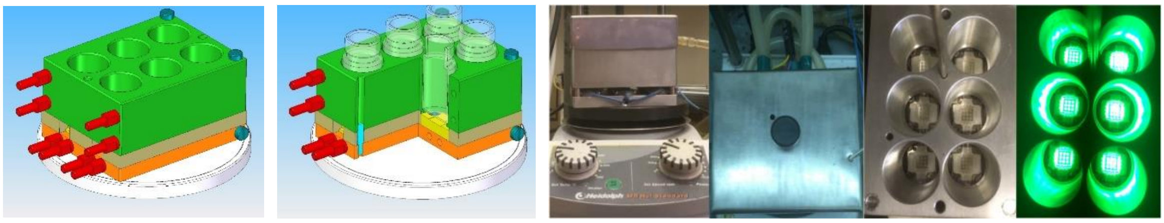
Final report on the NKFIH project NN114495 entitled "Utilization of visible light activated photoredox catalysis in organic syntheses"

Design of novel photoreactor for high throughput screening

In order to perform the optimizations of the photocatalytic reactions faster and more reproducible, we designed new photoreactors which enables the parallel reactions with accurate temperature control using high power LEDs as light sources. The design of this reactor was necessary for the screening studies. As a result of the project two prototypes of a 6-hole (for vials) and 9-hole reactor is available for us to perform the screening experiments more efficiently. In order to perform the optimizations of the photocatalytic reactions faster, we constructed 10 photoreactors covering the 440-650 nm wavelength range to have accessible broad wavelength range. Moreover, the major benefit of the designed reactor is the precise temperature control, which can be maintained between -20 to 80°C with high accuracy in the aluminum blocks with the use of flow thermostats.

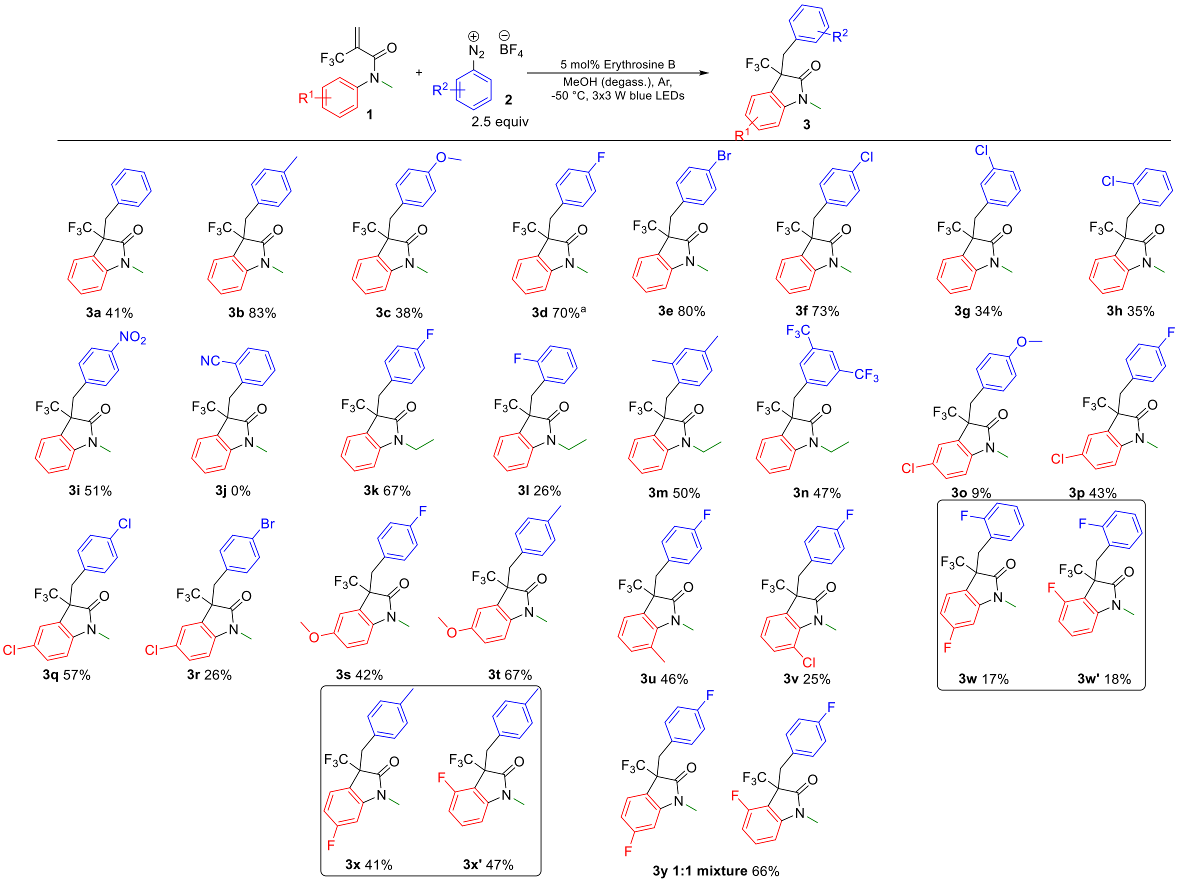


Scheme 1. The designed 6-hole photoreactor

Synthesis of trifluoromethyl oxindoles through visible light induced cyclization in the presence of organic photocatalysts

According to the project proposal, we studied the photocatalytic cyclization reactions of acrylicamide derivatives and diazonium salts. During our research we have developed a novel method for visible-light photoredox arylation-cyclization of *N*-alkyl-*N*-aryl-2-(trifluoromethyl)acrylamides resulting 3-(trifluoromethyl)indolin-2-one derivatives. The aryl radicals were generated from aryldiazonium tetrafluoroborate salts. For this reaction we tested several organic dyes as photosensitizers, and we have found that this reaction works efficiently when food colorant erythrosine B was used as novel organic photocatalyst. The photocatalytic transformation was carried out at -50 °C, irradiation by blue light LEDs, and the reaction was followed by in situ time-resolved infrared spectroscopy at room temperature. With the utilization of the optimized reaction conditions, wide variety of 3-(trifluoromethyl)indolin-2-one compounds were synthesized (Scheme 2, 27 examples) in good chemical yields. The results were summarized in a scientific paper published in European Journal of Organic Chemistry ("Erythrosine B catalyzed visible-light photoredox arylation-cyclization of N-alkyl-N-aryl-2-(trifluoromethyl)acrylamides to 3-(trifluoromethyl)indolin-2-one derivatives", Zsombor Gonda, Ferenc Béke, Orsolya Tischler, Milán Petró, Zoltán Novák, Balázs L. Tóth, *Eur. J. Org. Chem.* **2017**, *15*, 2112-2117. DOI: 10.1002/ejoc.201601493).

