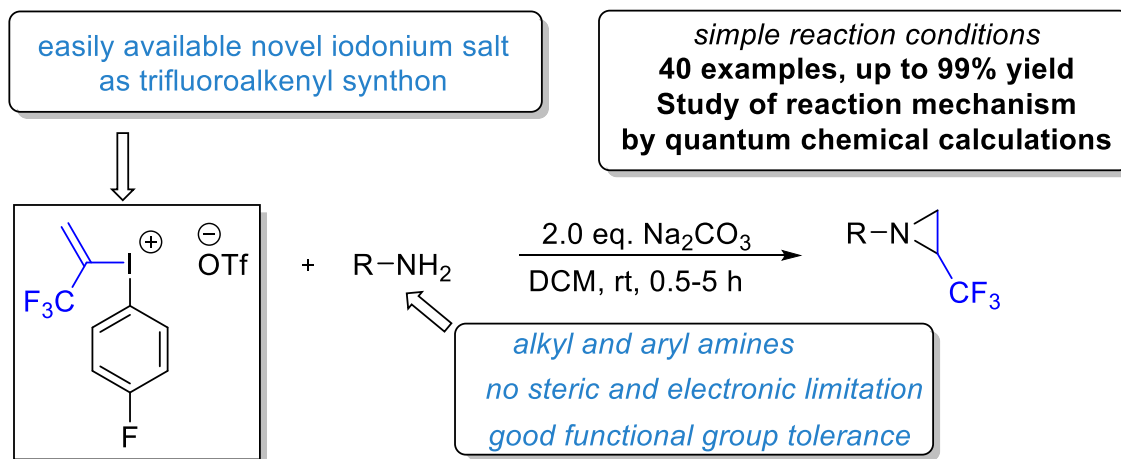


Final report on the NKFIH project KH125120 entitled “Design and Application of Novel Transition Metal Catalysts and Onium Salts in Organic Synthesis”

1. Design and utility of novel alkenyl-iodonium salt

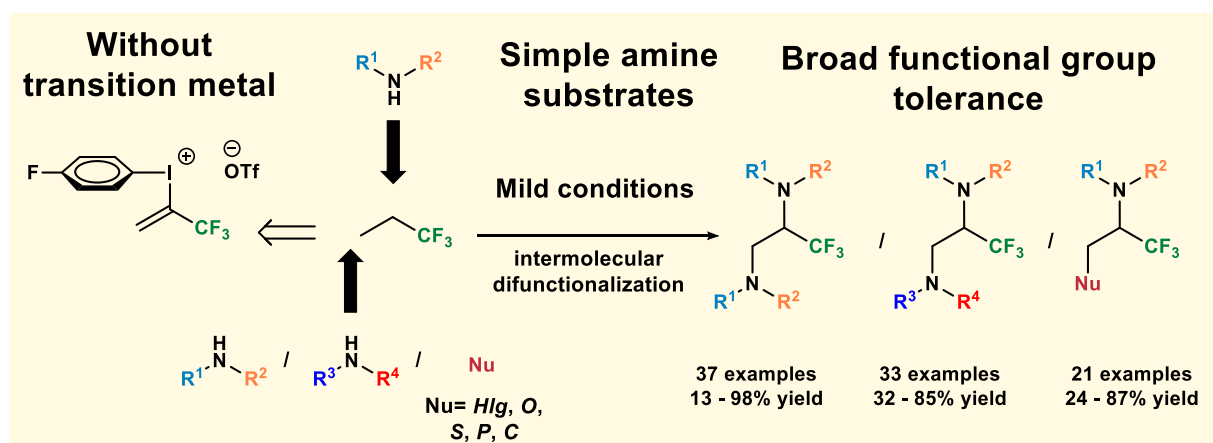
The synthesis of fluorinated building blocks is important in synthetic organic and pharmaceutical chemistry. Although these compounds are widely used, the efficient synthesis of trifluoromethylated nitrogen heterocycles can be challenging. In our work, we designed a novel aryl-alkenyl-iodonium salt as a trifluoroalkenyl synthon. With the utilization of the new salt, we synthesized various *N*-substituted 2-trifluoromethylaziridines in one-step reaction, under mild conditions directly from aryl and alkyl amines in the absence of any transition metal catalyst. The key development step was the stabilization of the reagent. In this respect, we found that 4-fluorophenyl counterpart and triflate anion for the iodonium salt ensures optimal stability and excellent reactivity. Optimization of the synthesis conditions lead to the synthesis of a new bench stable fluorinated alkenyl iodonium salt even on multigram scale. Using this salt, we experienced the cyclization reaction resulting 2-trifluoromethylaziridines. Optimizing this reaction, we found sodium carbonate as the best base. The optimal solvent is dichloromethane followed by diethyl ether, but other solvents, such as acetonitrile and THF also can give good yields. Low excess (20%) of iodonium salt results the highest yield. With the utilization of the optimized parameters, we explored the scope of the reaction to find it a robust, easily reproducible method without almost no steric and electronic limitation regarding the amine substrates through more than 40 examples. Additionally, the reaction mechanism was examined by quantum chemical calculations. These calculations were also confirmed by experiments, like aziridination of deuterated aniline (incorporation of deuterium determined by ¹H-NMR) and varying the conditions on a large scale.



