale
Simple procedure
Solvent free

To achieve the next step, we investigated the reactivity in an ATRA reaction with phenylacetylene, and we observed significant difference from the previous photoaddition reaction.

The use of TMEDA in order to form electron-donor acceptor complexes sensitive to visible light proved ineffective, and a photosensitizer had to be used in order to promote the radical formation. Testing parallel an iridium based catalyst {Ir[dF(CF)$_3$ppy](dtbpy)PF$_6$} and a metal free alternative 4CzIPN [1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene] it became evident that the well-established organic dye can facilitate the transformation effectively. The ATRA reaction proceeded smoothly producing the desired vinyliodide intermediate as a stereoisomer mixture. Unfortunately, these conditions also promoted the slow degradation of our alkyl iodide reagent, which produced halogens (I_2 or ICl) which was also active in the radical addition forming byproducts. However, their amount was non-significant and did caused problem during the purification. As an additional important parameter, we studied the effect of concentration on the reaction. The reaction time dropped significantly while using less solvent for higher concentrations. Additionally, we could lower the required amount of fluoroalkyl iodide reagent while maintaining relatively low reaction.

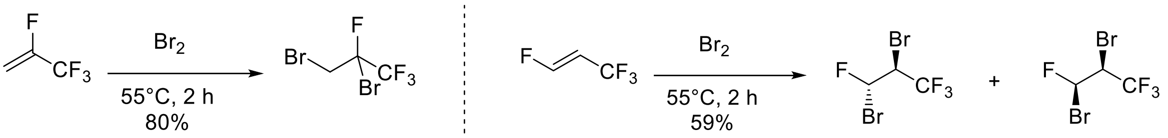


Using the optimized reaction conditions, we expanded the reaction scope. We prepared various aromatic and heteroaromatic derivatives using different aryl and heteroaryl alkynes and the reaction proceeded smoothly producing the appropriate products as a diastereomeric mixture Electron donating and halogenated substrates posed no limitation and could be prepared in good yield. However, when electron withdrawing groups were present in the alkyne substrate, the rate of the reaction dropped significantly. This was solved by adding half equivalent of Ag_2CO_3 to these reactions. The silver helped to bound halide ions, which could inhibit the reaction. To our delight not only aromatic acetylenes were active but propargyl esters as well, and we were able to extend the scope of available structures. The various substitution pattern on the aromatic core did not influence greatly the transformation and the derivatives could be isolated in good yields. In this case the addition of silver expedited the reaction and in most cases were necessary for keeping the reaction times short.



2.4. Synthesis of 2,3-dibromo-1,1,1,2- and 1,1,1,3-tetrafluoropropane

In this research topic, we wanted to carry out other addition reaction of the HFO gases. To do this, we used Br_2, to prepare the corresponding dibrominated products, and we were able to isolate the target dibromide in 80% yield on multigramscale. Using the same procedure, we prepared the isomers of 2,3-dibromo-1,1,1,3-tetrafluoropropane from HFO1234ze gas in the same reaction as above in 56% yield.

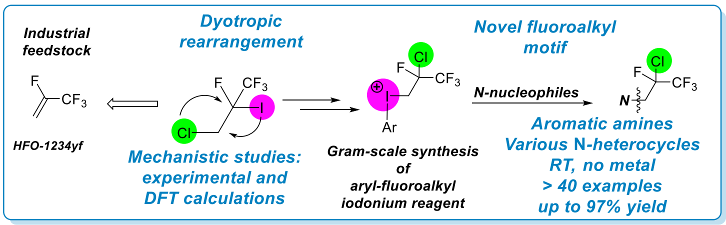


These two starting materials will be available on large scale for further transformations, and we intend to use the bromo functions to further functionalizations. We will use these species as starting materials to construct new molecules with trifluoropropyl and trifluoropropenyl fragments.

2.5. Synthesis and utilization of novel fluoroalkyl reagents

We prepared new fluoroalkylating agents from the previously prepared HFO-ICl adducts. Iodonium salt has been prepared from the relatively inexpensive industrial refrigerant gas 2,3,3,3-tetrafluoroprop-1-ene (R1234yf). While the synthesis gave non-conventional product, we studied the mechanism of the iodonium salt synthesis. We found that the reaction took place through dyotropic rearrangement of iodane group and chlorine atom in multiply-halogenated alkyl fragment through simultaneous [1,2] shift. Experimental, spectroscopic and DFT studies were performed for the mechanistic exploration of this unprecedented phenomenon which provides valuable information to the class of rearrangement reactions. Beyond the implications of the mechanistic studies, we demonstrate the synthetic utility of the dyotropic rearrangement with the design of multigram scale synthesis of iodonium based fluoroalkylating reagent bearing alternative fluorous molecular motif, with the utilization of industrial hydrofluoro-olefin feedstock, HFO-1234yf gas.