In continuation of the cyclizations we explored the possibility to expand the scope of the reaction with different acrylate derivatives using optimized reaction conditions (5 mol% erythrosine B photocatalyst, 2.5 equivalent aryldiazonium salt and deoxygenated and distilled methanol solvent in an argon atmosphere). Acrylamides that were not alkylated on their nitrogen atom did not show any reactivity, similarly to the thiophenyl ester and acrylic acid. At the same time, phenyl methacrylate produced the desired benzofuranone derivate within 24 hours, with a conversion rate of 46%. When investigating the acrylic esters of cyclic secondary amines, pyrazolyl or indazolyl acrylates failed to produce results, while a cyclic product could be achieved in a marginal ratio in case of indolyl acrylate and with almost total conversion in case of tetrahydroquinolinyl acrylate.



Scheme 2. Substrate scope of the photocatalytic trifluormethyl oxindole synthesis

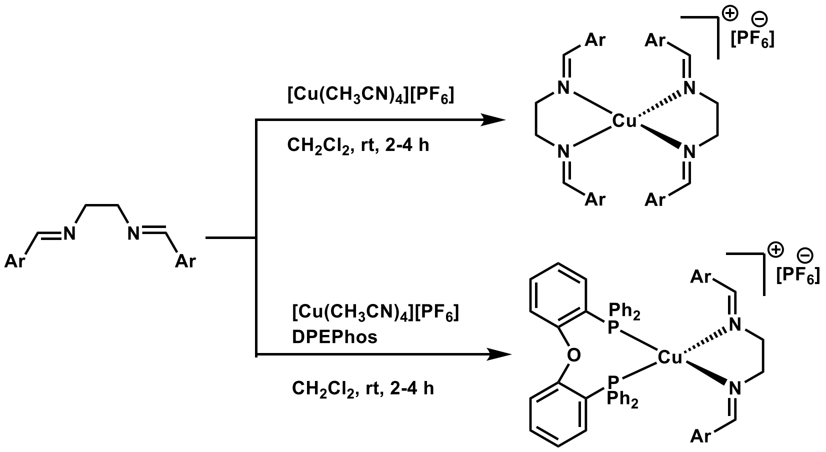
The yield of 60% was reached when using a CFL bulb was only slightly better compared to reactions performed under blue or green LEDs. Still, out of the tested acrylate derivatives, this substrate proved to be the most effective when inducing ring closure. We investigated the formation of rings comprising more than five members, in particular of the less favored six-membered rings using alkyl-metacryloyl benzamides, which produced the closed-ring product with a total conversion on -50 °C under blue LED light, however, the yield was only 40%. In order to validate the suitability of the used photocatalyst, we tested other pigments, but still erythrosine B was the most effective, and only ethyl eosin resulted in a similar conversion rate. When carrying out the reaction with another starting substance, *N*-methylnaphthyl methylamine acrylate suitable for producing a six-membered ring molecule. However, after several synthetic attempts, finally we were not able to develop conditions which eligible to prepare compounds with acceptable chemical yield for publication.

Design and utilization of novel copper-based catalysts in visible light photoredox chemistry

The role of Cu complexes as photosensitizers in photoredox catalysis has been well established in the last 5 years. These copper compounds offer cheap and sustainable alternatives for the most frequently used precious metal (Ru, Ir) photocatalysts. However, their scope needs extension and the currently employed Cu(NN)$_2$X and [Cu(NN)(PP)]X type complexes feature relatively expensive 2,9-diaryl-1,10-phenanthroline or bisphosphine (eg. Xantphos) ligands.

We surmised that replacing the key phenanthroline ligand with easily available diimine (NN) ligands might lead to efficient, readily accessible photosensitizers. Therefore, in the first period of the project a series of NN ligands were prepared via one-step condensation reactions from commercially available starting materials. We investigated their complexation behavior with Cu(I) and the resulting metal complexes were evaluated in photoredox catalysis.

The reaction between benzaldehyde derivatives and diamines (ethylene diamine, cyclohexanediamine) in alcohol solvents gave diimines ArHC=NCH$_2$CH$_2$N=CHAr and ArHC=N(C$_6$H$_{10}$)N=CHAr respectively, in good yields. A wide range of benzaldehydes were employed in order to study both steric (eg. ortho-Me and para-Me) and electronic effects (eg. para NO_2 and para MeO). Furthermore, the different diamine backbones provide additional opportunity to tune complexation behavior (eg. changing from 'in-plane' ethylene diamine to trans-cyclohexanediamine). In the same vein, diazabutadiene (DAB) ligands were obtained by treating aqueous glyoxal solution with two equivalents of the corresponding aniline in alcohol solvents. Bis(aryl)acenaphthenequnonediimine (BIAN) ligands were also prepared by a template directed approach using acenaphthenequinone, aniline and $ZnCl_2$ to afford (BIAN)$ZnCl_2$. The free ligand was accessed upon decoordination assisted by $Na_2(C_2O_4)$.

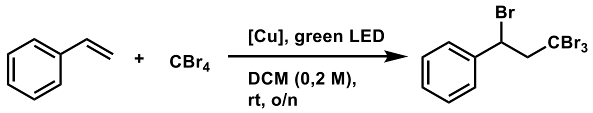


Entry	NN	PP	Product	Yield / %
1	EtNN	-	[Cu(EtNN)$_2$][PF$_6$]	88
2	EtNN	DPEPhos	[Cu(EtNN)(DPEPhos)][PF$_6$]	85
3	EtNN^{pCl}	-	[Cu(EtNN^{pCl})$_2$][PF$_6$]	50
4	EtNN^{pOMe}	-	[Cu(EtNN^{pOMe})$_2$][PF$_6$]	52
5	EtNN^{pNMe2}	-	[Cu(EtNN^{pNMe2})][PF$_6$]	75
6	EtNN^{pNMe2}	DPEPhos	[Cu(EtNN^{pNMe2})(DPEPhos)][PF$_6$]	84
7	*cis*-CyNN	-	[Cu(*cis*-CyNN)$_2$][PF$_6$]	78
8	*trans*-CyNN	-	[Cu(*trans*-CyNN)$_2$][PF$_6$]	83
9	*trans*-CyNN	DPEPhos	[Cu(*trans*-CyNN)(DPEPhos)][PF$_6$]	83
10	DAB^{OMe}	-	[Cu(DAB^{OMe})$_2$][PF$_6$]	73
11	DAB^{OMe}	DPEPhos	[Cu(DAB^{OMe})(DPEPhos)][PF$_6$]	94
12	DAB^{OMe}	Xanthpos	[Cu(DAB^{OMe})(Xanthpos)][PF$_6$]	89
13	DAB^{NMe2}	DPEPhos	[Cu(DAB^{NMe2})(DPEPhos)][PF$_6$]	91
14	BIAN	-	[Cu(BIAN)$_2$][PF$_6$]	85
15	BIAN	Xanthpos	[Cu(BIAN)(Xanthpos)][PF$_6$]	87
16	BIAN	DPEPhos	[Cu(BIAN)(DPEPhos)][PF$_6$]	87