We published our results at internationally acknowledged chemistry journal (*Design of Trifluoroalkenyl-iodonium salts for Hypervalency Aided Alkenylation-Cyclization Strategy: Metal-free Construction of Aziridine Ring*, Ádám Mészáros, Anna Székely, András Stirling, Zoltán Novák, *Angew. Chem. Int. Ed.* **2018**, 57, 6643-6647. DOI: [10.1002/anie.201802347](https://doi.org/10.1002/anie.201802347)) and this work was highlighted in the journal *Organic Process Research and Development* in the monthly selection for “Some Items of Interest to Process R&D Chemists and Engineers”.

2. Reaction of fluoroalkenyl iodonium salts with N-, O-, S-, P- and C-nucleophiles

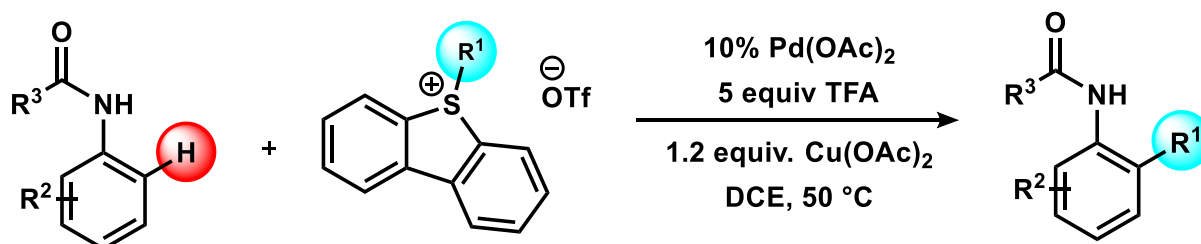
In continuation of the reactivity studies of the (4-fluorophenyl)(3,3,3-trifluoroprop-1-en-2-yl)iodonium triflate, we optimized the reaction conditions to achieve simple and mild synthetic procedure for the preparation of *N,N'*-homofunctionalized 3,3,3-trifluoropropane-1,2-diamines from secondary amines. We have investigated the scope of reaction, regarding the electronic and steric effects of secondary amines, and isolated the corresponding diamines in considerable to excellent yields (7-98%). In case of secondary amines, the reaction mechanism was examined by ¹⁹F-NMR spectroscopy, which revealed the intermediacy of aziridinium ions. After detailed study, selective generation of aziridinium ion was achieved in mild reaction conditions from (4-fluorophenyl)-(3,3,3-trifluoroprop-1-en-2-yl)iodonium triflate. Aziridinium ion intermediate was reacted with wide variety of N-nucleophiles to afford regioselectively the *N*, *N'*-heterofunctionalized diamines in moderate to good yields (54-80%). Next, the steric and electronic effects of secondary amines were evaluated in the aziridinium ion formation step and converted these intermediates to the corresponding *N*, *N'*-heterofunctionalized diamines with complete regioselectivity in low to good yields (36-84%). Application of other heteroatom (O, S, P) and carbon nucleophiles provided the corresponding β-substituted amines in moderate to good yields (49-82%), without observable formation of regioisomers. Overall, we demonstrated the applicability of the procedure with 91 synthetic examples. The results of the work were published in Nature Communications (*Vicinal difunctionalization of carbon-carbon double bond for the platform synthesis of trifluoroalkyl amines*, Ferenc Béke, Ádám Mészáros, Ágnes Tóth, Bence Béla Botlik, Zoltán Novák, *Nat. Commun.* **2020**, 5924. DOI: [10.1038/s41467-020-19748-z](https://doi.org/10.1038/s41467-020-19748-z)).