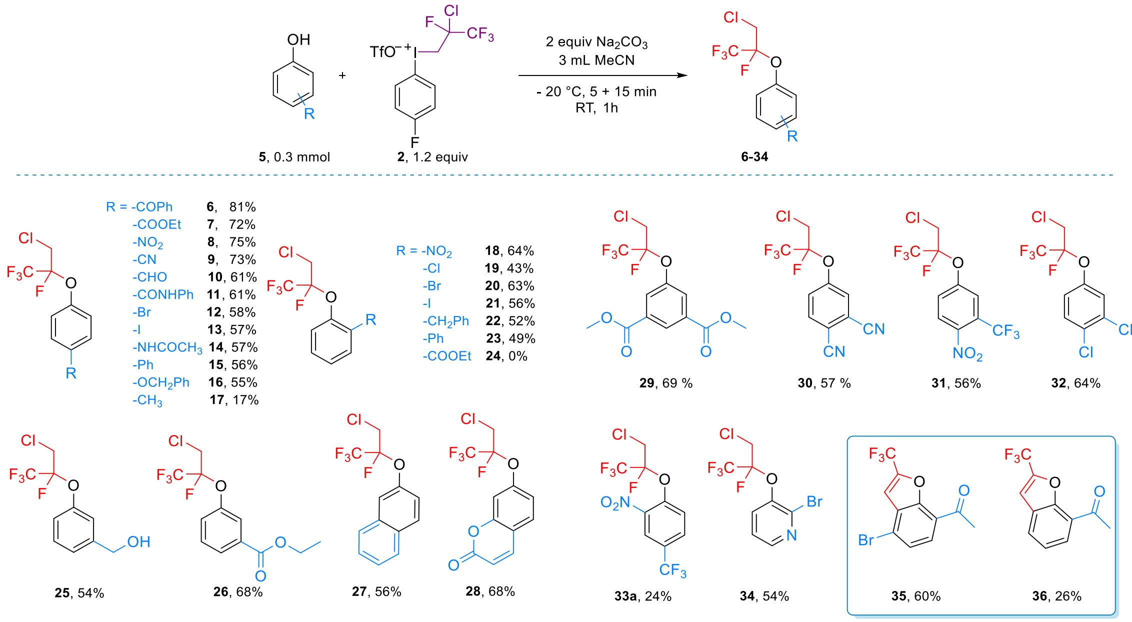
We showed that the iodonium species is an excellent electrophilic fluoroalkylating agent and reacts with various *N*-nucleophiles including heterocycles under mild, metal-free conditions (more than 40 examples, up to 97% yield). Taking into account the chemical nature of the reactants, the simple reaction conditions, our developed methodology provides versatile and efficient access to *N*-fluoroalkylated species, which broadens the chemical space of fluoroalkyl tagged molecules.



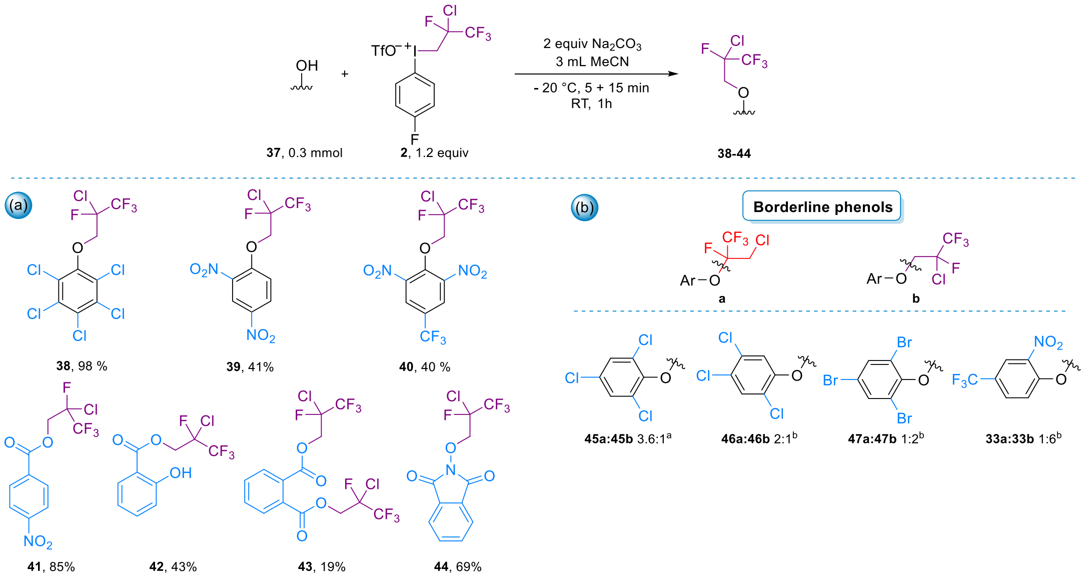
As a result, we published our work in Angewandte Chemie International Edition. (János T. Csenki, Balázs L. Tóth, Ferenc Béke, Bálint Varga, Dr. Péter P. Fehér, Prof. András Stirling, Dr. Zsuzsanna Czégény, Prof. Attila Bényei, Prof. Zoltán Novák, *Angew. Chem. Int. Ed.,* **2022**, *61*, e202208420.)

In the continuation of our work, we explored their applicability in further nucleophilic substitution reactions. While this iodonium salt provides new opportunity in the case of group transfer reactions, we studied their reactions toward *O*-nucleophiles, and observed elimination-Michael addition sequence when obtained other fluoroalkyl isomer of the phenol ethers. We exploited the opportunity in this reactivity feature, and optimized reaction conditions for hetero-substitution to get tetrafluoro propane linked phenols in good yield. Our initial observation in the reaction of salt 2 and phenol substrate was the formation of fluoroalkyl-phenylether. The structure analysis of the product revealed that the chlorine changed position in the alkyl chain, and the oxygen attacked to the α-carbon, which suggests a different reaction path compared to the previously developed amination. We presumed that, in the presence of Na_2CO_3, in situ generation of alkenyliodonium salt occurs via HCl elimination, then the phenolate anion attacks the new electrophilic center in a Michael-type addition. The reaction ends with the attack of the previously eliminated chloride anion to the other electrophilic center producing a different fluoroalkyl structure. Considering this presumed reaction path, we optimized the reaction conditions for the synthesis of aryl-fluoroalkyl ethers and exploit the benefit of the difunctionalization strategy with the interruption of the reaction with other nucleophiles before the re-attack of the chloride ion. After the initial findings, we performed optimization to find the ideal reaction conditions, and we found that MeCN-Na_2CO_3 solvent base pair was perfect for the fast reaction. Under the optimized conditions, we explored the scope and the limitations of the *O*-alkylation reaction.