Scheme 3. *Synthesis of homoleptic and heteroleptic copper complexes*

Treatment of [Cu(CH_3CN)$_4$][PF$_6$] with the appropriate diamine ligand (2 equiv) in dichloromethane (DCM) smoothly gave the corresponding [Cu(NN)$_2$][PF$_6$]. Some of these complexes have been previously described, but we are not aware of any reports on their application in photoredox catalysis. The homoleptic complexes show good stability in DCM and acetone, however decompose in $CDCl_3$ (likely due to acid sensitivity). Treatment of [Cu(CH_3CN)$_4$][PF$_6$] with the Xanpthos or DPEPhos ligands (1 equiv) in DCM followed by the addition of the appropriate diimine ligand (1 equiv) gave access to heteroleptic [Cu(NN)(PP)][PF$_6$]. ^{1}H NMR spectroscopic studies showed that these complexes tend to go through solvent dependent ligand scrambling. We found that such ligand exchange is favored in DCM-d_2 and is less pronounced in acetone-d_6.

The homoleptic $[Cu(NN)_2][PF_6]$ (where NN is an ethylene diamine or cyclohexanediamine derivative) complexes showed good activity, although lower than that of $Cu(dap)_2Cl$ (dap = 2,9-di-para-anisole-1,10-phenanthroline), in the atom transfer radical addition (ATRA) of CBr_4 to styrene. Among the complexes tested the best results were achieved with the $pTolHC{=}NCH_2CH_2N{=}CHpTol$ ligand. Control experiments showed that both light (irradiation by green LED) and the presence of the copper complex is necessary in order to reach a successful outcome. The heteroleptic $[Cu(NN)(DPEPhos)][PF_6]$ complexes showed no appreciable activity in the ATRA reaction. Interestingly, a reverse trend in catalytic activity was observed with complexes featuring the DAB ligand. In this case, while the homoleptic complex did not provide the ATRA product, the heteroleptic complex showed moderate activity. Neither the homo- nor the heteroleptic Ar-BIAN complexes afforded the ATRA product.

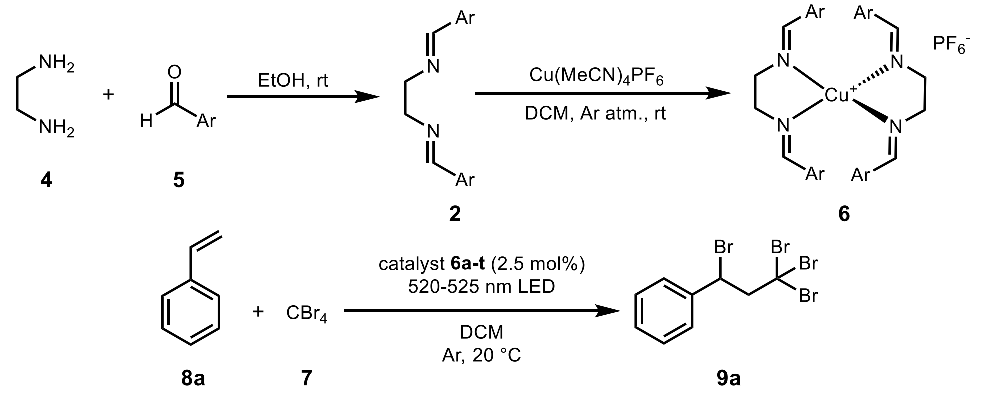


Entry	Photocatalyst	cat %	GCMS / % (yield)	Note
1	$[Cu(EtNN)_2][PF_6]$	1	73 (73)	
2	$[Cu(EtNN)_2][PF_6]$	1	0	in dark
3	$[Cu(EtNN)_2][PF_6]$	1	0	without LED
4	EtNN	2	0	without Cu
5	$[Cu(EtNN)_2][PF_6]$	1	0	without Ar
6	$[Cu(EtNN)(DPEPhos)][PF_6]$	1	traces	
7	$[Cu(EtNN^{pOMe})_2][PF_6]$	2,5	83 (83)	
8	$[Cu(EtNN^{pCl})_2][PF_6]$	2,5	94 (86)	
9	$[Cu(EtNN^{pNMe2})][PF_6]$	2	34	blue LED
10	$[Cu($*trans*-$CyNN)_2][PF_6]$	2	60	
11	$[Cu(DAB^{OMe})(DPEPhos)][PF_6]$	2,5	67	
12	$[Cu(DAB^{OMe})(Xanthpos)][PF_6]$	2	19	
13	$Cu(dap)_2Cl$	0,3	(88)	

Scheme 4. Photocatalytic activity of copper complexes

Having identified $[Cu(pTolHC{=}NCH_2CH_2N{=}CHpTol)_2][PF_6]$ as the most active amongst the tested complexes we explored its activity in a variety of ATRA type reactions. Although the catalyst showed appreciable activity in 5 out of 7 tested substrate combinations the efficiency was lower compared to $Cu(dap)_2Cl$. 2,9-dianisole-1,10-phenanthroline (dap) and its corresponding complex $Cu(dap)_2Cl$, together with the previously described photosensitizers $[Cu(dmp)(Xantphos)][PF_6]$ and $[Cu(dmp)(DPEPhos)][PF_6]$ where dmp = 2,9-dimethyl-1,10-phenanthroline were also prepared in order to explore new reactivity pathways between olefins and fluorinated alkyl iodonium salts.

On the basis of the preliminary structural screening we turned our attention to the fine tune of substituents on the Ar group of bis imine backbone of the catalyst with $Cu(ArHC{=}NCH_2CH_2N{=}CHAr)_2][PF_6]$ general formula. The new copper-diimine complexes were obtained by a two-step synthesis. At first, ethylenediamine and two equivalents of appropriate substituted benzaldehydes were stirred in ethanol at room temperature. The products were isolated in the average good yields. In the second step, two equivalents of ligands were stirred with tetrakis-acetonitrilo-copper(I) hexafluorophosporate in absolute dichloromethane. In most cases, the pure complexes could be obtained in excellent yields, altogether 20 examples were prepared.

