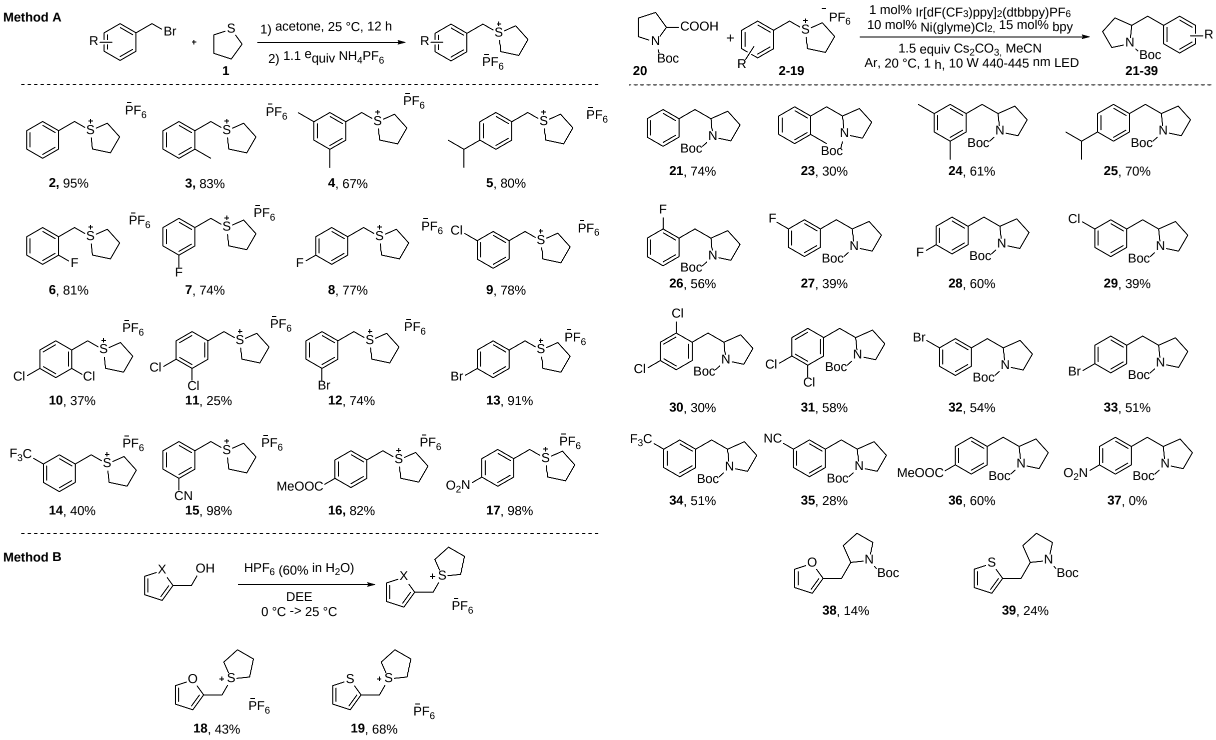
Final report on the NKFIH project PD124592 entitled “Synthesis of heterocyclic molecules in photocatalytic transformations”

Development of novel nickel-iridium dual photocatalytic couplings

In the first period of the project, we studied the nickel-iridium dual photocatalytic coupling reactions are in the focus of organic synthesis.

One of the major groups of these transformations is the decarboxylative coupling reaction of carboxylic acids and aryl and alkyl halides to form new carbon (sp^2) – carbon (sp^3) bonds. As a new approach to the C-C bond formation we aimed to examine the coupling of sulfonium salts a prospective coupling partner instead of aryl halides. We first examined the proposed coupling by using *S*-(2-benzyl)-tetramethylenesulfonium hexafluorophosphate, *N*-Boc-proline, and a wide range of photoredox and ligated nickel catalysts. We found that the combination of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and $NiCl_2$•glyme (glycol ether), bipyridyl (as ligand), in the presence of 1.5 equivalents of Cs_2CO_3 base, in deoxygenated acetonitrile solvent, under argon atmosphere at room temperature and blue (445-450 nm) LED, achieved the desired fragment coupling in 74% yield. During our optimization studies, we found that the reaction has good functional group tolerance with substituted benzyl-sulfonium salts. Unfortunately, among the protected natural aminoacids, only *N*-Boc-proline reactant give good yields. We found that benzyl-sulfonium salts better than photosensitive benzyl-bromide, because the photodegradation of benzyl-bromide give 1,2-diphenyl-ethane byproduct. We optimized the photocatalytic conditions of this reaction and found that the simple organic photocatalyst the tetracarbazolyl substituted isophthalonitrile dyes under blue (445-450 nm) LED irradiation gave the same efficiency than the expensive $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ photocatalyst under argon atmosphere at room temperature.

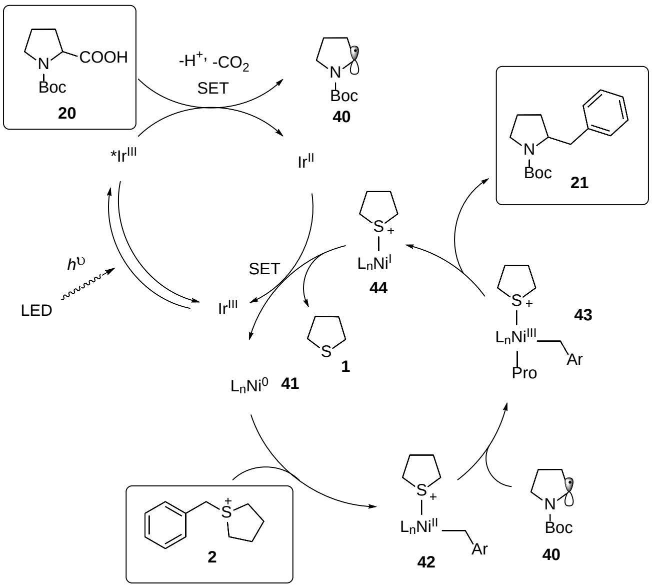
However, with our model reaction catalyzed by transition metal catalysts we transformed *N*-Boc-proline into *N*-Boc-2-benzylpyrrolidine using 2-benzyl-tetramethylenesulfonium hexafluorophosphate, with the following reaction conditions: $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and $NiCl_2$•glyme (glycol ether) for catalysts, bipyridyl (as ligand), in the presence of 1.5 equivalents of Cs_2CO_3 base, in deoxygenated acetonitrile solvent, under argon atmosphere at room temperature and blue (445-450 nm) LED irradiation. This transformation can be used for the synthesis of a large number of *N*-Boc-2-benzylpyrrolidine. We were able to demonstrate this with the use of 16 differently substituted benzyl sulfonium salts and 2 different heterobenzylic salts (Scheme 1, left, 25-98% yield range)., as we prepared the desired benzylpyrrolidine derivatives (Scheme 1, right, 14-74% yield range).