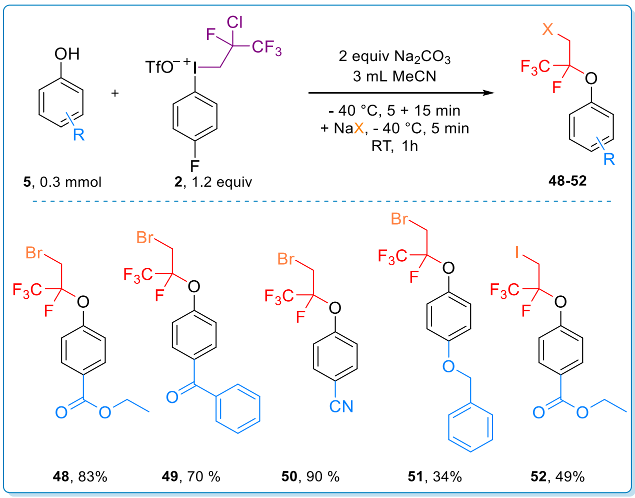
Various ortho, meta and para substituted phenol derivatives were O-alkylated in good yields (**6**-**26**, 49-81%), where the presence of electron withdrawing groups gave better yields (**6**-**11**, **18**, **26**, 61-81%) with the exception of ortho-ester which was completely inactive in the transformation (**24**, 0%). In the case of *para*-cresol, the formed product **17** was found to be volatile and this derivative was isolated only in 17% yield. The presence of an aldehyde function was tolerated by the reaction, and product **10** was isolated in 61% yield. The reaction was selective in the presence of aliphatic hydroxyl group (**25**, 54%). Electron deficient di-substituted phenols were also successfully transformed and the corresponding products (**29**-**33**) were isolated in the 24-69% yield range, as well as in the case of the heteroaryl compound, 2-bromopyridin-3-ol (**34**, 54% yield). Surpris-ingly, in the cases of ortho-acylated phenols, ring formation was observed and 2-trifluoromethylbenzofuran derivatives **35** and **36** were obtained in 60% and 26% yields.



During the study of the scope of phenol derivatives, some substrates were found where the chloride did not migrate in the reaction, and the alkyl group preserved its structure in a direct substitution path. This reactivity was characteristic for highly electron deficient (more acidic) phenols, and the products were isolated in excellent yield (98%) in the case of pentachlorophenol (**38**) and in moderate yields (40-41%) in the case of **39** and **40**. Considering the importance of acidic function in the altered behaviour, we studied the reactivity of carboxylic acids toward the iodonium reagent. Using para nitrobenzoic acid, the product (**41**) was obtained in 85% yield, and functionalization of salicylic acid underwent selectively on the carboxyl group despite the presence of the hydroxyl group, and the product (**42**) was obtained in 43% yield. Both of the carboxyl groups reacted in the case of phthalic acid, and diester **43** was isolated in 19% yield. Additionally, *N*-hydroxy phthalimide provided **44** in 69% yield in the trans-formation. In some borderline cases in terms of acidity, the formation of both isomeric derivatives was observed among many other side products.21 Trichlorophenols (**45**, **46**), 2,4,6-tribromophenol (**47**) and 2-nitro-4-(trifluoromethyl)phenol (**33**) gave mixture of isomers formed in double substitution and in direct substitution. In these cases, we did not isolate the products (exception of **33a** which was isolated in 24% yield), only their ratio (a:b) was determined and varied between 3.6:1-1:6.

