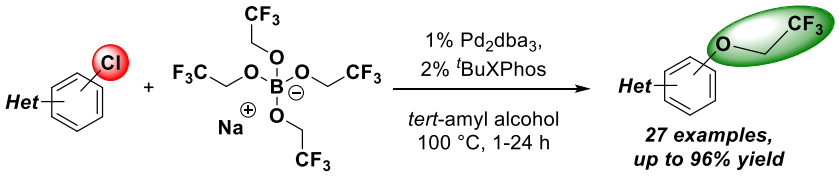
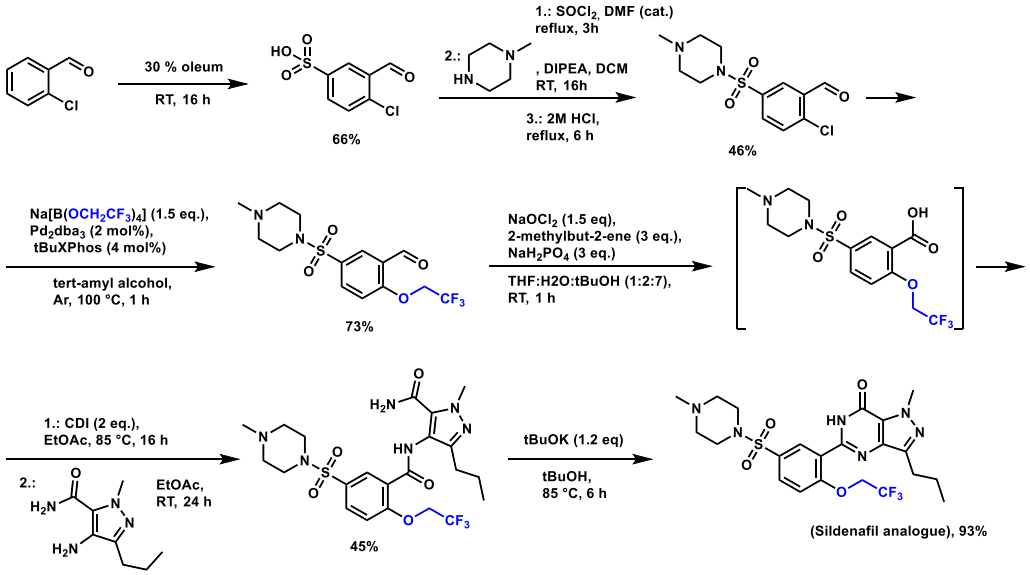
Final report on the NKFIH project KH125230 entitled "Development of Novel Synthetic Methods Based on Borate and Fluoroalkyl Motifs"

Trifluoroethoxylation of aromatic and heteroaromatic chlorides with novel borate salts in palladium catalyzed cross-coupling reactions

In the last few decades, fluoroorganic molecules received high attention in most fields of the chemical industry due to their unique physical and chemical properties. In particular, fluoroalkoxy groups can be found in numerous drug molecules and candidates. Additionally, modification of lead compounds or current pharmaceuticals with fluorous functional groups can lead to better ADME properties. The classical route for the synthesis of aryl-2,2,2-trifluoroethyl ethers, which utilize phenol derivatives and trifluoroethyl electrophiles (eg.: Iodide, Iodonium salts, sulphonates, etc.). The drawback of these transformations is the limited functional group tolerance. The application of trifluoro-ethanol or its salts in aromatic nucleophilic substitutions is also a viable path, but this requires the utilization of electron-poor aryl-fluorides as substrates. Thus, recently several procedures were elaborated for the 2,2,2-trifluoroethoxylation of aryl-halides, granting a new approach to trifluoroethyl aryl ethers. These methods contributed largely to the straightforward synthesis of trifluoroethoxy arenes. In contrast, the transformation of aryl chlorides to the corresponding triflouroethyl-ethers is extremely limited. For this reason, a simple and convenient method for the introduction of 2,2,2-trifluoroethoxy group to various aromatic and heteroaromatic chlorides was elaborated in our research group in the frame of the research project. Our novel process utilizes a tetrakis(2,2,2-trifluoroethoxy) borate salt as an inexpensive and readily available fluoroalkoxy source, in a solvent-assisted palladium catalyzed cross-coupling reaction. Both Pd(0) and Pd(II) sources were found active in the transformation, however bulky, dialkyl-biphenyl-phosphine ligands were necessary for the efficient coupling reaction.