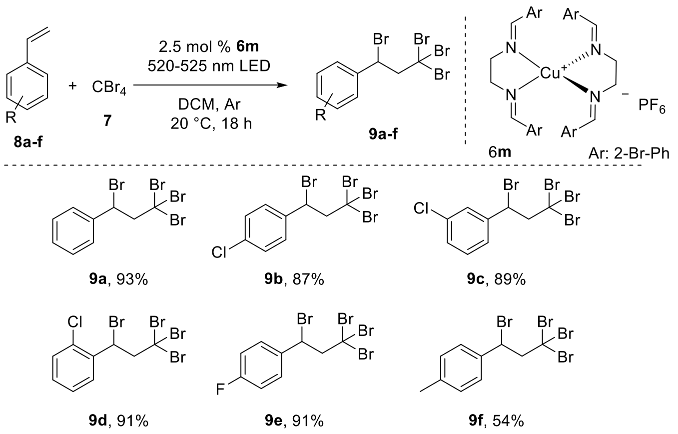


Entry	Aldehyde	Ar (in 5, 2 and 6)	Yield (2, %)	Yield (6, %)	Yield (9a, %)
1	**5a**	C_6H_5	85	80	73
2	**5b**	4-Me_2N- C_6H_4	82	75	8
3	**5c**	4-MeO-C_6H_4	44	86	53
4	**5d**	2-MeO-C_6H_4	82	92	76
5	**5e**	2-Ph-C_6H_4	70	94	88
6	**5f**	4-Cl-C_6H_4	90	92	62
7	**5g**	3-Cl-C_6H_4	88	53	79
8	**5h**	2-Cl-C_6H_4	82	89	90
9	**5i**	2,4-Cl_2-C_6H_3	88	95	83
10	**5j**	2,6-Cl_2-C_6H_3	88	93	4
11	**5k**	2-F-C_6H_4	51	88	88
12	**5l**	4-Br-C_6H_4	95	91	88
13	**5m**	2-Br-C_6H_4	69	74	93
14	**5n**	4-F-C_6H_4	71	78	83
15	**5o**	3-F-C_6H_4	75	96	76
16	**5p**	4-F_3C-C_6H_4	76	90	88
17	**5q**	2,4-F_2-C_6H_3	79	87	84
18	**5r**	3-Br-C_6H_4	65	91	83
19	**5s**	3-MeO-C_6H_4	53	85	55
20	**5t**	2-F-4-Br-C_6H_3	91	81	81

Scheme 5. *Synthesis of novel copper bis-imine photocatalysts*

After their synthesis, the series of complexes were tested in an atom-transfer-radical addition (ATRA) reaction between styrene and carbon tetrabromide. Under the optimization process, several circumstances were varied, such as catalyst loading, light source and stage of isolation of the reaction from environment. We found that, using 2.5 mol% catalyst loading is much more favorable than 1 mol%. The photocatalytic nature of the reaction was also examined. In the dark, no reaction was observed. Sunlight is not enough for the reaction, and 520 nm LED gives higher yield compared to the 440 nm LED. Presence of copper is also essential for the success. However, no reaction took place in the presence of only the starting copper compound. Using inert atmosphere and dry, degassed solvent are also required for the successful transformation. After having the optimal conditions, an extended structure-activity relationship examination was carried out, when the substituents in the complexes were systematically changed. The highest yield of the ATRA reaction was reached with the bis 2-bromophenyl ethylene diimine derivative (Entry 13, 93%).

After that, another structure-activity relationship examination was performed, this time from the perspective of the styrene. The photocatalytic ATRA reaction was carried out with the best catalyst of the previous series, and variously substituted styrenes was involved. There is no significant difference between the reactivity of the unsubstituted styrene and halogenated styrenes, from which the desired compounds were obtained in 54-93% yields. In contrast, in the case of methoxy substituent no ATRA reaction occurred, instead, a full decomposition of starting material was observed.

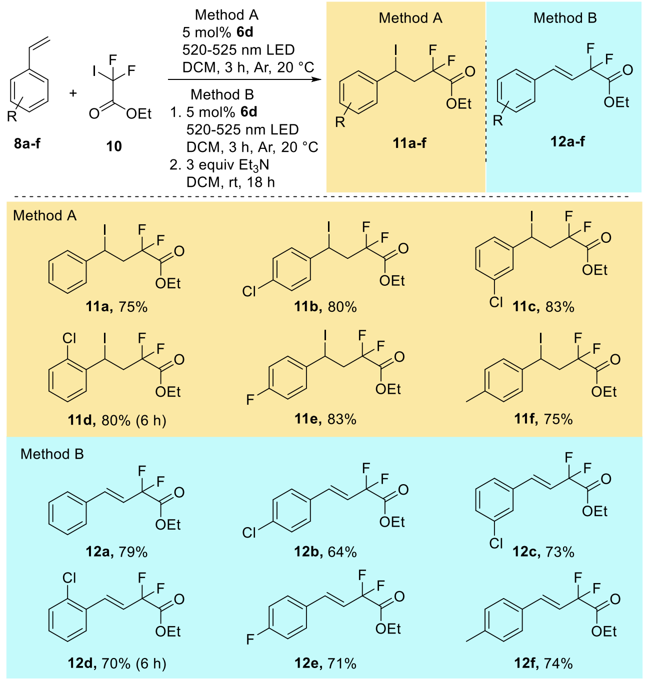


Scheme 6. *Copper catalyzed ATRA reaction of CBr$_4$ and styrene derivatives*

As an analogy to the well known 2,9-dianisole-1,10-phenanthroline (dap) ligand and its corresponding complex Cu(dap)$_2$Cl, we prepared five additional new phenanthroline ligands bearing various aryl substituents in positions 2 and 9 of the phenanthroline frame, and its copper complexes. We also examined their reactivity in ATRA reaction, but neither of the prepared complexes gave higher catalytic activity the original Cu(dap)$_2$Cl complex.

We examined the possibility and additional effect of the ligand dissociation in this atom-transfer-radical addition (ATRA) reaction. Experiments were made with different loadings of complexes and extra mol% ligands. We found that the extra ligand loading does not affect the outcome of the reaction. Moreover, we studied that how the reaction performs with in situ generated complex. With 2.5 mol% copper-source and 5 mol% ligand we obtained the appropriate product with 38% yield, which is 55% less than with the optimized 2.5 mol% Cu(I)-complex. In conclusion, this photoredox transformation requires the isolated Cu(I) complex.

The copper-(bis-bromophenyl ethylene diimine) complex, which was designed by us was successfully applied as photocatalyst in the ATRA reaction of styrene and CBr$_4$, was also tested in another ATRA type reaction. We examined the photochemical addition of ethyl iododifluoracetate was used to be added onto styrene. Under the optimization process, several circumstances were varied, such as catalyst loading, light source and stage of isolation of the reaction from environment.