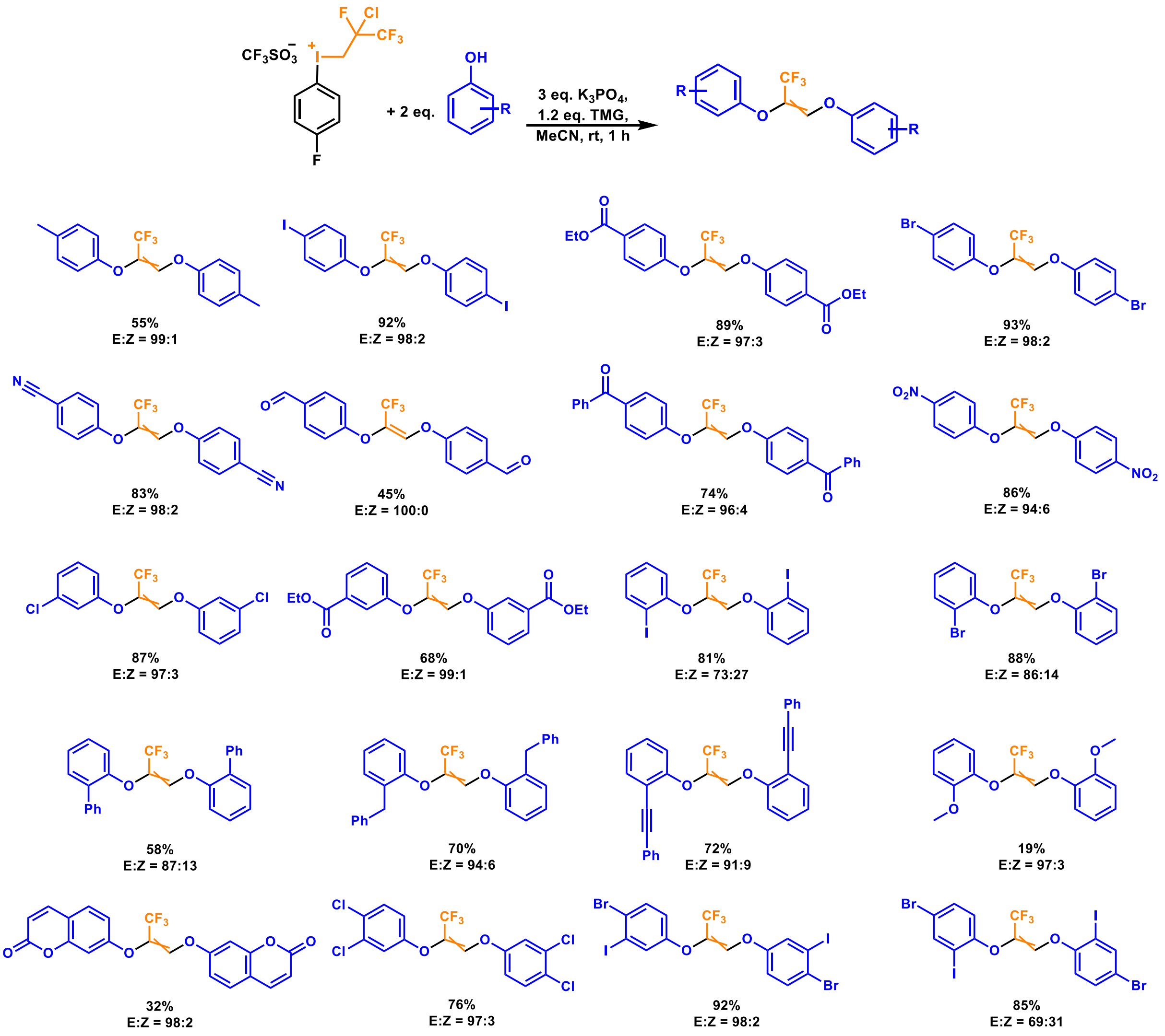


Next, we aimed to prove the mechanism and to take ad-vantage of the supposed HCl elimination step, which result-ed the *in situ* generation of alkenyliodonium salt from **2**. We wondered whether we could incorporate other nucleophiles instead of the chloride. First, NaBr was used in the reaction, and the incorporation of the bromide anion was successful, however the brominated compound was obtained more efficiently at -40 °C.21 The corresponding bromoalkylated compounds were isolated in four cases (**48**-**51**) in up to 90% yield, and an iodoalkylated derivative (**52**) was also isolated in 49% yield using NaI. These experiments showed that better nucleophiles can replace the chloride in the double substitution and open up new possibilities for a highly modular alkene difunctionalization.



By the end of the project period, we finished the substrate scope, and wrote the manuscript on the O-fluoroalkylation reaction which is going to be submitted very soon.

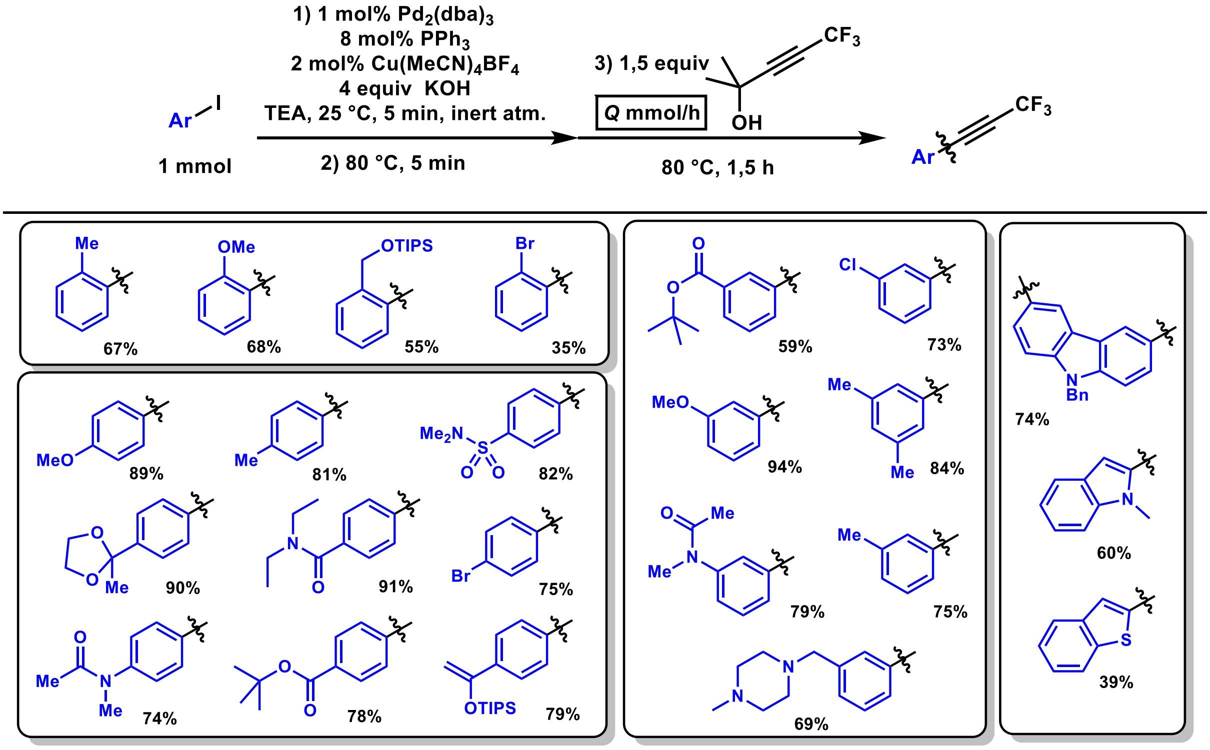
As a continuation of the *O*-substitution reaction, we find that the change of the reaction condition could direct the reaction into another path. With the use of K_3PO_4-tetramethylguanidine (TMG) base pairs for the *O*-functionalization, we were able to synthesize unique diaryloxy-ethene motif. After the optimization of the reaction conditions, we demonstrated the applicability of the reaction in the synthesis of various products containing the trifluoropropene linker between the phenol fragments.