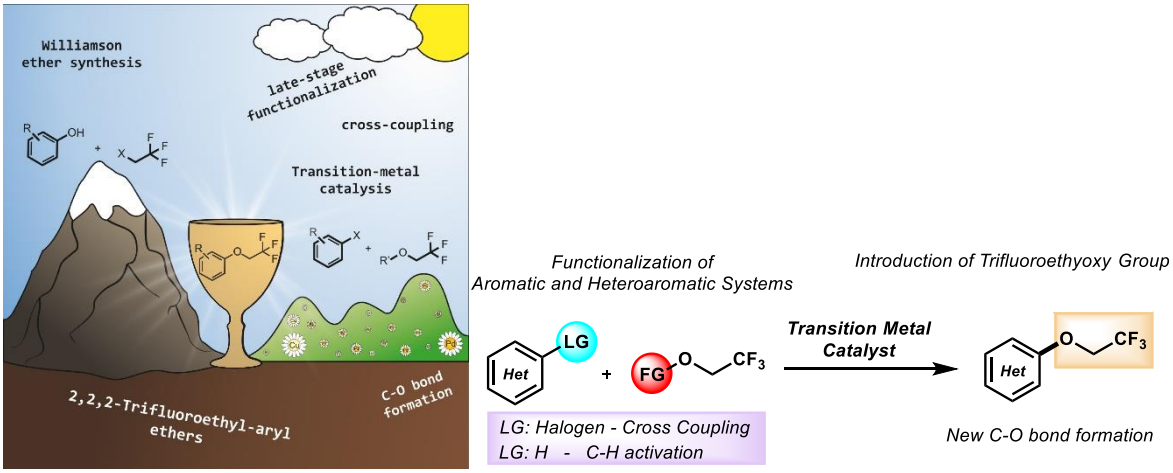
The synthesis of variously substituted aryl- and heteroaryl-trifluoroethoxides was carried out starting from the appropriate chlorides (27 examples, up to 96% yield), as well as the total synthesis of a drug molecule's trifluoroethoxy-analogue. The physico-chemical properties of this compound showed slight differences with Sildenafil, including a weaker affinity towards intramolecular H-bond formation. The fluorinated analog showed enhanced metabolism too, which might not be disadvantageous, considering the therapeutic field of Sildenafil.



The result was published in Chemistry a European Journal (Palladium Catalyzed 2,2,2-Trifluoroethoxylation of Aromatic and Heteroaromatic Chlorides Utilizing Borate Salt and the Synthesis of Trifluoro Analog of Sildenafil,

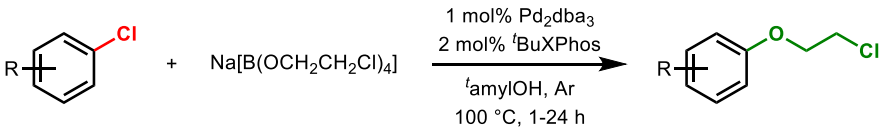
Bálint Pethő, Márton Zwillinger, János Csenki, Anna Káncz, Balázs Krámos, Judit Müller, György Tibor Balogh, Zoltán Novák, *Chem. Eur. J.* **2017**, *62*, 15628-15632. DOI: 10.1002/chem.201704205: Impact Factor: 5.16)

We have published a review paper on the existing trifluoroethyoxylation methods in the Asian Journal of Organic Chemistry (Synthesis of aryl- and heteroaryl-trifluoroethyl ethers: aims, challenges and new methodologies, Zoltán Novák, Bálint Pethő *Asian J. Org. Chem.* **2019**, 568-575; DOI: 10.1002/ajoc.201800414, Impact factor: 2.496). This article covers the synthetic tools based on transition metal catalyzed trifluoroethoxylation of aromatic and heteroaromatic molecules which provide novel approach to trifluoroethyl arylethers. The summarized methodologies could have widespread application in the synthesis of biologically active molecules having trifluoroethoxy group, and further developments in the future.

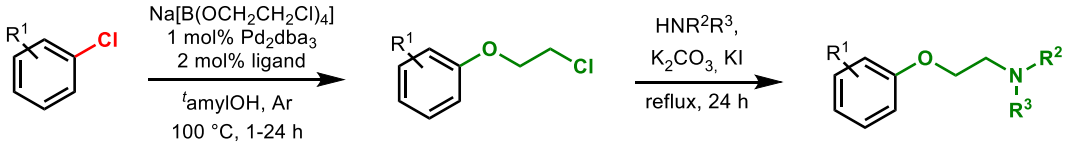


Chloro- and amino-ethoxylation of aromatic and heteroaromatic chlorides with novel borate salts in palladium catalyzed cross-coupling reactions

Additionally, we have developed an alternative, simple and convenient synthetic route to the access of 2-chloroethoxy-arenes using palladium-catalyzed cross-coupling reaction of aryl chlorides and tetraethoxyborates. This methodology is orthogonal to nucleophilic substitution and enables the modular synthesis of various molecules containing ethoxy linkers between nucleophilic centers (eg. amines) and aromatic cores.



The utilization of a novel borate salt ensures efficient transformation with good functional group tolerance due to the absence of external base, and eliminates synthetic difficulties of the traditional alkoxylation with haloalcohols. This special feature of the transformation provides a new synthesis concept in the field of C-O bond forming reactions. With a subsequent simple nucleophilic substitution reaction step, wide variety of 2-aminoethoxy-arenes can be prepared in a one-pot manner.