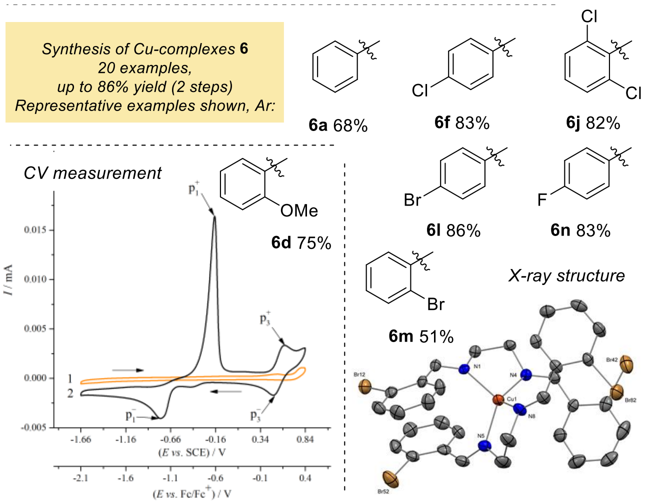


Scheme 7. *Photocatalytic addition of iododifluoroacetates*

We found that, using 5 mol% catalyst loading is much more favorable than 2.5 mol%. We proved the photocatalytic nature of the reaction, while we did not observed reaction in the dark. Presence of copper is also essential for the reaction. Using inert atmosphere and dry, degassed solvent are also required for the successful transformation. Among our complexes, the 2-methoxy derivative had the best catalytic activity and the ATRA product could also be obtained with 75% yield. After this modification, a series of ATRA products were prepared from ethyl iododifluoracetate and styrene derivatives with 69-83% yields. The product compounds have not been described in the literature before. During the synthesis of the new compound family, a slight decomposition of products could be observed, which gave the corresponding alkene derivatives by the loss of an HI molecule. Treatment of the freshly prepared iodide with triethyl amine gave the corresponding trans-alkenes up to 79% yields. To exploit this behavior, we prepared 6 fluoroalkenylated products in the photochemical addition-elimination sequence (Scheme 7).

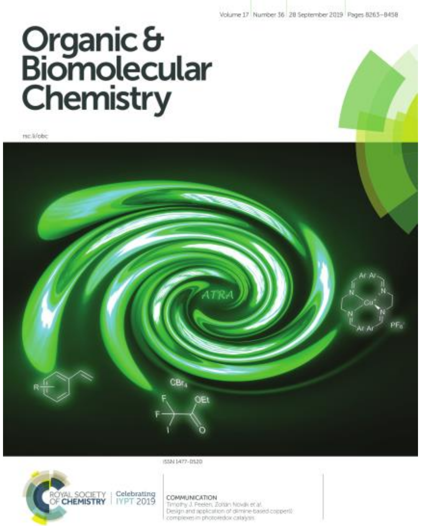
Next, we examined the photophysical properties of the new copper-diimine complexes. Their UV-Vis spectra were recorded, and we found that the light absorption of our photocatalysts is in the blue region with a maximum between 404-437 nm, so we needed to find an answer, why is our photocatalyst is working in green light when the absorption is in the blue region. We compared the absorption spectrum of our photocatalyst with the emission spectrum of our green LED, and we find an overlap around 500 nm. It has been observed before that Cu(I) complexes work well with green light even if the absorption maximum is low at this wavelength range. To understand the working mechanism of this complexes we performed laser flash transient absorption measurements in cooperation with Attila Demeter from MTA TTK. From these measurements a long lived (15 ms) species can be detected at 460 nm, as well as the depletion of the ground state compound at 400 nm, both are indicating that the absorption spectrum of the long-lived excited species slightly shifted to red. Even more, at presence of CBr_4 a further kinetic increase may be seen at 460 nm with a characteristic time parameter of 100-200 μs. The 30 ms time range would be enough for a bimolecular reaction, especially if one of the reactants makes a weak complex with the catalysts even at ground state.

The structure of our main photocatalyst, the bis 2-bromophenyl ethylene diimine derivative was determined by single crystal X-ray crystallography. The X-ray pictures shows that the geometry around the Cu(I)-center is pseudo-tetrahedral and the C=N bonds in the ligands show trans orientation. In collaboration, the electrochemical properties of the photocatalysts were determined by CV measurements.



Scheme 8. *Structure determination of copper complexes*

After the full characterization of the catalyst and the study of their catalytic activity in the ATRA reaction, we summarized the results in a manuscript which was accepted for publication in Organic and Biomolecular Chemistry (Design and application of diimine-based copper(I) complexes in photoredox catalysis, Tamás Földesi, Réka Adamik, Gellert Sipos, Bálint Nagy, Balázs L. Tóth, Attila Benyei, Krisztina Szekeres, Győző Láng, Attila Demeter, Timothy Peelen, Zoltán Novák, Org. Biomol. Chem. 2019, 17, 8343-8347; DOI: 10.1039/C9OB01331H). A cover art of our scientific work was also published on the front page of the issue of Org. Bioomol. Chem.).



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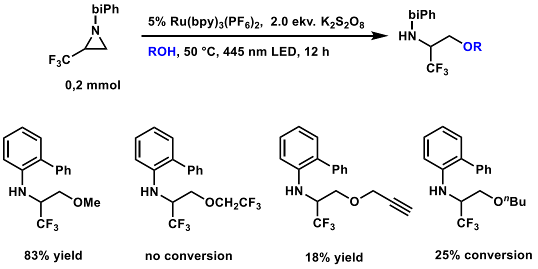
COMMUNICATION
Timothy J. Feelen, Zoltán Novák et al.
Design and application of diimine-based copper(I) complexes in photoredox catalysis

Scheme 9. *Cover art for our Organic and Biomolecular Chemistry paper*

Additionally, an MSc. and a TDK (Student Scientific Research) thesis work was completed on this topic.