Scheme 1. *The scope of sulfonium salt synthesis and the photochemical reaction*

The production of *N*-Boc-2-benzylpyrrolidines could be made much simpler because our method does not use sensitive or hard to handle starting materials or reagents as other methodologies constructing this structure. Moreover, this moiety bears biological activity in the indication of osteoporosis, sleep disorders and cardiovascular diseases.

Regarding the mechanism of the dual photocatalyzed coupling of *N*-Boc-proline and benzyl sulfonium salts we propose the following catalytic cycles for the transformation (Scheme 2). It is established that the photoexcited Ir bearing high reducing potential (Ir(III) {E1/2red [*Ir(III)/Ir(II)] = +1.21 V vs SCE in CH_3CN} and initiates a SET reaction with the deprotonated Boc-proline [(Boc)-Pro-OCs, E1/2red = +0.95 V vs. SCE in CH_3CN] producing the 40 radical species in a oxidative quenching and gives Ir(II) in the process. Concurrently, the sulfonium salt (**2**) coordinates to a Ni(0) species (**41**) and participates in oxidative addition producing Ni(II) (**42**). This complex intercepts the radical **40** generating the Ni(III) organometallic adduct **43**. From this the desired product is formed by reductive elimination expelling a Ni(I) intermediate (**44**). Then another SET event occurs, simultaneously reducing the Ni(I) to Ni(0) (E1/2red[Ni(II)/Ni(0)] = −1.2 V vs SCE in DMF) and oxidizing Ir(II) to Ir(III) {E1/2red [Ir(III)/Ir(II)] = –1.37 V versus SCE in CH_3CN} closing both catalytic circles at the same time.

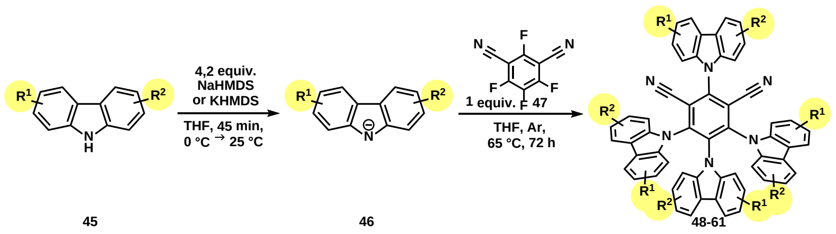


Scheme 2. *The proposed mechanism of the reaction*

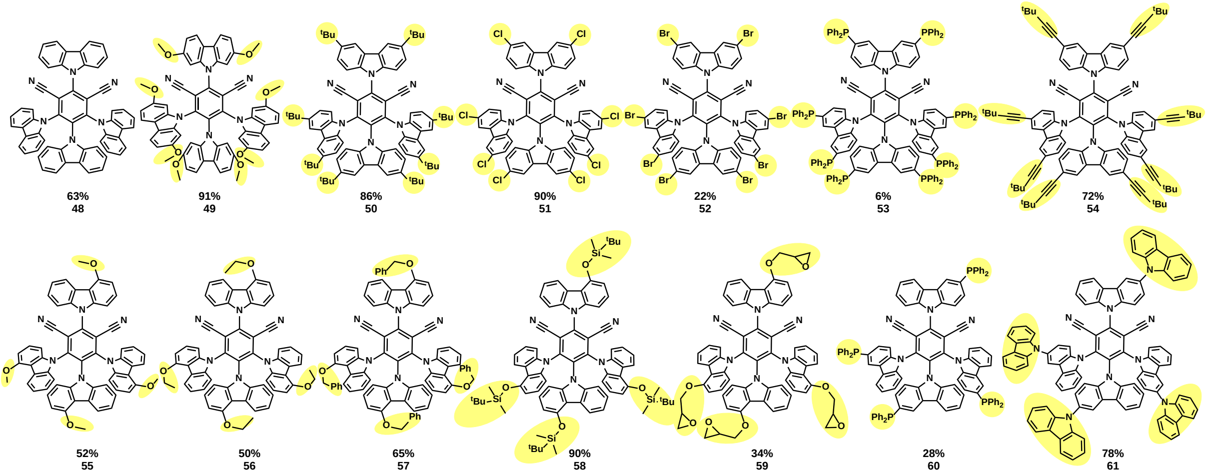
Our results were reported to international professional community through a poster presentations at Markovnikov Congress on Organic Chemistry (2019, Kazan, Russia). After the full development of the applicability were published in European journal of Organic Chemistry (Development of Ni-Ir dual photocatalytic Liebeskind coupling of sulfonium salts for the synthesis of 2-benzylpyrrolidines, Bálint Varga, Zsombor Gonda, Balázs L. Tóth, András Kotschy, Zoltán Novák, *Eur. J. Org. Chem.* **2020**, 1466-1471. DOI: 10.1002/ejoc.201900957).

Development of novel photocatalytic dyes (unpublished results)

During the first period of the project, we synthetized 13 differently substituted tetracarbazolyl-isophthalonitrile (CzIPN) dyes . The designed new dyes contain mono and disubstituted carbazole units. To expand the versatility of the carbazole frame we prepared the not commercially available substituted carbazoles. The CzIPN dyes were obtained by a two-step sequential synthesis. At first, 4.4 equivalents of appropriate substituted carbazole and 4.2 equivalents of sodium or potassium bis(trimethylsilyl)amide were stirred in THF at 0 °C to room temperature. The potassium bis(trimethylsilyl)amide was better reagent than sodium analogue. In the second step, one equivalents of tetrafluoro isophthalonitrile were stirred with deprotonated carbazole derivative at 65 °C to 72 hours. (Scheme 3a). After the purification by column chromatography and recrystallization the dyes were obtained in 6-91% yields (Scheme 3b).