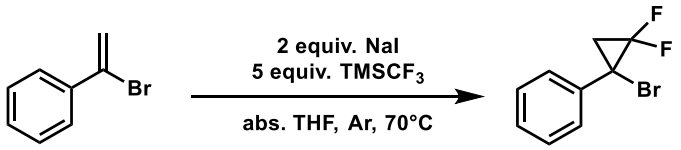
Beyond several aminoalkoxylated model compounds, the applicability of the two step one-pot reaction was demonstrated with the synthesis of a Bazedoxifene-analogue and the final intermediate of Raloxifene. Thus, previously unavailable synthetic routes to bioactive molecules can be performed with the application of this method, which can be an alternative, efficient tool for generic and original pharmaceutical research. The new methodology paves the way for versatile alkoxylation reactions to the direct access of aryl-haloalkyl ethers which are susceptible for further transformations with various nucleophiles. The results were published in Organic and Biomolecular Chemistry (Palladium Catalyzed Chloroethoxylation of Aromatic and Heteroaromatic Chlorides: an Orthogonal Functionalization of Chloroethoxy Linker, Bálint Pethő, Dóra Vangel, János Tivadar Csenki, Márton Zwillinger, Zoltán Novák, *Org. Biomol. Chem.* **2018**. *16*, 4895-4899. DOI: 10.1039/C8OB01146, Impact Factor: 3.423

Synthesis of difluorocyclopropanes and cyclopropene derivatives

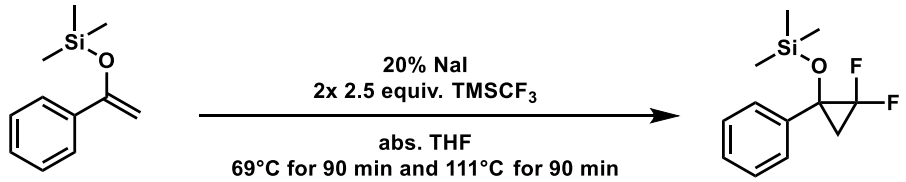
Fluorinated aliphatic compounds are highly desirable moieties and goal of several pharmaceutical and agrochemical related bioactive compound research. Their synthesis is precedented in the recent literature, and is known as a field of "difluorocarbene-chemistry". Depending on the utilization of the proper carbene precursor and promoter, the procedures alter from harsh cold conditions through mild heated or room temperature to harshly heated reaction conditions. The consensus is the utility of trialkylsilyl-CF_2-halide in the presence of iodide anion as promoter. The most readily available and most inexpensive reagent for this purpose is the trimethylsilyl-trifluoromethane, described by Prakash group. For this purpose, we chose this reagent and started with the synthesis of difluorocyclopropanes and -cyclopropenes.

First, we followed the procedure of Oláh and Prakash, carried out in pressure-proof vials in batch reaction. Phenylacetylene, (1-bromovinyl)benzene, 2-phenylacrylicacid, cinnamic acid and its simple alkyl ester and Redox Active Ester (RAE) counterpart made from N-hydroxy phthalimide, trimethyl((1-phenylvinyl)oxy)silane and n-butyl acrylate were chosen as model substrates, bearing the potential for further transformations.

The reactions were carried out under anhydrous conditions and argon atmosphere in 2 mmol scale. For the construction of difluorocyclopropan ring we used 20 mol% NaI, 2.5 equivalent of $TMSCF_3$ in 1.5 mL/1 mmol substrate volume freshly distilled THF (from potassium, using benzophenone as an indicator) using Schlenk technique. After 2 hours at 65 °C, we were able to reach full conversion in case of (1-bromovinyl)benzene and trimethyl((1-phenylvinyl)oxy)silane and isolated the appropriate products in 33-54% yields (multiple batch).

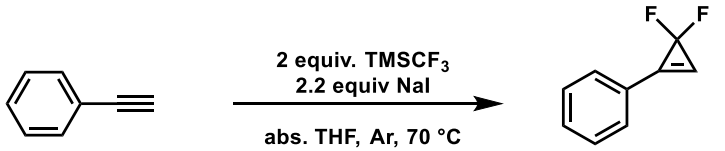


40%



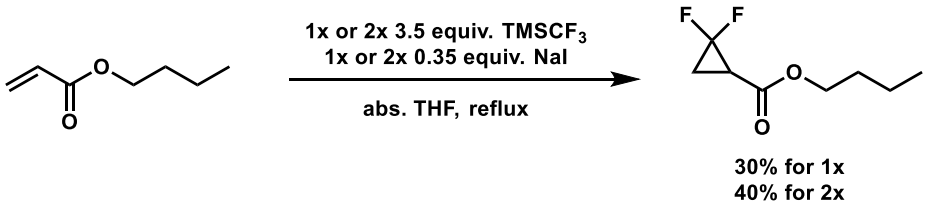
54% isolated

The utility of phenylacetylene needs modified conditions: 2.2 equivalent of NaI is needed in larger volume of solvent (3.0 mL THF/1 mmol substrate) and slightly smaller amount, 2.0 equivalent of reagent at 110 °C. It also reacted readily in pressure-proof vial at first try, but we couldn't reach the same result in that vial, so we adapted it to induction reactor. This way, the reaction was carried out 4 times with success in 1-2 mmol scale.