3. Application of novel alkyl-diarylsulfonium salt for the alkylation aromatic systems through C-H activation

We have developed a new and efficient catalytic method for the direct *ortho* alkylation of aromatic amide and urea derivatives with the utilization of palladium catalyzed C-H activation under mild reaction condition. We demonstrated that *S*-alkyl-dibenzothiophenium salts are suitable alkylating reagents for the C-H activation. With the application of this reagent the alkylation of aromatic ureas can be achieved for the first time in the presence of Pd(OAc)₂ catalyst and TFA. The general feature of the methodology is the applied relatively mild reaction condition. The scope and limitation of the developed palladium catalyzed *ortho*-alkylation of aromatic urea and anilide derivatives was demonstrated on 31 examples and the desired products were isolated in 18-89% yield. The results were published in *Organic Letters* (*Sulfonium Salts as Alkylating Agents for Palladium-*

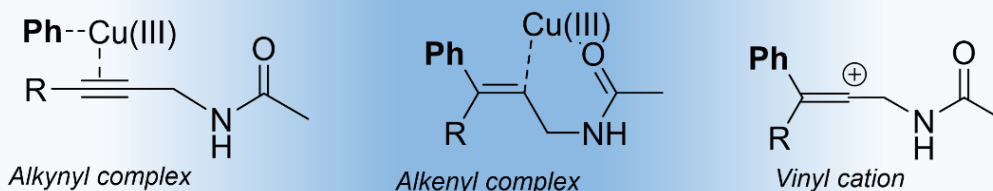
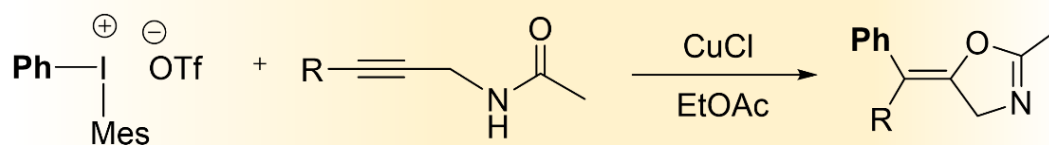
Catalyzed Direct Ortho Alkylation of Anilides and Aromatic Ureas, Dániel Cs. Simkó, Péter Elekes, Vivien Pázmándi, Zoltán Novák, *Org. Lett.* **2018**, 20, 676-679. DOI: [10.1021/acs.orglett.7b03813](https://doi.org/10.1021/acs.orglett.7b03813).