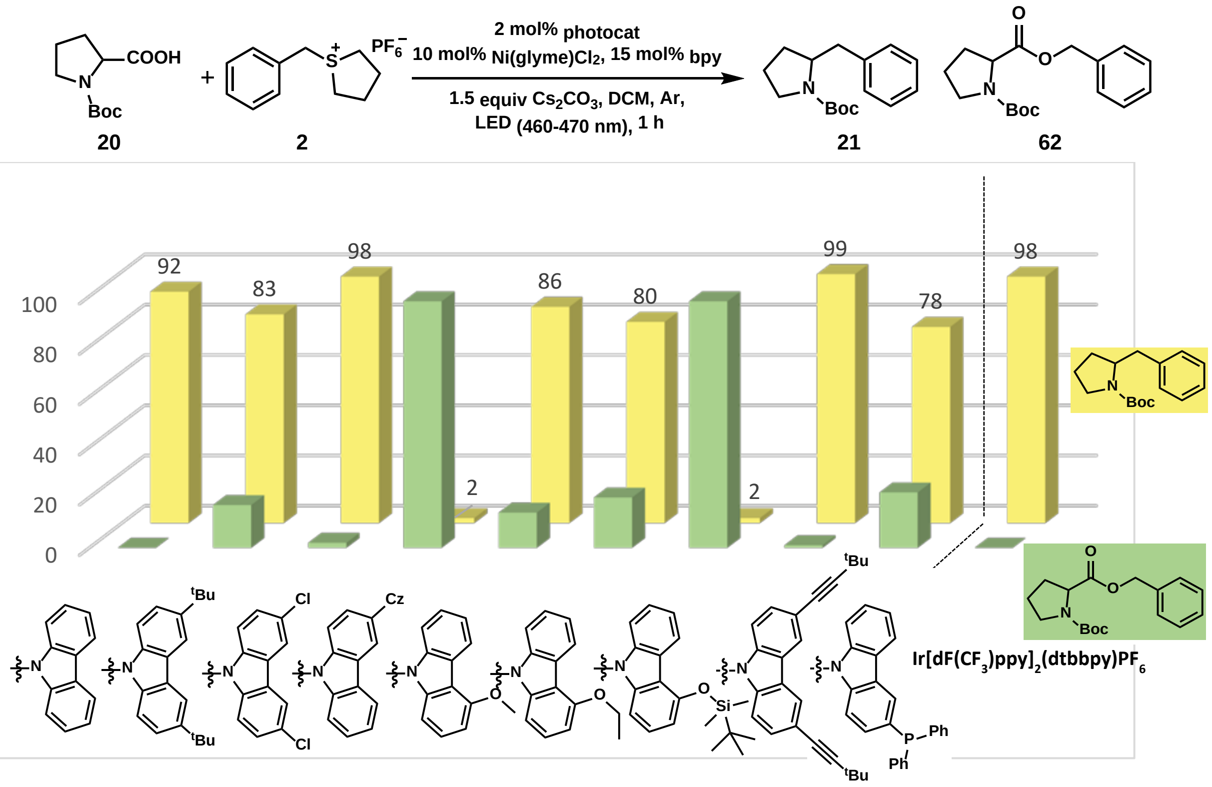


Scheme 3a. *Synthesis of new CzIPN based organic photocatalysts*



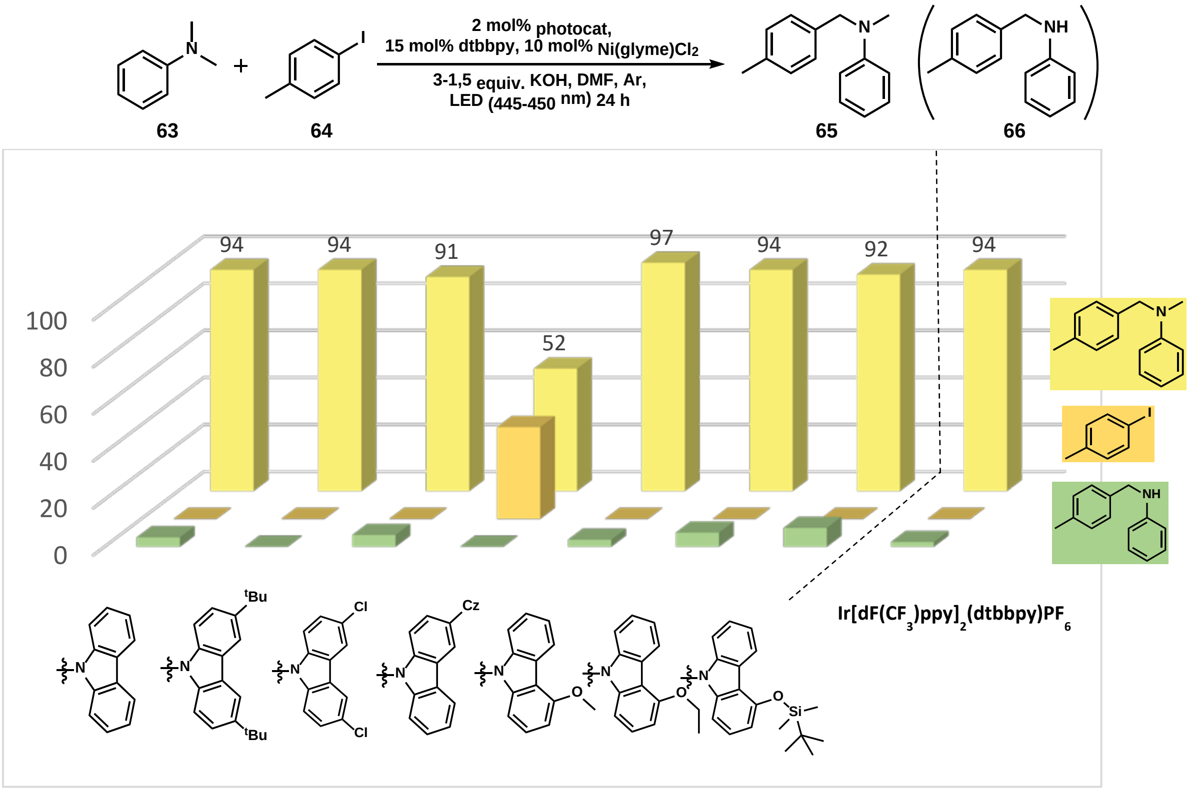
Scheme 3b. *Collection of new CzIPN based organic photocatalysts*