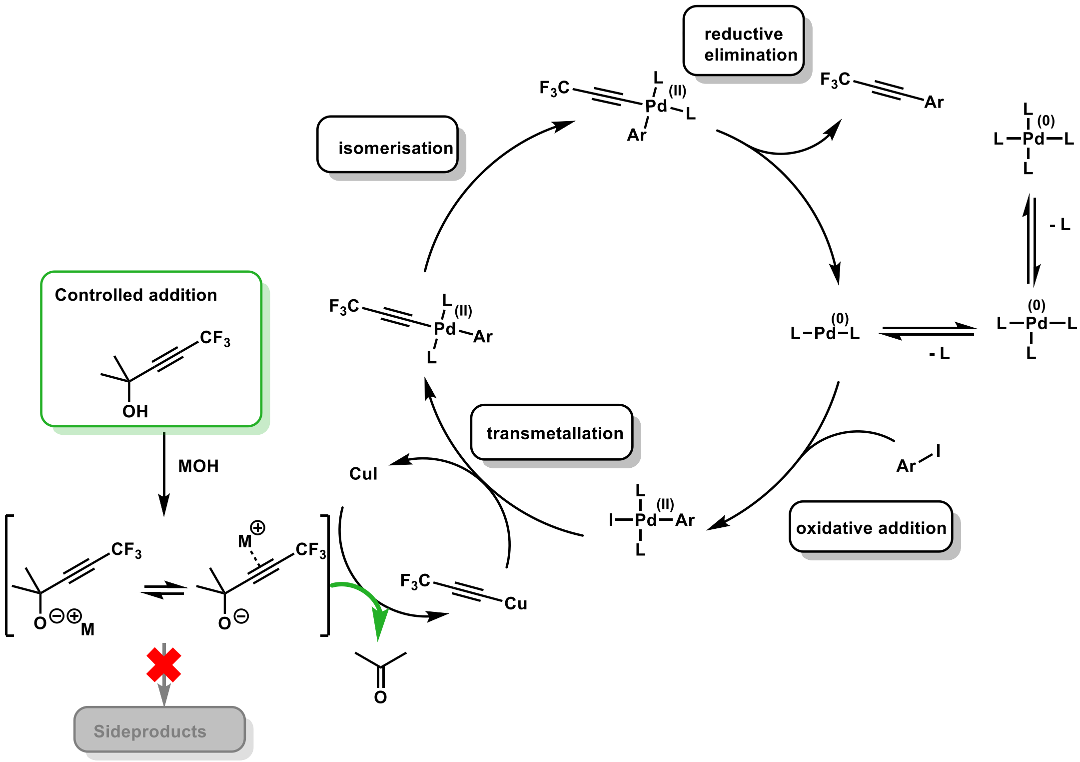
We have finished the optimization of the reaction conditions, and finished the substrate scope we plan to write the manuscript which summarizes the result of this chapter of our work.

2.6 Synthesis of trifluoromethylacetylene surrogates from HFO gas.

Synthesis and utilization of 3,3,3-trifluoropropyn is problematic due to the gaseous form of the compound at rt and atmospheric pressure. However, introduction of this group into organic molecules would provide novel molecular scaffolds. Thus, we aimed to design novel reagents which could serve as bench-stable reagents for direct catalytic incorporation of the trifluoromethylethynyl scaffold. As starting material, the cheap and readily available refrigerant gas HFO-1234yf served excellent raw material for the preparation of novel reagent. After treatment with base, we trapped the in situ generated trifluoromethylacetylide with carbonyl derivatives and prepared the corresponding carbinols in excellent yields. These carbinols are actually acetylene derivatives with a protecting group which could be used as trifluoromethylacetylene surrogates for organic and catalytic processes. These synthetic opportunities were studied in the project and after careful optimization studies we developed a procedure for the palladium catalyzed alkynylation of aryl iodides, and explored the substrate scope of the coupling reaction. As a result, we prepared more than 20 examples including aromatic and heteroaromatic systems.



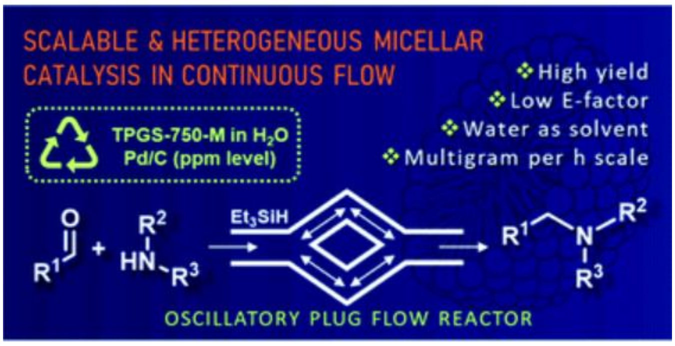
During the optimization studies we found that the addition rate of the alkynyl surrogate is very important for the successful and efficient coupling we studied the mechanism of the transformation, and proposed a catalytic cycle for the coupling reaction.