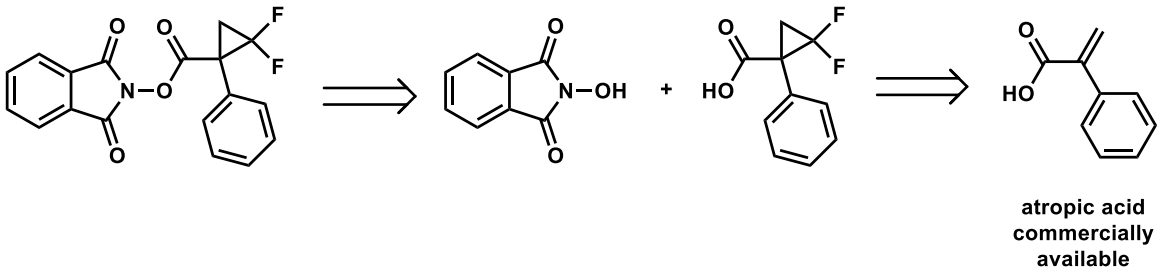


58% isolated

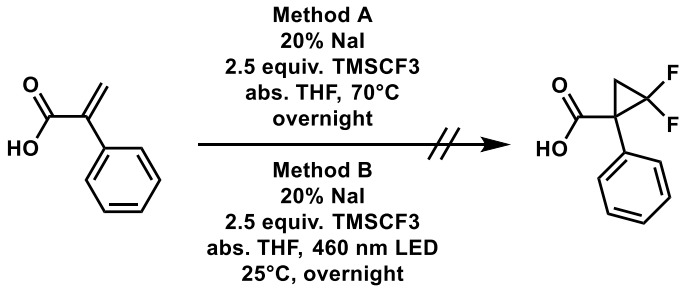
The more electron deficient butyl acrylate is described as a relatively inactive substrate in the Oláh-Prakash procedure, that's why we used the "slow addition" procedure, which can improve the yield of these substrates. For this, the dry THF solution (2.5 mL/1 mmol substrate) of acrylate in presence of 35 mol% NaI was refluxed under inert atmosphere. The 3.5 equivalent of reagent was added dropwise, with syringe pump with 1-2 mL/min flow rate. After boiling it for 4 hours, the GC-MS analysis revealed that the conversion was 30% without any trace of side reaction. In another experiment, we a further 35 mol% of NaI and another portion of 3.5 equivalent $TMSCF_3$ and refluxed for further 12 hours. In this case, the conversion was about 40%, but the product was also detectable in smaller 25% because of the side reaction resulting several unidentified side products. We concluded from this investigation, that the extreme dry conditions are essential for the outset of the reaction. The reaction was complete in maximum 2-5 minutes after outset, but for that, elongated reaction time was needed.



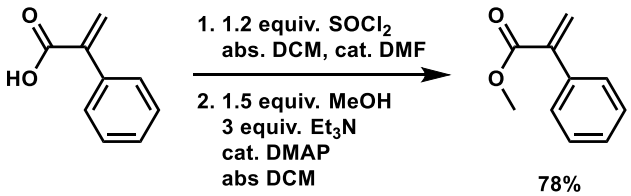
Next, we aimed to prepare new RAE of difluorocyclopropanes from the appropriate alkene. We thought that the synthesis could be based upon the commercially available atropic acid. After the cyclopropanation process, the appropriate carboxylic acid could be obtained, which would be suitable for coupling with *N*-hydroxyphtalimide.



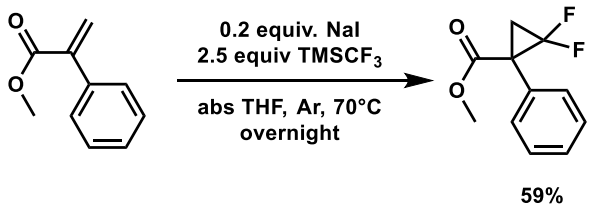
Although, we found a procedure for cyclopropanation of the atropic acid methyl ester (Adv Synth Catal, 2018, 360, 4104), we tried to build the cyclopropane ring directly on the carboxylic acid. Two methods were used, but neither the thermal nor the photocatalytic attempt was successful. In all reactions of this section, $TMSCF_3$ was added in one portion. Besides this, a slow polymerization side reaction was observed during storage of the atropic acid, this phenomenon caused lower yields in our further work.