After the successful preparation of the catalyst kit, we tested their photocatalytic activity in the nickel co-catalyzed coupling reaction of benzylsulfonium salt and *N*-Boc-proline in the presence of Cs_2CO_3 in DCM under argon atmosphere. We observed different selectivity as the outcome of the test reactions. Photocatalyst **48**, **51** and **54** proved to be selective to the formation of the desired benzylpiperidine, while other gave its mixture with the appropriate ester. These catalysts showed similar activity to the Ir based catalyst. (Scheme 4).



Scheme 4. *Reactivity study of new CzIPN fotocatalysts I.*

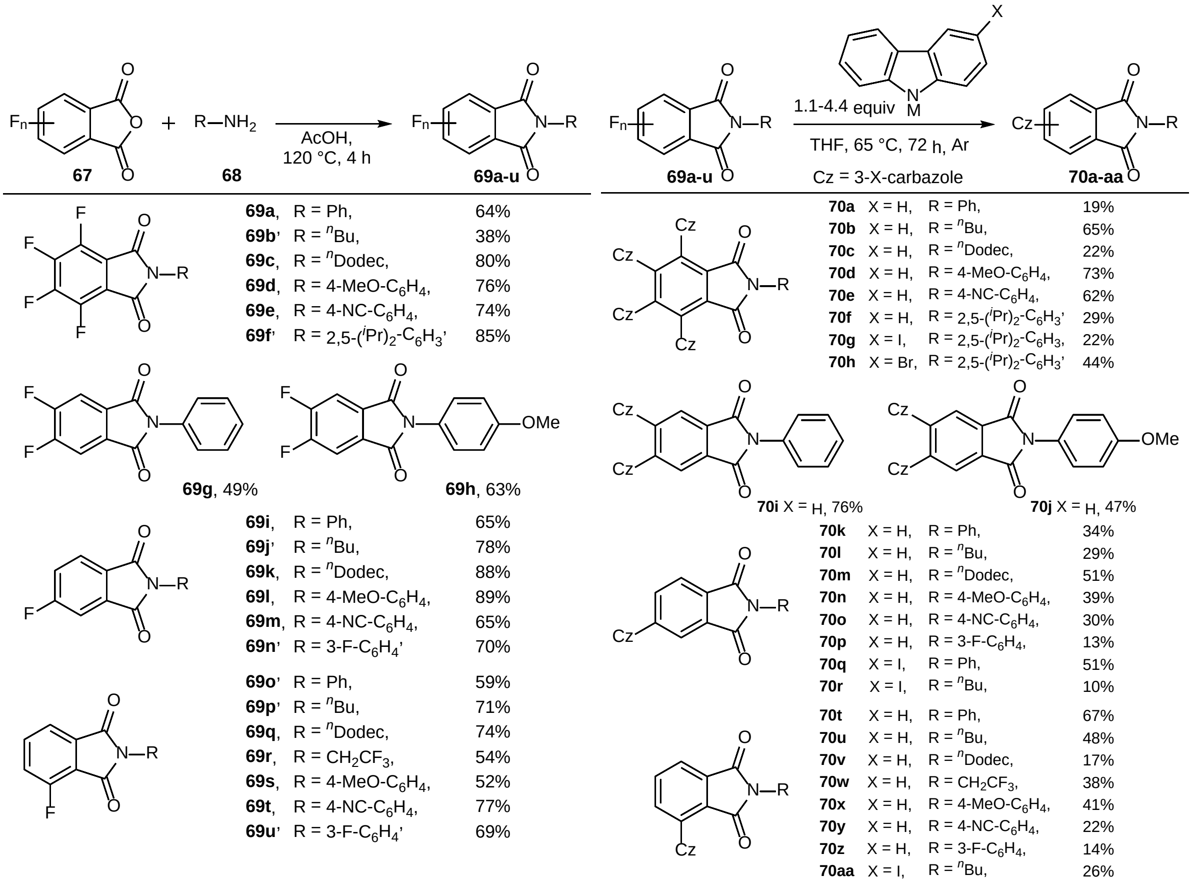
The catalyst kit was also tested in the C-arylation of *N*, *N*-dimethylaniline with 4-iodotoluene, and we found high activity of the catalyst in the photocatalytic transformation. Except **61** all photocatalyst proved to be selective to the formation of the desired *N*-methyl-*N*-(4-methylbenzyl)aniline (Scheme 5).