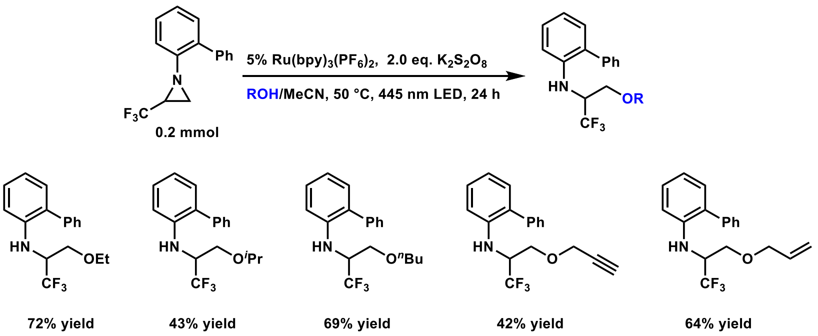
Development of Photo Acid Generators (PAG's) and its application in organic synthesis (unpublished results)

Photo acid generators are novel photochemical systems to the production of protons from organic molecules. However, their application to organic synthesis is rare compared to material and polymer science. We aimed to develop a photocatalytic system for a Bronsted acid catalyzed ring opening reaction of aziridines with the assistance of alcohols and halide ions, and their subsequent photocatalytic bromination, with or without the use of expensive noble metal based photocatalyst. First, we examined the ring opening of *N*-aryl-trifluoromethylaziridines with alcohols. During these experiments, we ascertained the proper reaction conditions. Blue light (ensured by 10 W 445 nm LED), ruthenium catalyst, potassium persulfate and minimum 50 °C temperature was necessary. Application of other light sources and peroxides caused side reactions or no reaction at all. These simple conditions are valid only for methanol though, where it functions as solvent and reagent. Using other alcohols, we determined acetonitrile to be a suitable cosolvent (1:1 ratio) to eliminate solubility problems. This way, we synthetized alkyl ether derivatives using methanol, ethanol, 2-propanol, n-butanol and propargyl alcohol. For the model compound we choose 1-([1,1'-biphenyl]-2-yl)-2-(trifluoromethyl)aziridine because its lower volatility compared to others and good detectability in GC-MS which can ease the reaction monitoring. First, we tried opening the ring with alcohols which was successful with MeOH using 5 mol% $Ru(bpy)_3(PF_6)_2$ photocatalyst with 2 equivalents $K_2S_2O_8$ under blue LED irradiation and 50 °C reaction temperature. However, using other alcohols, we found little to no conversion. (Scheme 10.)



Scheme 10. *Photocatalytic ring opening with alcohols*

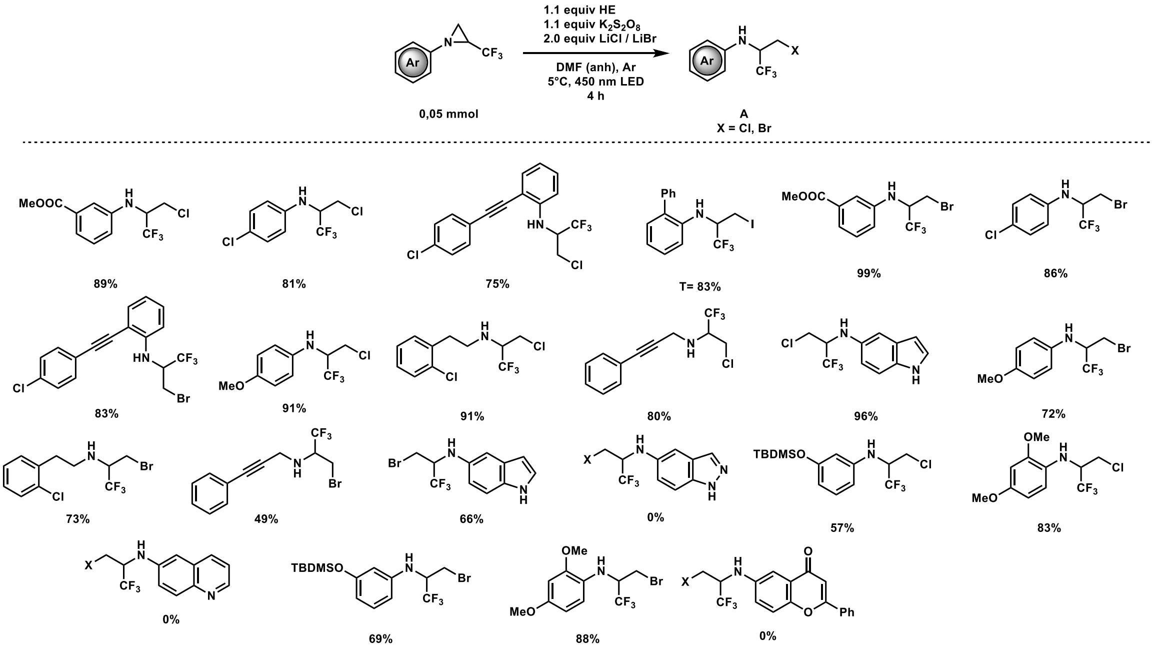
After investigating the problem, we found that the poor solubility of the starting material and reagents can cause the low conversions, so to avoid this we used DMF as co solvent. The conversions improved but a by-product from the solvent appeared in the reaction. Switching to acetonitrile improved our yield without any other product forming. (Scheme 11)



Scheme 11. Ring opening with alcohols using co-solvent

Reactions with other nucleophiles, such as iodide, bromide, chloride incorporation were achieved in the presence of Hantzsch ester as a H-source under oxidative conditions (potassium persulfate) to give alkyl halides. During these reactions, we experienced the formation of not only the alkyl halide coming from ring opening reaction, but also the halogenation of aromatic aniline ring. We found that the reaction doesn't requires any metal based photocatalyst. Using only potassium persulfate – Hantzsch ester system is enough for the induction of ring opening of the aziridine ring, then because of the oxidative conditions bromine formation causes the aromatic substitution. Furtherly examining the bromination reaction through monitoring by GC-MS under various conditions, we can state that the first step is clearly photoinitiated, and specific to 445 nm blue light. Until completion of the ring opening step, the purely photocatalyzed aromatic bromination cannot be observed. We achieved to selectively synthetize mono and dibrominated products separately. For the optimal reaction we used 2 equivalent lithium halide (LiCl or LiBr), 2 equivalent potassium persulfate, 1.1 equivalent Hantzsch ester in DMF at 5 °C, under argon atmosphere, using blue LED irradiation. The use of more halide promoted the aromatic halogenation such as raising the amount of persulfate. Due to solubility, we can find significant difference between reactivity of persulfates bearing other cations. In most articles, they recommend ammonium and sodium salts. In our case, these types of persulfates were too active and probably lead to the decomposition of aniline moieties while not serving as a reaction partner to Hantzsch ester.