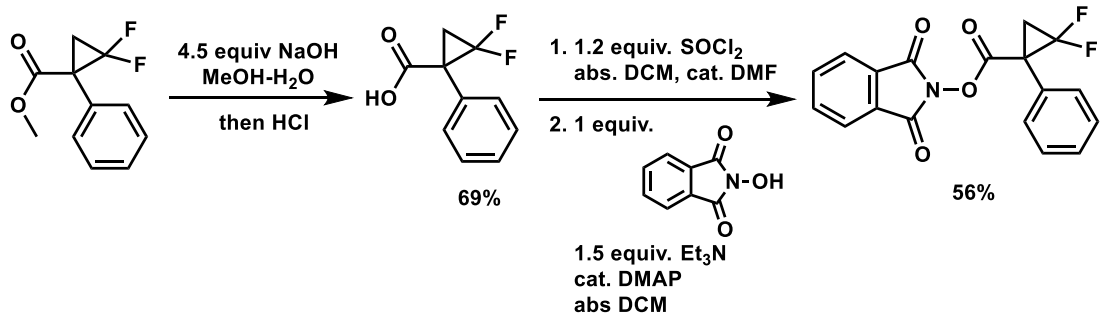
As the direct cyclopropanation of the carboxylic acid was unsuccessful, we decided to prepare the appropriate methyl ester and follow the literature processes to obtain the desired acid. In the first step, we performed the esterification via acyl chloride according to a literature procedure. The appropriate acyl chloride was prepared with $SOCl_2$ in dry DCM, then MeOH was added in the presence of Et_3N. The methyl atropiate was isolated with 78% yield by flash column chromatography.



The next step was the insertion of the CF_2 carbene onto the double bond. The reaction was carried out in an oven-dried pressure tube under argon atmosphere with 20% oven-dried NaI and 2.5 equivalent of $TMSCF_3$ in dry THF at 65°C. This reaction was repeated in several times in 1 and 2.5 mmol scale. The best yield was 59%. The obtained cyclopropane derivative is already stable for storage.



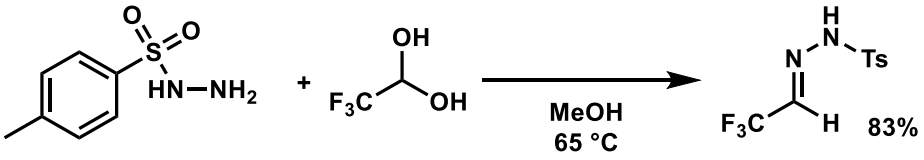
The target RAE was synthesized from this ester in three steps. At first, an alkaline hydrolysis was performed in the presence of 4.5 equiv of NaOH in aqueous MeOH, then the carboxylic acid was coupled with *N*-hydroxyphtalimide via acyl chloride. The required acid was obtained with 69% after acidification of the reaction mixture and recrystallization purification. The coupling was performed according to the starting esterification process, which is described above. The desired RAE was isolated with 56% yield from this step.



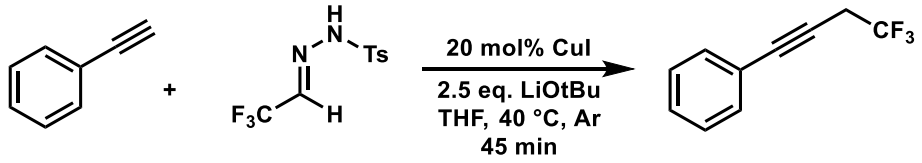
The prepared difluorocyclopropanes with the appropriate functional groups will be useful building blocks for further transformations, which will be examined in our following research.

Utilization of novel fluorous carbene source in copper catalyzed transformations

Copper catalyzed coupling reaction between terminal alkynes and in situ generated carbenes are well known in the literature. With high temperature and a strong base (usually lithium tert-butoxide) a functionalized acetylene or allene product is formed. The tosylhydrazone derivatives are one of the most frequently used sources of carbenes in this type of reactions. In basic media they lose a proton, a nitrogen molecule eliminates and the desired carbene is formed. The structure of the carbene is depends on the applied aldehyde in the synthesis of the tosylhydrazone. Our aim was to find an excellent fluorous carbene source, and by its application synthesize various fluorine containing structures. We synthesized the trifluoracetaldehyde *N*-tosylhydrazone derivative by condensation reaction of trifluoracetaldehyde monohydrate and p-toluenesulfonyl hydrazide in good yield (83%) in multigram scale, and isolated as bench stable crystalline white solid.



Next, we examined the reactivity of the prepared fluoroalkyl carbene source. In our fist experiment we applied the conditions generally used for the carbene generation from tosylhydrazones. We used phenylacetylene as our model substrate with 2 equivalents of tosylhydrazone and 3.5 equivalent of lithium tert-butoxide as a base and 20 mol% copper iodide as a catalyst. At 95 °C in 1,4-dioxane solvent we could detect the formation of the desired (4,4,4-trifluorobut-1-yn-1-yl)benzene by GC-MS but only in 30%. We discovered that the solution of the tosylhydrazone has to be added slowly dropwise to the reaction by syringe pump to achieve higher conversion. However, we noticed formation of a HF eliminated difluoro-ene-yne by-product, which can be controlled by temperature and the base loading. As the result of our multiparameter optimization studies, we found that the reaction works perfectly at 40 °C in THF, and 100% conversion can be reached beside minimal by-product formation. We investigated different copper salts in the coupling reaction and we found that the copper halides are the most efficient catalysts, any ligands on the copper inhibits the formation of the product.