4. DFT calculations on the mechanism of Copper-Catalysed Tandem Arylation-Cyclization Reaction of Alkynes and Diaryliodonium Salts

In our work we have shown that the copper catalyzed carboarylation-ring closure reaction of alkynyl substrates with diaryliodonium salts includes the following plausible elementary steps: first the Cu(III)-aryl electrophile forms an intermediate with the triple bond of the reactant, then the aryl moiety migrates to the activated triple bond which is followed by a fast ring closing step. The performed calculations revealed new insights into the ring closing reaction. We concluded that the deprotonation can take place only after the tandem arylation-cyclization sequence. The suggested reaction mechanism shows a very limited sensitivity in a wide range of substituents installed on the reactants. We also find that copper-oxygen interaction is responsible for the very high stereoselectivity of the reaction and it also excludes the formation of vinyl-cation intermediates. The obtained results could serve as a useful and more general description of the mechanism of the carboarylation-ring closure strategy based on the utilization of alkynes and diaryliodonium salts. The results of the mechanistic studies were published in the Beilstein Journal of Organic Chemistry (*DFT calculations on the mechanism of copper-catalysed tandem arylation–cyclisation reactions of alkynes and diaryliodonium salts*, Tamás Károly Stenczel, Ádám Sinai, Zoltán Novák, András Stirling. *Beilstein. J. Org. Chem.* **2018**, 14, 1743-1749. DOI: [10.3762/bjoc.14.148](https://doi.org/10.3762/bjoc.14.148)).

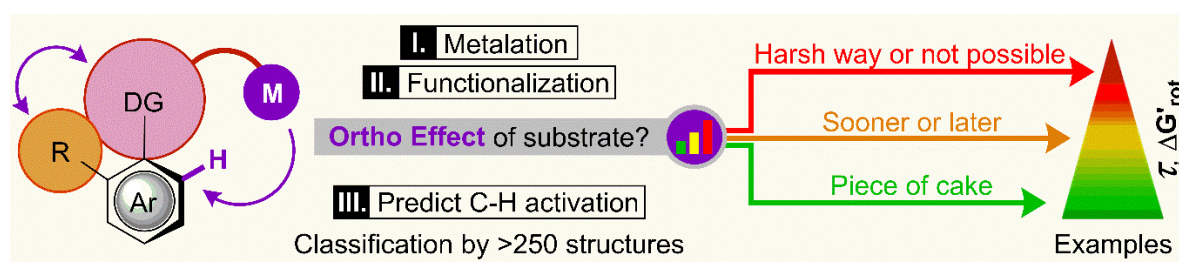
Ring Closure - Carboarylation Strategy - Synthesis of Oxazolines Study of Mechanism by Quantum Chemical Calculations