__Scheme 5.__ Reactivity study of new CzIPN photocatalysts II.

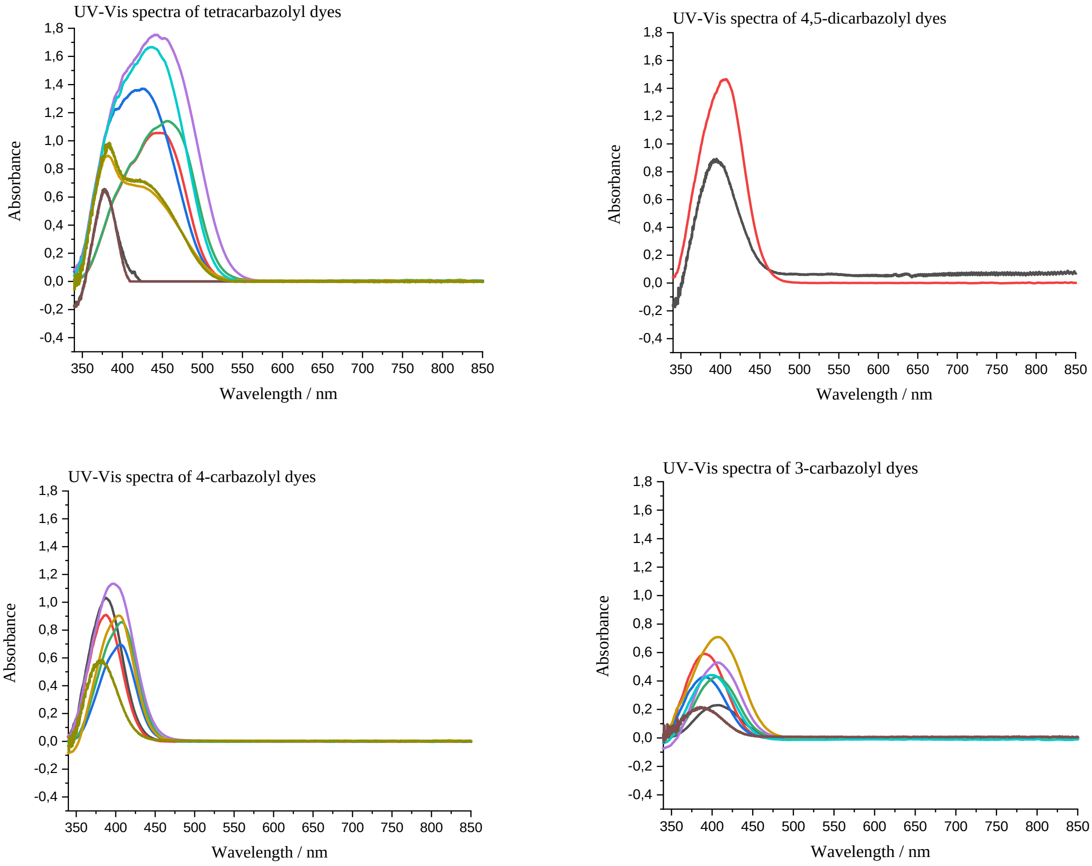
These results were reported to international professional community through a poster presentations at Markovnikov Congress on Organic Chemistry (2019 Kazan, Russia).

Similar to CzIPN dyes we designed another dye family, namely the carbazole substituted *N*-alkyl and *N*-aryl phthalimides. The starting materials was tetra-, di- and monofluoro phthalic anhydrides. These materials were refluxed with one equivalents of appropriate substituted amines to 2-4 hours, then the crude product was purified recrystallization (Scheme 6, left). The carbazolyl substitution was performed under similar conditions to the CzIPN derivatives, and we successfully prepared 26 new phthalimide based organic photocatalysts (Scheme 6, right).



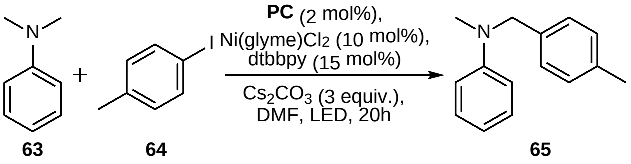
Scheme 6. *Synthesis of novel phthalamide based photocatalysts*

The UV-VIS spectra of the products show absorption in the visible light section, which will be eligible for excitation in photocatalytic transformations. Representative examples are indicated on Scheme 7.



Scheme 7. *Physicochemical properties of phthalamide based photocatalysts*

Finally, before the closing of the project we tested the photocatalytic activity of dyes in four different reaction. The first, nickel-iridium dual photocatalytic coupling reaction of *N*,*N*-dimethylaniline and 4-iodotoluene, similarly to the previous studies of different CzIPN catalysts. We have found that dicarbazolyl *N*-phenyl (**70i**) and carbazolyl *N*-dodecyl (**70v**), *N*-trifluoroethyl (**70w**) derivate has superior activity (Scheme 8), and reached the efficiency of the expensive, generally used Ir[dF(CF_3)ppy]$_2$(bpy)PF_6 photocatalyst.

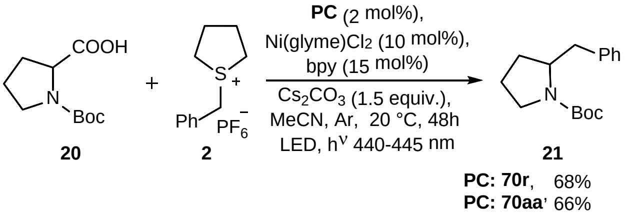


Entry	PC	LED (nm)	Yield (%)[b]
1	[Ir][c]	400	70
2	**70v**	400	84
3	[Ir][c,d]	440-445	75[e]
4	**70i**	440-445	93
5	**70w**	440-445	87

[a]Reaction conditions: PC (2 mol%), Ni(glyme)Cl_2 (10 mol%), dtbbpy (15 mol%), **64** (0,1 mmol, 1 equiv.), **63** (3 equiv.), Cs_2CO_3 (3 equiv.) in abs. DMF (5 mL) LED irradiation at 20 °C under Ar atmosphere, [b]Isolated yield of the product after 20 hours, [c][Ir] = Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6, [d]1 mol% photocatalyst, [e]4 hours reaction time

Scheme 8. *Dimethylaniline C–H arylation with iodotoluene*

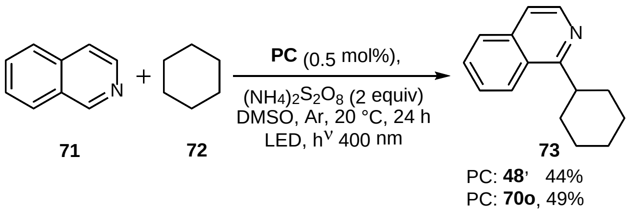
The second reaction similarly to the previous studies wherein we tested their photocatalytic activity in the nickel co-catalyzed coupling reaction of benzylsulfonium salt and *N*-Boc-proline in the presence of Cs_2CO_3 in DCM under argon atmosphere. We have found that iodo-carbazolyl *N*-butyl (**70r**) and (**70aa**) derivate has good activity (Scheme 9).