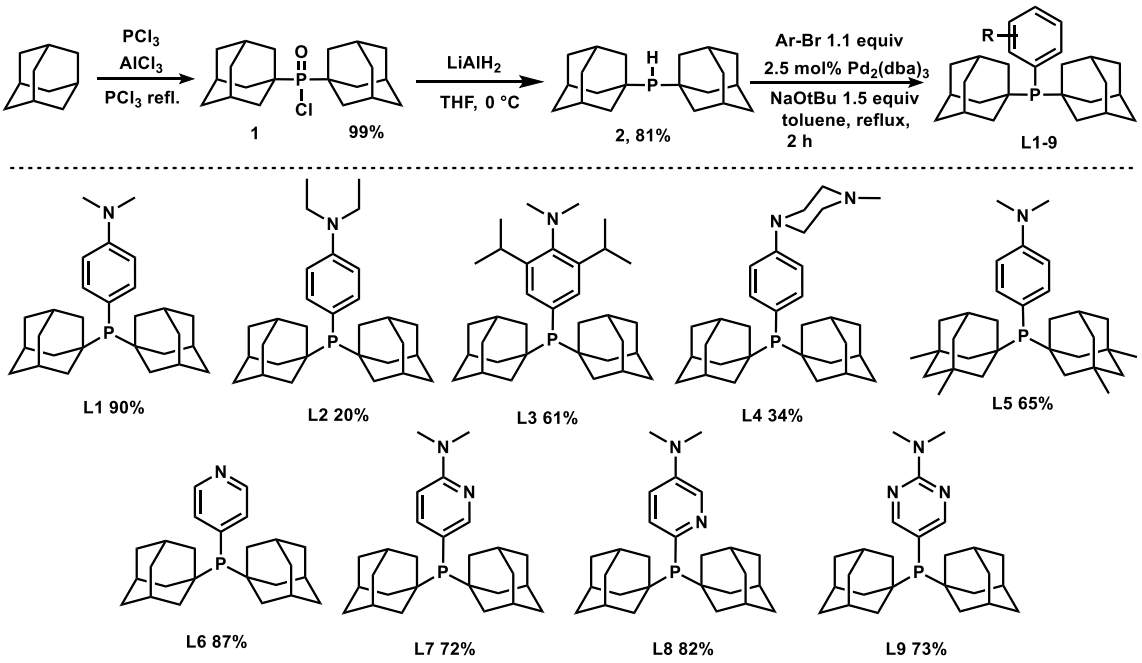


The highest conversion (90%) was achieved using copper iodide. We tried to use different silver and gold salts but they showed no activity. We also investigated the amount of copper needed, we observed that the reaction needs 20 mol% copper loading. The best base was the originally applied lithium tert-butoxide, with sodium carbonate, tripotassium phosphate, cesium fluoride or organic bases like diethyl amine we couldn't detect any product. However, we could reduce the amount of lithium tert-butoxide needed, with 2.5 equivalent base we accomplished the reaction without conversion loss.

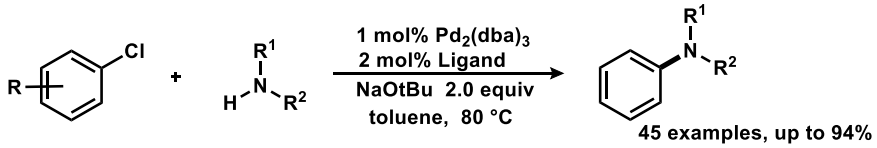
With the optimized conditions in hand we isolated the (4,4,4-trifluorobut-1-yn-1-yl)benzene in 22% yield. The biphenyl and naphtyl derivatives were isolated in 54-64% yield. We applied the reaction to several *N*-propargyl aniline derivatives as well (34-41%). Further study of the scope and limitation is in progress in our laboratory.

Synthesis of new bulky phosphane ligands for cross-coupling reactions

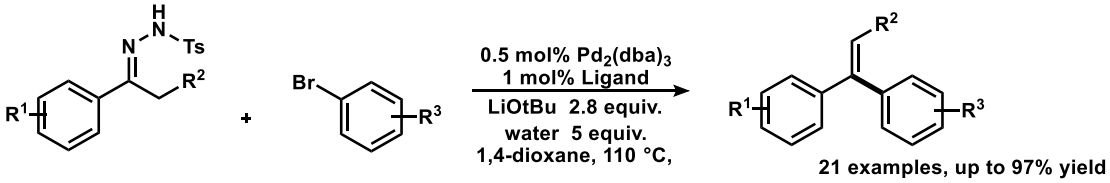
A new phosphine ligand kit was developed, which could be efficiently used in cross-coupling reactions. The advantage of the new ligands is the easy synthetic accessibility from cheap reagents on multigram scale. To exploit this beneficial feature, we efficiently synthesized a collection of nine bulky aryl-diadamantyl phosphine ligands. Their structure contains one para amino substituted aryl or heteroaryl ring attached to the phosphorous center, besides two bulky adamantane ring. Detailed spectroscopic analysis (including X-ray and NMR) was performed to describe the structure of the new ligands, and explain their spectral characteristics.