Possible Intermediates - Preference of Copper Alkenyl complex

5. Experimental and theoretical study of steric effect in C-H activation reactions

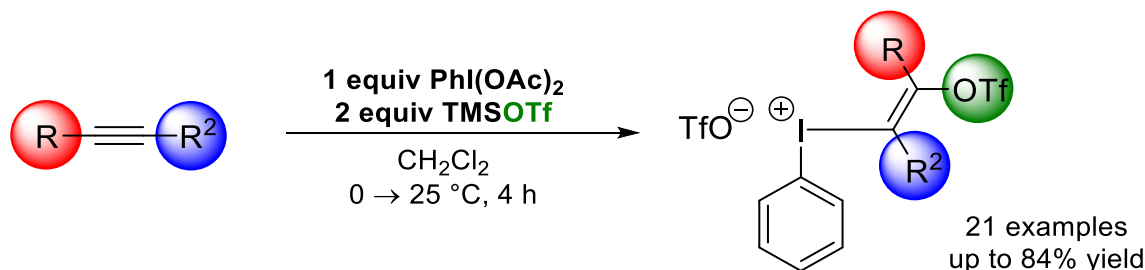
During the studies of the palladium catalyzed C-H activation reaction we discovered interesting reactivity pattern of the chemical transformation. We found that, the presence of ortho substituents next to the directing group has deleterious effect on the C-H activation in special structural cases. With the analysis of existing procedures in the literature, together with our findings we settle a comprehensive theory, which try to define and explain the connection between structural properties and reactivity. With the analysis of more than 300 examples, we determined a relationship between the torsion angle (aryl ring – directing group) and the activation energies of the C-H activation step by DFT calculations. Building a multiparameter field tool allows to understand complex steric and electronic problems and achieve a predictable system in C-H activation. The validation of the predictions was tested on several substrates, and in the matching cases the palladium complexes were prepared, and their structure were determined by NMR and X-ray measurements. In the experimental part we found that, the presence of ortho substituents next to the directing group has deleterious effect on the C-H activation in special structural cases. We analyzed the existing literature procedures with the process of available data to fine-tune our theory for the description of relationship between the torsion angle (aryl ring – directing group) and the activation energies of the C-H activation step. Moreover, we performed new DFT calculations, synthesized additional Pd-complexes which were analyzed with X-ray and NMR, and performed catalytic experiments to support our hypothesis on the influence of ortho substituents. As a result, we have finally defined the “ortho-effect” for directed metal catalyzed C-H activation reactions and developed comprehensive studies and description regarding this phenomenon, and built a simple model for prediction and explanation of reactivities of any substrates subjected for ortho C-H activation. The results of the experimental and theoretical study were published in Chemical Science (*The Ortho Effect in Directed C–H Activation*, Balázs L. Tóth, Anna Monory, Orsolya Egyed, Attila Domján, Attila Bényei, Bálint Szathury, Zoltán Novák, András Stirling, *Chem. Sci.* **2021**, *12*, 5152-5163. DOI: [10.1039/D1SC00642H](https://doi.org/10.1039/D1SC00642H)).



6. Synthesis of novel alkenyl-aryliodonium salts

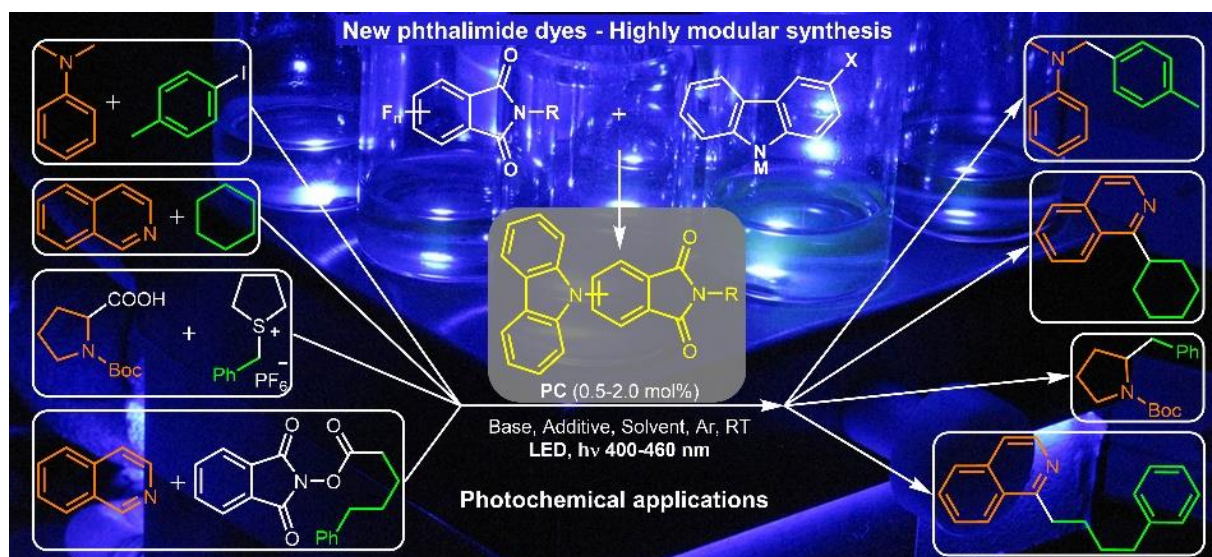
In this working period, we improved the preparation of aryl(trifloxyvinyl)iodonium triflate salts and developed a practical synthesis to obtain aryl(vinyl)iodonium compounds with high efficiency. This one-pot transformation starts easily from acetylenes, commercially available (diacetoxyiodo)benzene (DIB) and trimethylsilyl triflate to prepare wide variety of aryl(trifloxyvinyl)iodonium salts in good yields. Our procedure allowed to synthesize 25 new highly reactive phenyl(trifloxyvinyl) iodonium triflate salts functionalized with alkyl, aralkyl, aryl and heteroaryl groups (21 examples, up to 84% yield). Geometry of the C=C double bond in these