[a]Reaction conditions: **20** (0.1 mmol, 1 equiv.), PC (2 mol%), Ni(glyme)Cl$_2$ (10 mol%), bpy (15 mol%), **2** (1 equiv.) and Cs$_2$CO$_3$ (1.5 equiv) in MeCN (5 mL) LED irradiation at 20 °C, 48 h under Ar atmosphere [b]Isolated yield of the product

Scheme 9. *Ni–Ir dual photocatalytic decarboxilative coupling of sulfonium salt*

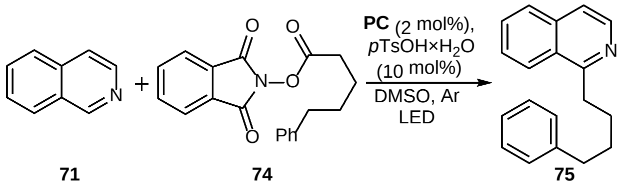
The third reaction wherein we tested their photocatalytic activity in the oxidative photocatalyzed coupling reaction of izoquinoline and cyclohexane in the presence of $(NH_4)_2S_2O_8$ in DMSO under argon atmosphere. We have found that monocarbazolyl *N*-4-cyanophenyl (**70o**) and CzIPN (**48**) derivate has similar activity (Scheme 10).



[a]Reaction conditions: **71** (0.1 mmol, 1 equiv.), **72** (2 mL), **PC** (0.5 mol%), $(NH_4)_2S_2O_8$ (2 equiv), and DMSO (1.8 mL) LED irradiation at 20°C under Ar atmosphere. [b]Isolated yield of the product

Scheme 10. *Cross-dehydrogenative coupling of cyclohexane with izoqinoline*

The last test reaction wherein we tested their photocatalytic activity in the photocatalyzed coupling reaction of izoquinoline and redoxactive esther in DMSO under argon atmosphere. We have found that tetracarbazolyl *N*-phenyl (**70a**) monocarbazolyl *N*-3-fluorophenyl (**70z**) derivate has better activity than CzIPN (**48**) (Scheme 11).



Entry	PC	LED (nm)	Yield (%)[b]
1	**48**	450-460	48[c]
2	**70a**	450-460	52
3	**70b**	450-460	43
4	**70e**	450-460	48
5	**70z**	440-445	48
6	**70z**	440-445	79[c]

[a]Reaction conditions: **74** (0.05 mmol, 1 equiv.), **71** (2 equiv.), **PC** (2 mol%), *p*TsOH×H$_2$O (10 mol%) and DMSO (1 mL), LED irradiation at 20°C under Ar atmosphere, [b]Isolated yield of the product after 24 h, [c]0.4 mmol scale

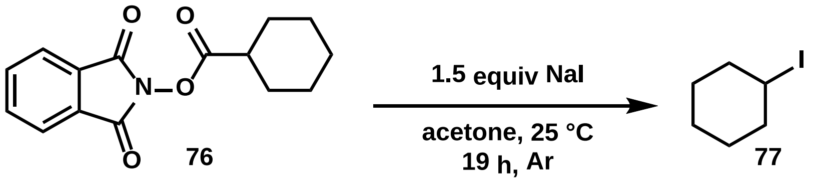
Scheme2. *Decarboxilative izoquinoline with redoxactive ester*

In conclusion, we developed new organic dyes with promising catalytic activities, which could serve as non-metallic alternative of expensive iridium-based catalyst systems. Our results were reported to international professional community through a poster presentations at International Conference on Chemistry (2019 Cluj, Romania). After the full development of the applicability were published in Synthesis (Modular Synthesis of Carbazole-Substituted Phthalimides as Potential Photocatalysts, Zsombor Gonda, Tamás Földesi, Bálint Nagy, Zoltán Novák, *Synthesis* **2021**, ASAP. DOI: 10.1055/a-1647-7292).

Photocatalytic transformation of redoxactive esters- utilization of novel photoactivation mode (unpublished results)

Besides the design and utilization of new metal and organic photocatalysts we turned our attention to the exceptionally and new concept of photoactivation. Recently, it was discovered that the NaI-PPh_3 system could be applicable for the generation of alkyl radicals from phthalimide derivatives, and the alkyl radical can undergo various transformations. After the study of the literature background, we aimed to develop new functional group transformation, namely the conversion of COOH group to I function. This decarboxylative iodination of alkyl species generally undergo under high energy UV light. Thus, we started to study the transformation of activated alkyl carboxylic acids under visible light irradiation using NaI-PPh_3 system. After a deep optimization study, we found the optimal reaction conditions for the reaction, and in the presence of 2.5 mol% PPh_3, 1.5 equiv of NaI in acetone at 25 °C the redox active ester was completely transformed to cyclohexyl iodide, which were isolated in 69% yield (Scheme 12).

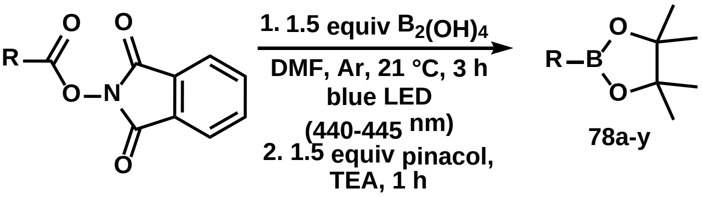
After the preparation of this representative example, we intend to continue the substrate scope considering the structural features of the carboxylic derivatives.