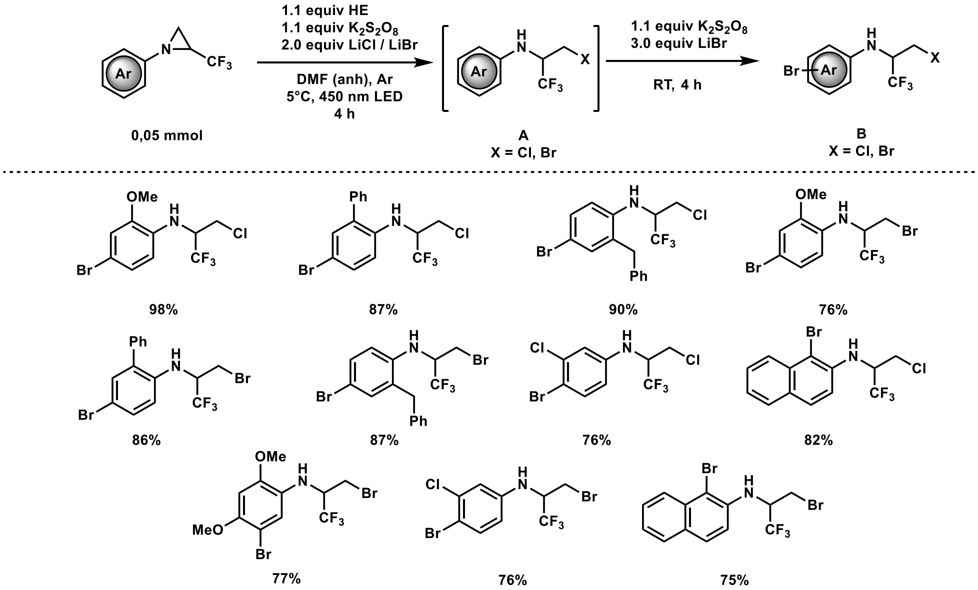
With these conditions in hand we could investigate the scope of our transformation. In each case, we used 5 °C reaction temperature for the first step, so the photoinitiated ring-opening can occur selectively. Then if it was possible, we added more persulfate and lithium halide to the system and executed the thermic aromatic bromination.



Scheme 12. *Substrate scope of the selective ring opening of trifluoromethylaziridines*

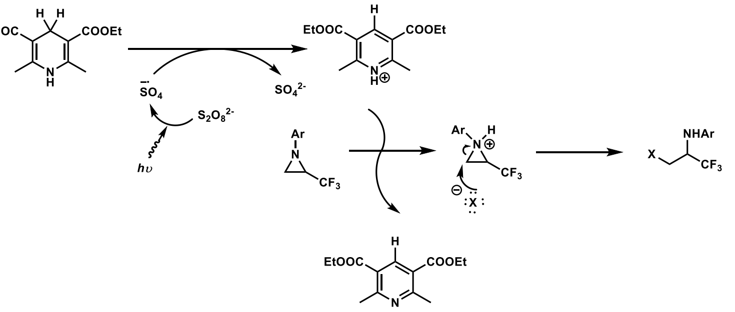
The first step showed remarkably good toleration toward a variety of substrates. Both electron donating and withdrawing groups were tolerated in the reaction. If another nucleophile is present, we only observed decomposition, so in the case of the phenol derivative silyl ether protection was needed. But after masking the interfering group the ring opening could be achieved. Some sensitive compound such as quinoline or flavone decomposed in the conditions of the reaction, so not even the ring opening could be achieved. Surprisingly we could even react acetylene compounds without the detection of any bromine addition to the triple bond. On Scheme 12 the products of the ring opening of the aziridines is summarized, which couldn't be brominated in the second step.

In the cases where the second bromination step occurred without any problem we didn't isolate the ring opened intermediate instead we added the excess lithium halide and more persulfate and waited until the second step was complete. After the GC-MS analysis confirmed the end of the reaction we isolated the products using column chromatography.



Scheme 13. *The products of the two step ringopening-halogenation*

We also conducted experiments to explore the mechanism of the reaction. One crucial part of the transformation is the Hantzsch ester which acts as a proton source. Substituting it with any other H atom source didn't result in reaction. One possible mechanism is the formation of the amino radical from the aziridine, but adding trapping agents did not produce the appropriate product but also didn't stop the reaction. Only TEMPO a non-specific radical scavenger halted the transformation. Adding Proton-sponge to the mixture also didn't give products indicating that protonation is part of the mechanism. Using these results, the proposed mechanism starts with the photolysis of the persulfate ion into sulfate radical anion, which can oxidase the Hantzsch ester into piridine. This species in turn can protonate the aziridine, activating it. The last step is the attack of the nucleophile at the sterically less hindered position.



Scheme 14. *The proposed mechanism*

In conclusion, we developed a mild and metal-free method for the regioselective ring-opening of various *N*-aryl substituted trifluoromethyl aziridines using visible light photo initiation. We could separate the photoreaction from a thermic bromination, which in some cases can be used to produce valuable intermediates for further transformation.

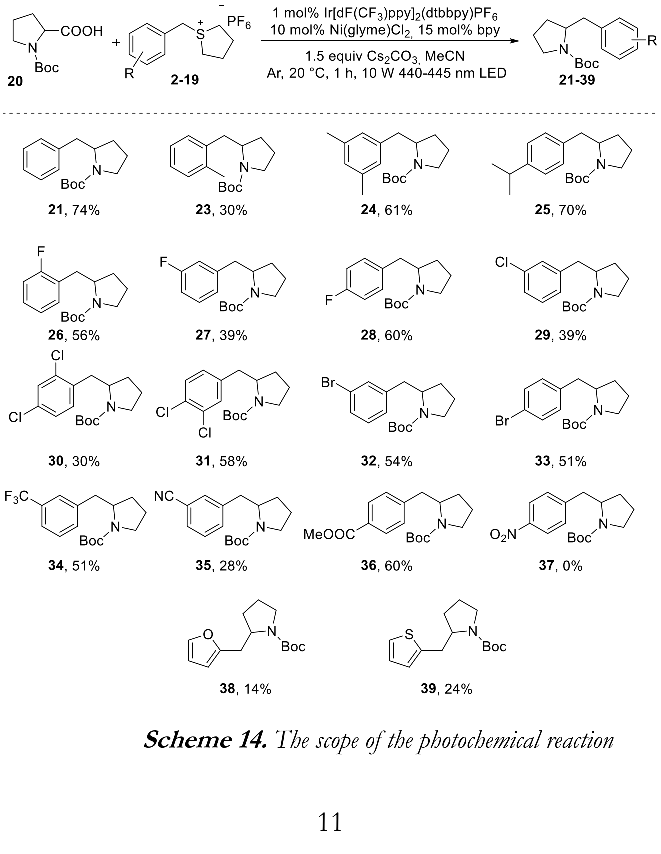
With these results we successfully demonstrated a PAG system and its novel use in producing new molecules witch then can serve as useful building blocks in organic synthesis, and we are currently making the final experimental adjustments for prepare the manuscript submission.