We found that controlled addition of the carbynol provide an appropriate amount of acetylide for the transmetalation step, and prevent the quick decomposition of the trifluoropropynyl anion formed rapidly when the acetylene surrogate added in one portion.

3. Development of Pd-catalyzed reductive amination under micellar flow conditions

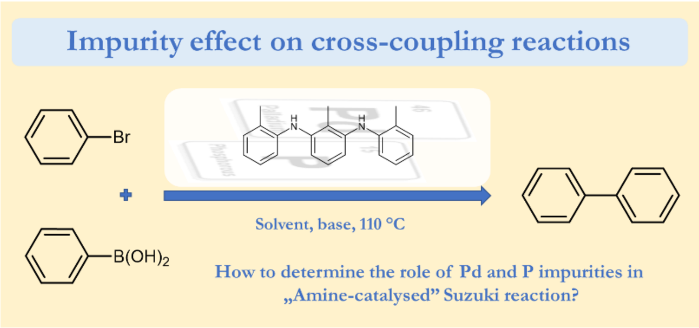
Beyond the planned topic of the project, we focused to some more general methodology development, which will be suitable for the synthesis of fluorinated species in the future. Despite the fact that continuous flow processing exhibits well-established technical advances, aqueous micellar chemistry, a field that has proven extremely useful in shifting organic synthesis to sustainable water-based media, has mostly been explored under conventional batch-based conditions. This is particularly because of the fact that the reliable handling of slurries and suspensions in flow is a significant technical challenge. In collaboration with other research groups, we demonstrate that the strategic application of an oscillatory plug flow (OFR) reactor that combines active and passive mixing enables heterogeneous catalytic reductive aminations in aqueous micellar media enhancing mass transport and facilitating process simplicity, stability and scalability. The micellar flow process enabled a broad range of substrates, including amino acid derivatives, to be successfully transformed under reasonably mild conditions utilizing only very low amounts of Pd/C as a readily available heterogeneous catalyst. The preparative capabilities of the process along with the recyclability of the heterogenous catalyst as well as the aqueous reaction media were also demonstrated. In this work, a continuous flow process has been demonstrated for reductive aminations under heterogeneous catalytic micellar conditions in water using an OFR. The process relied on Et3SiH as reducing agent along with ppm amounts of Pd/C as heterogeneous catalyst and TPGS-750-M as a commercially available surfactant. Due to the beneficial combination of an oscillatory flow regime and multiple static mixing elements, the flow system proved as a robust platform for performing reactions under aqueous micellar conditions, whilst ensuring enhanced mixing and mass transfer between the reacting phases. Following thorough optimization of the most important reaction conditions, such as pulsation parameters, temperature, residence time and catalyst carrier, high yielding reductive aminations were achieved applying comparatively mild conditions, whilst maintaining a stable suspension of the biphasic micellar media alongside the reactor. Reductive aminations of a diverse set of aldehydes with various amines were achieved, including a number of amino acid derivatives as pharmaceutically relevant building blocks. The preparative utility of the flow process was verified by a 7 h long-run furnishing straightforward multigram-scale production with low waste formation. The sustainable nature of the process was further elaborated by successfully recycling the heterogenous catalyst as well as the aqueous surfactant solution over 5 consecutive runs. To the best of our knowledge, this is the first demonstration of aqueous micellar catalysis in an OFR system. Notably, the process developed herein offers a straightforward scaling-up strategy by using a commercially available pilot-scale reactor, which maintains all the major process characteristics, including channel dimensions, residence time distribution and heat- and mass transfer.



The results were published in Green Chemistry (Continuous flow heterogeneous catalytic reductive aminations under aqueous micellar conditions enabled by an oscillatory plug flow reactor, Michaela Wernik, Gellért Sipos, Balázs Buchholcz, Ferenc Darvas, Zoltán Novák, Sándor B. Ötvös, C. Oliver Kappe, *Green Chem.* **2021**, **23**, 5625-5632. DOI: 10.1039/D1GC02039K)

4. Revisiting of amine-catalyzed Suzuki coupling

In our work, we demonstrated that the recently developed "amine-catalyzed" Suzuki-Miyaura coupling reaction in focus took place with the participation of Pd and P impurities supplied by the amine component, ruling out the role of amine as organocatalyst in the transformation. As an additional information the experimental results clearly show that even phosphorous derivatives are present in the organic products even after chromatographic purification step, supposedly due to the co-elution of various Pd-phosphine species with the Buchwald-Hartwig products. We hope this approach could turn the curse of any impurity effect to the blessing of a novel and highly efficient catalyst systems developed in chemical research, which is the case of the present observation. The recently developed methodology emphasizes the greatness of Suzuki-Miyaura reaction which provides access to versatile and complex molecules including API-s with a "homeopathic" amount of palladium loading and the selection of appropriate reaction conditions, even on large scale.