The catalytic applicability of the new ligand class was examined in palladium catalyzed Buchwald-Hartwig amination reaction of aryl chlorides (45 different isolated coupled amine products).



Additionally, the new ligand class was also tested in the coupling reaction of aryl bromides with aryl tosylhydrazones in the presence of palladium catalyst. We demonstrated the synthetic utility of the diadamantyl ligand with 21 isolated coupled products.

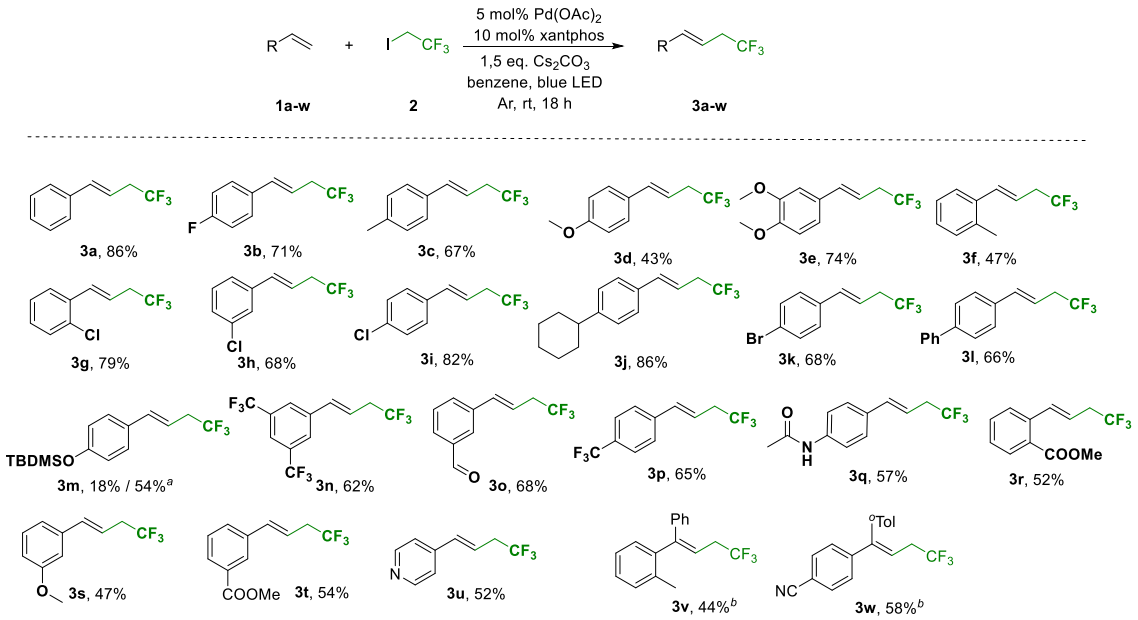


In our synthetic studies we found that the new aryl-diadamantyl phosphines served as efficient ligands for the selected palladium catalyzed cross-coupling reactions, and they have higher reactivity than the known studied phosphane ligands. With the exploitation of the enhanced reactivity versatile sterically congested molecular structures could be obtained through their utilization.

The designed ligand class could provide good alternative to the existing ligands and offer new and efficient catalytic system for frequently performed organic transformations in diverse fields. The results of this study were summarized in a scientific paper, which was published recently (Synthesis, Structural Analysis and Application of Aryl-Diadamantyl Phosphine ligands in Palladium Catalyzed Cross-Coupling Reactions, Ádám Sinai, Dániel Csaba Simkó, Fruzsina Szabó, Attila Paczal, Tamás Gáti, Attila Bényei, Zoltán Novák, András Kotschy, *Eur. J. Org. Chem.* **2020**, *9*, 1122-1128).