Entry	PPh_3 (mol%)	light	GC-MS (%)	
			S.M.	**product**
1	0	460 nm	17	82
2	2,5	460 nm	-	100 (69* isolated yield)
3	5	460 nm	-	100
4	10	460 nm	-	100
5	20	460 nm	-	100
6	20	ambient	86	-
7	20	dark	88	-

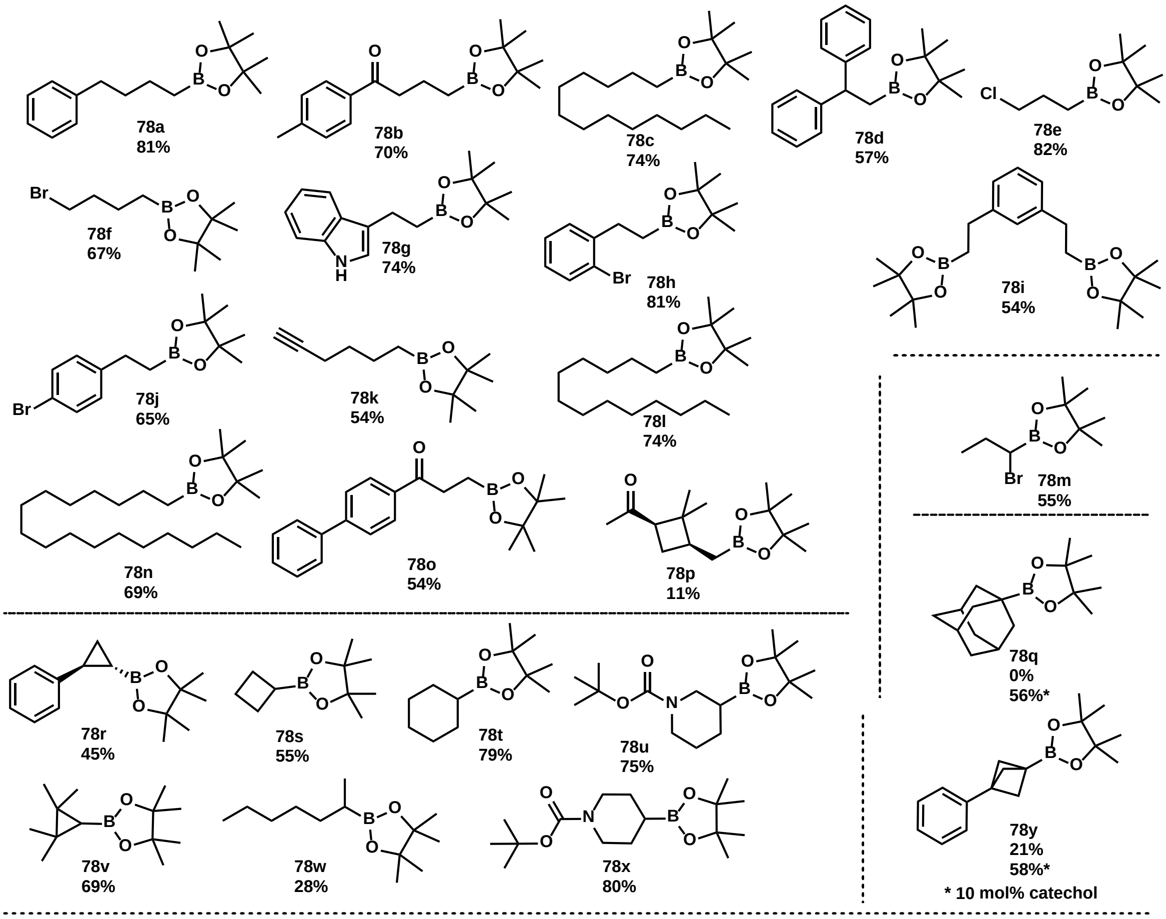
Scheme 3. *Photocatalytic transformation of active esters to iodide with NaI-PPh_3 system under visible light irradiation*

Parallel to the iodination reactions we examined the radical boronation of the esters. We found that the 1.5 equivalents of $B_2(OH)_4$ is an applicable boron source for the boronation, and followed by an esterification step we isolated the pinacolboronate in 71% yields. (Scheme 13)



Scheme 4. *Photocatalytic transformation of active esters to boronates under visible light irradiation*

We have just started the extension of the reaction and prepared four primary, secondary and tertiary alkyl pinacolyborate ester using the optimized reaction conditions in 11-82% yields (Scheme 14).



***Scheme 14.** Photocatalytic transformation of active esters to boronates under visible light irradiation*

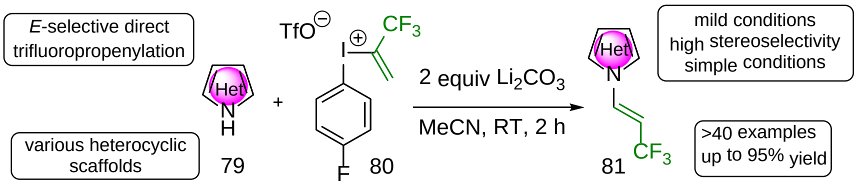
After the completion of the synthetic part of the project, we studied the reaction mechanism of the borylation procedure, and found that the formation of boryl radicals has important role in the transformation, and the alkyl radicals generated by visible light irradiation from the redoxactive esters. Spectroscopic investigation and quantumchemical studies were used to reveal the mechanistic details of the transformation.

The submission of the manuscript is in due course in our group.

Non-photocatalytic transformation

1. *Synthesis of trifluoropropenylated heterocyclic molecules with iodonium reagent*

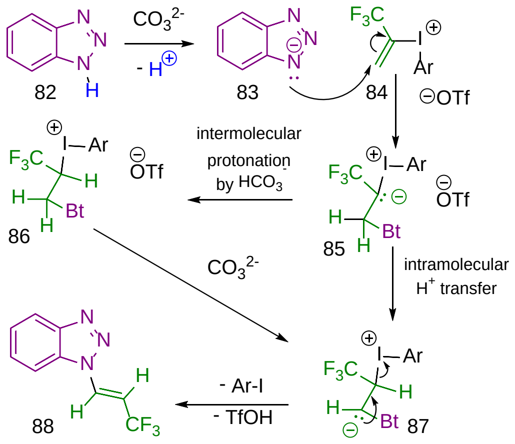
Enamine type moieties are important building blocks for synthetic chemistry. Perfluorinated olefins react readily with almost any kind of nucleophiles. They can be turned easily into the proper perfluorinated enamine derivative through nucleophilic substitution with high regio- and stereoselectivity 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. (Scheme 15).



***Scheme 15.** Synthesis of trifluoropropenylated heterocycles*

At the beginning of the project, we used benzotriazole as model substrate for our optimization studies. 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. 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 trifluoropropenylat-ed. 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 suc-cessfully synthesized more than 40 new compounds in up to 95% isolated yield. (Scheme 15).

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 16).