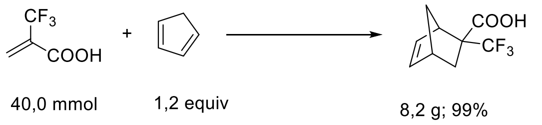


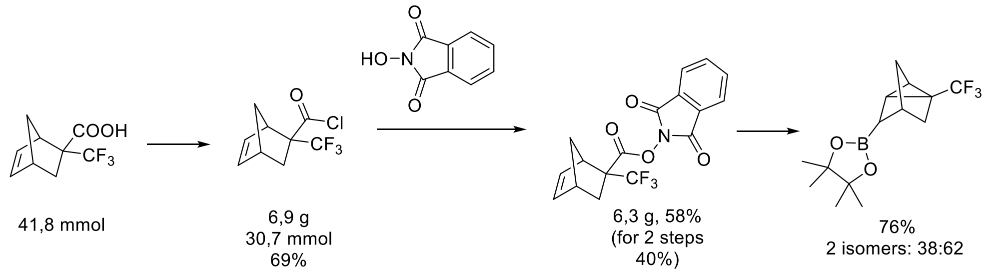
The results were published in Nature Catalysis (Zoltán Novák, Réka Adamik, János T. Csenki, Ferenc Béke, Regina Gavaldik, Bálint Varga, Bálint Nagy, Zoltán May, János Daru, Zsombor Gonda, Gergely L. Tolnai, Nature Catal. 2021, 4, 991–993. DOI: 10.1038/s41929-021-00709-8); and highlighted in C&EN (Cover Story; https://cen.acs.org/magazine/100/10006.html ; 2022, 100, 6, 20-26), Chemistry World (https://www.chemistryworld.com/news/the-curious-incident-of-the-catalytic-amine-that-never-was/4014901.article), and Nature (Nature 606, 448-451 (2022) doi:/10.1038/d41586-022-01612-3; https://www.nature.com/articles/d41586-022-01612-3).

5. Miscellaneous transformations

5.1. Synthesis of fluoroalkylated bridged building blocks

According to the project proposal we designed novel molecular fragments equipped with CF_3 group. The synthesis of the norbornene scaffold was quantitatively was performed with the cycloaddition of cyclopentadiene and the trifluoromethyacrylic acid. This building block was transformed to the redox-active ester on multigram scale which serves excellent source for radical transformations. Currently, we are studying the applicability of this synthon, and as the best synthetic result, we prepared the bridged system having boronic ester group, which offers versatile transformability, and we aim to develop procedures for the introduction of this trifluoromethyl tricyclic systems into various molecular frameworks, as novel bioisosteric fragment.





After finishing the founded project, we continue these studies to exploit the synthetic potential of these synthetic transformation.

5.2. Synthetic utilization of ESF

Ethenesulfonyl fluoride (ESF) was synthesized based upon a previous literature procedure in 80% total yield. Then, ESF was converted into ESF-I by a two-step manner. In the first step, 1,2-iodoethansulfonyl fluoride was prepared via addition of ICl onto the double bond of ESF in a neat reaction. After that an on-water elimination process was carried out with the use of magnesium oxide. Target compound was obtained in moderate yields (55-65%).

The newly synthesized ethenylsulfonyl fluoride iodide (ESF-I) was tried out in several coupling rections in order to map the transformation possibilities. Suzuki reactions with phenylboronic acid in presence of different palladium catalysts, potassium carbonate in absolute THF resulted full decomposition of ESF-I, the use of MgO instead of the potassium carbonate yielded the survival of the ESF-I but no coupling reaction occurred. Potassium triphosphate also tolerated by ESF-I but no reaction took place neither in this case. Palladium-catalyzed reactions with aryldiazonium salts or phenylacetylene also failed. Sonogashira couplings using para-trifluorophenylacetylene and palladium acetate with different bases and solvents were also unsuccessful.

The Michael-type reaction of ESF-I with aniline was successful. Initial experiments were planned along a literature procedure, later acid catalyst was left and solvent was replaced to acetonitrile instead of the original acetic acid. Michael addition of N-methylaniline and ESF-I gave the corresponding adduct in 92% yield. Although aziridine formation was also expected during this reaction, the latter did not occur in any cases. Several experiments were performed with primary and secondary amines too, but these Michael adducts proved to be too unstable to be isolated. Addition reaction with phenol was also unsuccessful, thiophenol was converted into diphenyl disulfide by ESF-I, the desired adducts were not detected. Reaction with an azulene derivative also failed. Experiment to prepare a sulfonium salt from tetrahydrothiophene was also unsuccessful, ESF-I remained unchanged.

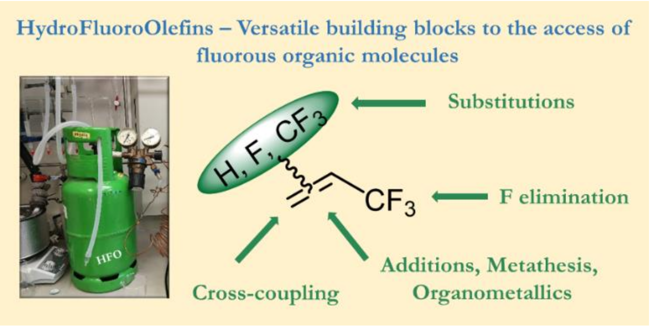
With the N-methylaniline-ESF-I adduct in hand, we tried out several substitution and coupling reactions. It can be generally stated that iodine atom of the starting material is prone to reduction or elimination. N-methylaniline could also be detected in these reactions, which was generated by decomposition processes. Photochemically induced ATRA reactions with a styrene derivative were unsuccessful, the desired product was not seen, similar result was obtained with a phenylacetilene derivative. Substitution experiments with aniline failed, only deiodo byproduct and N-methylaniline were obtained. Phenol reacted with the sulfonyl fluoride moiety to obtain sulfonic acid ester and its deiodo counterpart, thiophenol was oxidated to the corresponding disulfide. Complete decomposition was achieved in Sonogashira coupling reactions. In a nickel-catalyzed Gringard reaction, only iodobenzene was detected. Further transformations of novel ESF-derivatives are studied in the next research period.