Palladium catalyzed fluoroalkylation of alkenes

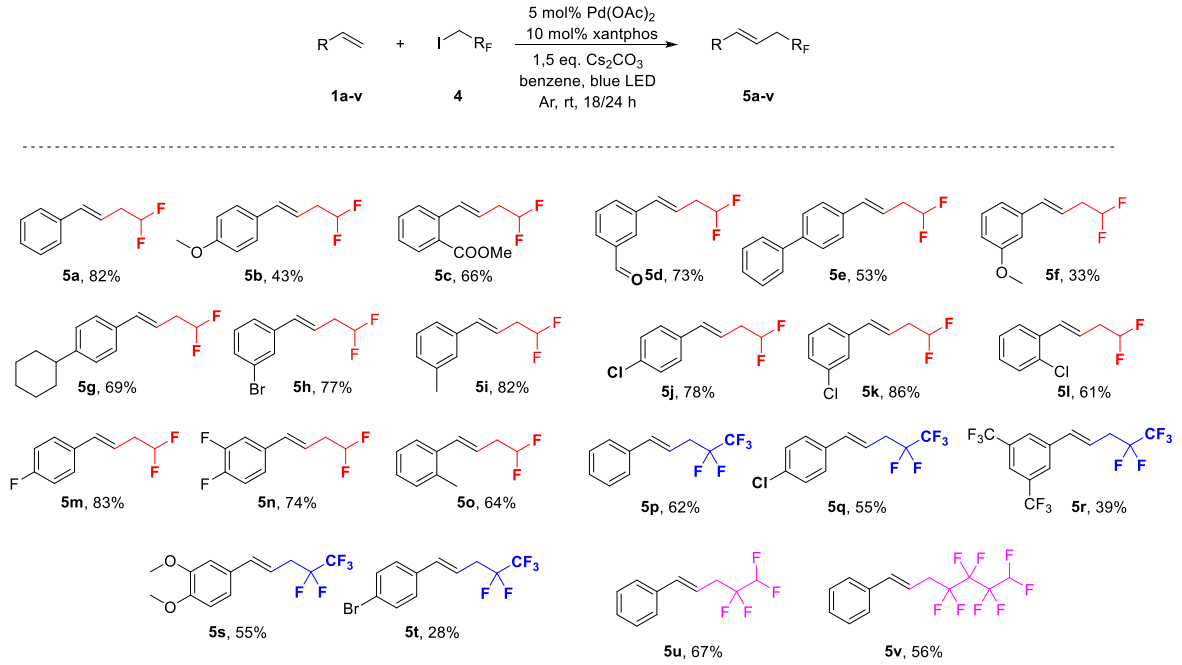
There are several different strategies to construct the trifluoroethylated styrene structure. It can be synthesized through several synthetic ways but the direct fluoroalkylation of C-C double bond in alkyl cross-coupling is a new approach. At the end of the project period we developed a new Heck type coupling method for introducing fluoralkyl groups into the styrene moiety using palladium catalysis under photocatalytic conditions. We started our investigation by optimizing the reaction conditions of the coupling reaction of styrene and trifluorethyl iodide. We found that the transformation 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. A control experiment without any irradiation indicated that the light is essential for this transformation. After the optimization studies we explored the scope and limitation of the reactions. The transformation went smoothly with styrene derivatives with electron-withdrawing and electron-donating groups as well regardless of their position on the aromatic ring. We synthetized different halogen (**3b**, **3g**-**i**), methoxy (**3d**, **3e**, **3s**), alkyl (**3c**, **3f**, **3j**) and aryl (**3l**) derivatives with good yields. Ester (**3r**, **3t**), aldehyde (**3o**), amide (**3q**) and silyl protected phenol (**3m**) functional groups are tolerated as well, however the conversion was not complete with the silyl ether, so the isolated yield is relatively low. Repeated experiment with longer reaction time provided the corresponding product (**3m**) with higher yield. Moreover, the pyridine derivative (**3u**) also coupled successfully in moderate yield.



On the other hand, 1,1-diphenylethylene derivatives were slightly more inactive in this transformation, increased catalyst and base loading is needed to accomplish the desired coupling. We managed to synthetize the **3v** and

3w derivatives with moderate yields. Altogether 23 different trifluorethylated products were prepared in this transformation.

Next the reactivity of different fluoroalkyl iodides was 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. Applying the 1,1-difluoro-2-iodoethane in the original conditions the conversion was not entirely complete. With increased reaction time (24 hours) we could isolate the corresponding difluoroethylated styrene product (**5a**) with 82% yield. With the slightly modified procedure 12 additional compounds were prepared with moderate to good yields (**5b**-**5o**).



1H,1H-Pentafluoropropyl iodide also gave the corresponding coupled products in the standard reaction conditions. In this case the pentafluoropropylated derivatives (**5p**-**t**) were isolated with moderate yields. Two other fluoralkyl iodides were also tested in this transformation, 1,1,2,2-tetrafluoro-3-iodopropane and 1H,1H,5H-octafluoropentyl iodide. Both iodides gave successfully the coupled product (**5u, 5v**), accordingly iodides with longer fluorous chains also can be used in this trans-formation.

In conclusion, we have successfully developed a palladium catalyzed Heck type coupling of styrenes and fluoroalkyl iodides at room temperature 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 great procedure to incorporate fluorine containing functional groups into styrene derivatives.

We almost completed our studies on this topic, after the closing date of the project some additional experiments and analytical measurements are needed. Then the results will be summarized in a manuscript which will be submitted to international chemistry journal.