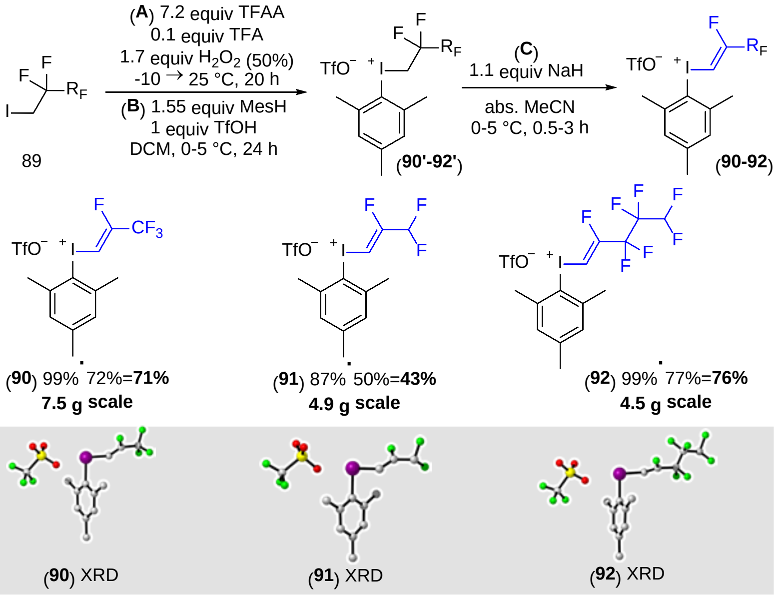


***Scheme 16.** Proposed mechanistic steps*

The results were summarized and published in *Chemistry A European Journal* (Impact factor: 5.236) (Stereoselective Direct *N*-Trifluoropropenylation of Heterocycles with Hypervalent Iodonium Reagent, János T. Csenki, Ádám Mészáros, Zsombor Gonda, Zoltán Novák *Chem. Eur. J.* **2021**, ASAP. DOI: 10.1002/chem.202102840).

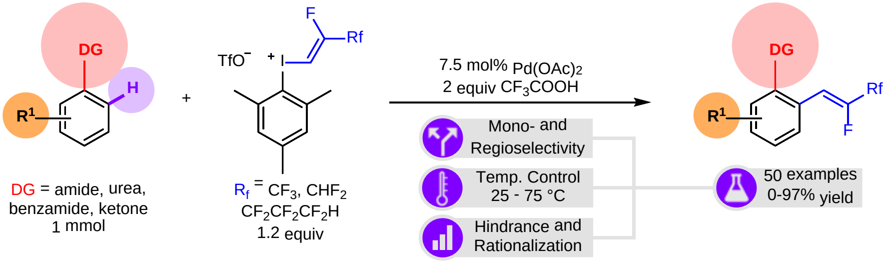
2. *Palladium catalyzed alkenylation of heterocycles and aromatic systems*

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. In our project 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 17).



Scheme 17. *Synthesis and characterization of novel alkenyliodonium reagents*

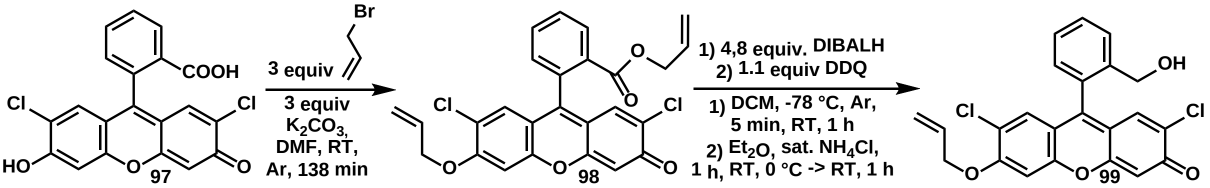
We demonstrated the application of these non-symmetrical aryl(fluoroalkenyl)-iodonium salts as fluoroalkenylating agents under mild reaction conditions. The scope and limitations have been thoroughly investigated and the feasibility has been demonstrated by more than 50 examples (Scheme 18). The manuscript can be accepted for publication in Advanced Synthesis and Catalysis (Impact factor: 5.837) (*Z*-Selective Fluoroalkenylation of (Hetero)Aromatic Systems by Iodonium Reagents in Palladium-Catalyzed Directed C-H Activation, Balázs L. Tóth, Gergő Sályi, Attila Domján, Orsolya Egyed, Attila Bényei, Zsombor Gonda, Zoltán Novák *Adv. Synth. Catal.* **2021**, 363, ASAP. DOI: 10.1002/adsc.202101108)



Scheme 18. *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, and 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 prove the role of the palladium impurities we synthesize and used fluorescent dyes for the detection of palladium traces in the organic compounds (Figure 1a and 1b). We found that the amine contains significant amount of palladium, which was confirmed by ICP-MS analysis. These results revealed that the amine, so-called organocatalyst is not the active species in the coupling reaction. Instead, palladium impurities are responsible for the catalytic cycle which served important information for synthetic and pharmaceutical community.



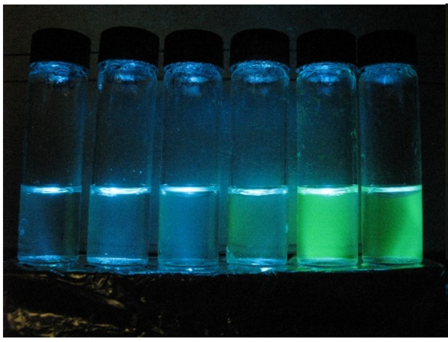


Figure 1a: Analysis of palladium stock solutions by fluorogenic Tsuji-Trost reaction, Pd concentration of vials, from left to right: 1 µg/kg, 10 µg/kg, 100 µg/kg, 1 mg/kg, 10 mg/kg, 100 mg/kg

Figure 1b: Analysis of batches of **AmineCat** by fluorogenic Tsuji-Trost reaction. Vials contained from left to right: Blank, **AmineCat-1-RC**, **AmineCat-30-RC**, **AmineCat-1**, **AmineCat-30**, 100 mg/kg $Pd(PPh_3)_2Cl_2$

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.