6. Review articles

In the research period, especially due to the pandemic period, we published several review papers.

6.1. Synthetic applicability of HFO gases

As our interest led to the extensive use of refrigerant, we also wrote a review regarding the synthetic uses of HFOs (hydrofluoroolefins). After processing the available literature, we managed to categorize and describe transformations such as additions, substitutions, organometallic processes, metathesis etc. HFO gases are state-of-the-art cooling agents with widespread household and industrial applications. Considering their structural benefits these fluorous feedstocks gained attention of organic chemists in the last couple of years. In this short review we summarized the existing synthetic transformations of these gaseous synthons and present their applicability in the synthesis of fluorine containing organic molecules, which have potential importance as building blocks and reagents for diverse syntheses.

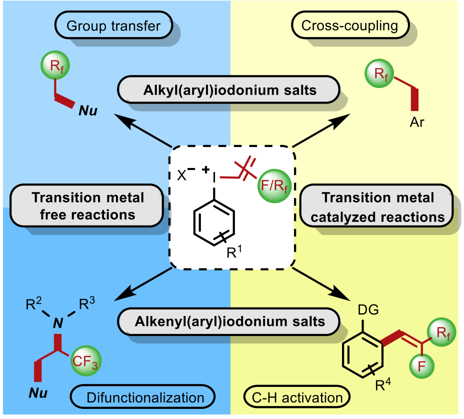


This work was published in the journal Synthesis (Application of Industrially Relevant HydroFluoroOlefin (HFO) Gases in Organic Syntheses; Bálint Varga, János T. Csenki, Balázs L. Tóth, Ferenc Béke, Zoltán Novák , András Kotschy; *Synthesis*, **2021**, *53*, 4313-4326.; DOI: 10.1055/a-1538-8344).

6.2. Fluoroalkylations and Fluoroalkenylations with Iodonium Salts

Synthesis and applications of fluoroalkyl and fluoroalkenyliodonium salts are summarized in this account article, focusing preferably to the reagents designed in our laboratory in the last decade. Among these reagents trifluoroethyl(aryl)iodonium salts have been used most frequently to build carbon-carbon and carbon-heteroatom bonds in simple nucleophilic substitutions and through transition metal catalyzed coupling reactions. Iodonium salts equipped with unsaturated fluorinated function showed diverse reactivity due to their electron deficient character, and these molecular motifs enable cycloadditions and nucleophilic additions to prepare fluorinated carbo- and heterocyclic molecules.

The existing fluoroalkyl and fluoroalkenyliodonium salts were successfully applied for the synthesis of fluoroalkylated and -alkenylated compounds through metal free or transition metal catalyzed functionalizations of aromatic and heteroaromatic species. With the aid of the reactive electrophilic iodonium species the transformations generally can be achieved under mild reaction conditions in relatively short reaction times and provides the desired products in high chemical yields. The fluoroalkyl reagents typically used for the alkylation of heteroatom nucleophiles such as amines, alcohols, thiols. Moreover, fluoroalkylation of more complex molecules such as saccharides, amino acids and peptides or functionalization of heterocycles were also achieved in a simple and efficient manner. The unsaturated fluorinated iodonium salts are capable for cycloaddition, and acts as excellent Michael acceptors. Additionally, their electrophilic character enables their application as coupling partner in palladium catalyzed C-H activation reactions. Considering the structural features of these iodonium salts, the development of novel reagents equipped with new fluorous motifs are in focus of current research, together with the study of their applicability in various chemical transformations to expand the chemical space of fluorinated molecules. Beyond the overview of existing transformations, with the presented collection, we aim to inspire future developments of iodonium reagents and their application in organic synthesis.



The literature review was published in The Chemical Reviews (Fluoroalkylations and Fluoroalkenylations with Iodonium Salts, Ferenc Béke, János T. Csenki, Zoltán Novák, *Chem. Rec.* **2023**, *23*, e202300083. DOI: 10.1002/tcr.202300083)

6.3. Use of micellar systems for building DNA-encoded libraries

DNA-encoded library (DEL) technology has become widely used in drug discovery research. The construction of DELs require robust organic transformations which proceed in aqueous media under mild conditions. Unfortunately, the application of water as reaction media for organic synthesis is not evident due to generally limited solubility of organic reagents. However, the use of surfactants can offer a solution to this issue. Oil-in-water microemulsions formed by surfactant micelles are able localize hydrophobic reagents inside them, resulting in high local concentration of the organic substances in an otherwise poorly solvated environment. Our review provides a conceptual and critical summary of micellar synthesis possibilities that are well-suited for DEL synthesis. Existing examples on micellar DEL approaches, together with a selection of micellar organic transformations fundamentally suitable for DEL are discussed.

The literature overview was published in Chemistry a European Journal (The Potential of Micellar Media in the Synthesis of DNA-Encoded Libraries, Réka Adamik, Balázs Buchholcz, Ferenc Darvas, Gellért Sipos, Zoltán Novák, *Chem. Eur. J.* **2022**, *28*, e202103967. DOI: 10.1002/chem.202103967)