compounds has been established by NOE-NMR experiments and X-ray crystallography. Our results were summarized in a paper published in ACS Omega (*Synthesis of Multifunctional Aryl(trifloxyalkenyl)iodonium Triflate Salts*, Balázs L. Tóth, Ferenc Béke, Orsolya Egyed, Attila Bényei, András Stirling, Zoltán Novák, *ACS Omega* **2019**, *45*, 9188-9197. DOI: [10.1021/acsomega.9b00728](https://doi.org/10.1021/acsomega.9b00728)).



7. Design and utilization of novel phthalimide based photocatalyst for C-H activation reactions

A new collection of carbazolyl substituted-phthalimide derivatives were synthesized in a modular fashion from fluorophthalic anhydrides derivatives. In the first step of the reaction sequence the corresponding phthalimides were prepared from fluorophthalic anhydrides and appropriate amines. The imide formation was followed by the nucleophilic substitution of the fluorine function with deprotonated carbazoles. In this simple reaction sequence several phthalimide dyes were prepared, and selected members of the compound library were tested in four different photocatalytic transformations chosen from recent literature, including radical C-H functionalizations of isoquinoline system. As the result of the studies, we concluded that some members of this new phthalimide compound collection are suitable as organic photocatalyst for different chemical transformations. Thus, the novel catalysts offer more economic replacement of existing noble-metal based photocatalysts, which provide opportunity for extensive photocatalytic applications in the future.



Our results were summarized in a paper published in *Synthesis*. (*Modular synthesis of carbazole substituted phthalimides as potential photocatalysts* Gonda, Zsombor; Földesi, Tamás; Nagy, Bálint; Novák, Zoltán, *Synthesis*, **2021**, DOI: <https://doi.org/10.1055/s2Fa-1647-7292>).

8. Z-selective Pd-Catalyzed 2,2,2-Trifluoroethylation of Acrylamides using a Mesityl(trifluoroethyl)iodonium Salt at Room Temperature.

In collaboration with Tatiana Besset Group at Normandie Univ, INSA Rouen, France we developed a straightforward protocol enabling the Pd-catalyzed α, α, α -trifluoroethylation of a panel of α -substituted acrylamide derivatives (19 examples, up to 73% yield) at room temperature using the 2,2,2-trifluoroethyl-mesityl iodonium salt, developed earlier in our laboratory, as the CH_2CF_3 source. With a practical and simple catalytic system, the transformation was completely regio- and stereoselective. The mechanistic studies shed light on the key steps involved in this catalytic cycle. This straightforward methodology for the α, α, α -trifluoroethylation reaction has an untapped potential for the functionalization of a wide variety of molecules and materials and will be of high interest for the scientific community.

The results were published in Chemical Communications (*Z-selective Pd-Catalyzed 2,2,2-Trifluoroethylation of Acrylamides at Room Temperature*, Ruyet Louise, LAPUH Ivana, Koshti Vijay S, Földesi Tamás, Jubault Philippe, Poisson Thomas, Novák Zoltán, Besset Tatiana, *Chem. Commun.* **2021**, 57, 6241–6244.