Development of novel nickel-iridium dual photocatalytic couplings

In the last couple of years, the nickel-iridium dual photocatalytic coupling reactions are in the focus of organic synthesis. In this context we published our review article on this topic (Recent advances in dual transition metal–visible light photoredox catalysis, Balázs L. Tóth, Orsolya Tischler, Zoltán Novák, Tetrahedron Lett. 2016, 57, 4505–4513. DOI: 10.1016/j.tetlet.2016.08.081)

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 (sp2) – carbon (sp3) bonds. As a new approach to the 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-bromid, because the photodegradation of benzyl-bromide give 1,2-diphenyl-ethane byproduct. As a further development the use of a bench-stable Ni(0) source, such as Ni(PPh_3)$_2$(CO)$_2$ give 1,3-diphenylaceton as product 50% yield in the presence of 10mol% N-Boc-proline and CO source. 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. Unfortunately, until the closing of the project we were not able to finish the development of a novel carbonylative coupling of sulfonium salt under dual photocatalytic coupling reactions.

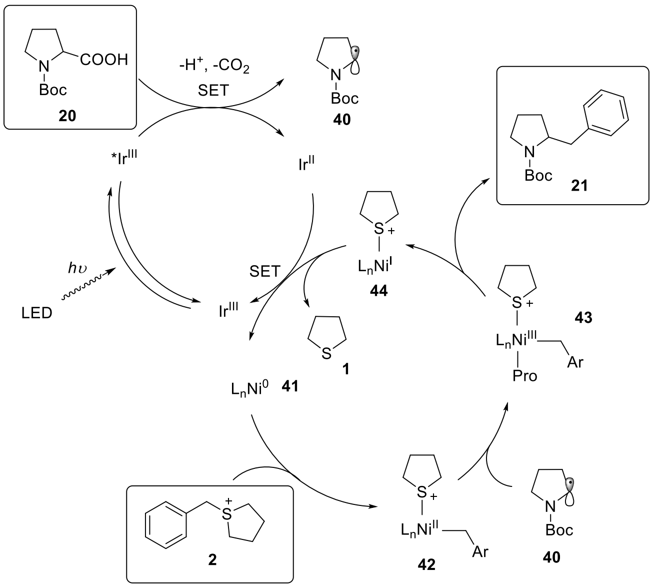
However, with our model reaction we transformed *N*-Boc-proline into N-Boc-2-benzylpyrrolidine using -(2-benzyl)-tetramethylenesulfonium hexafluorophosphate, with the following reaction conditions: Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 and $NiCl_2$•glyme (glycol ether) for catalysts, bipyridyl (as ligand), 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, as we prepared the desired benzylpyrrolidine derivatives (Scheme 14, 14-74% yield range).



Scheme 14. *The scope of 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 benzylsulfonium salts we propose the following catalytic cycles for the transformation (Scheme 15). 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 CH3CN} 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}[16] closing both catalytic circles at the same time.

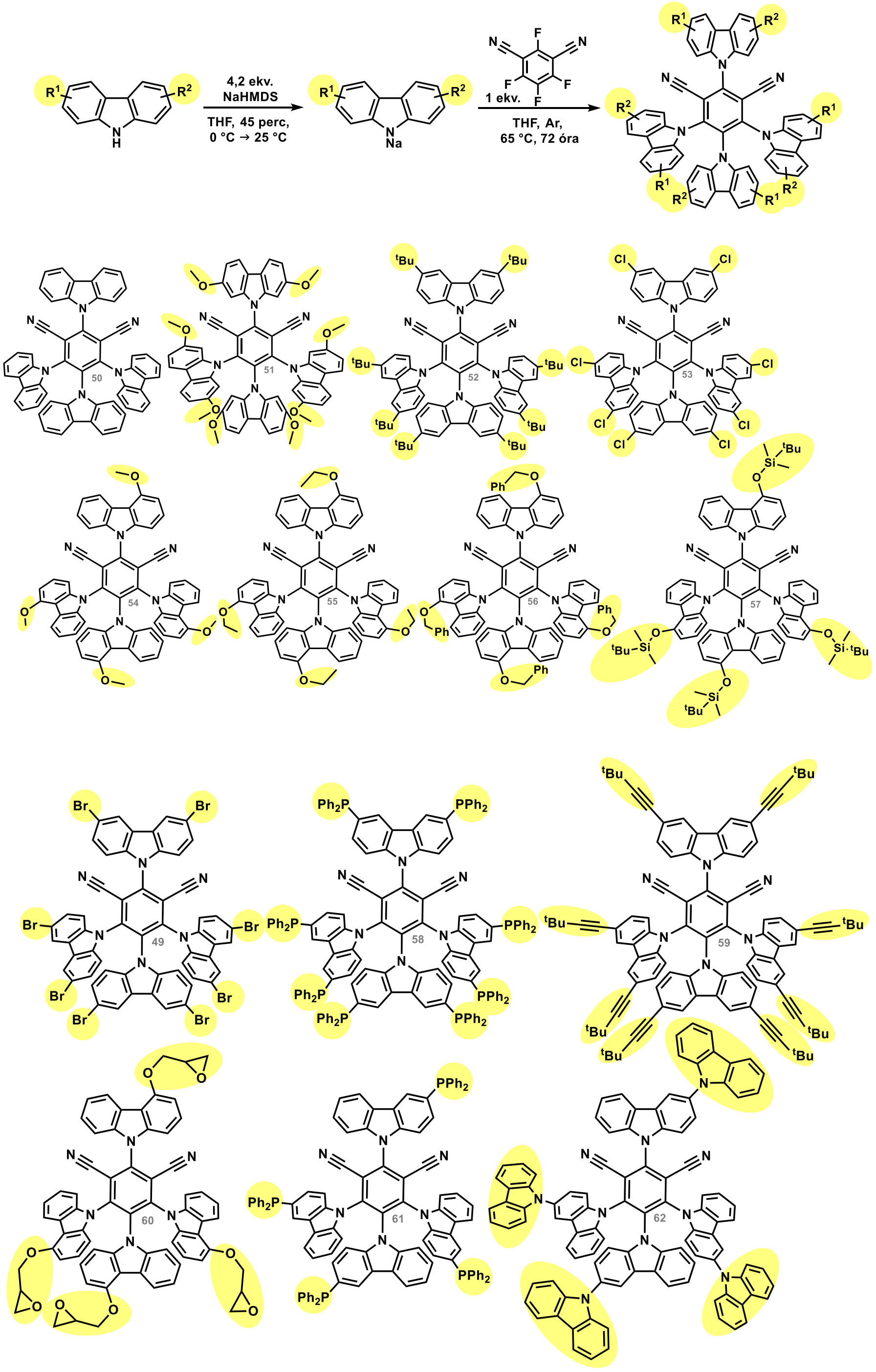


Scheme 15. *The proposed mechanism of the reaction*

Our Results 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.* **2019**. ASAP DOI: 10.1002/ejoc.201900957).

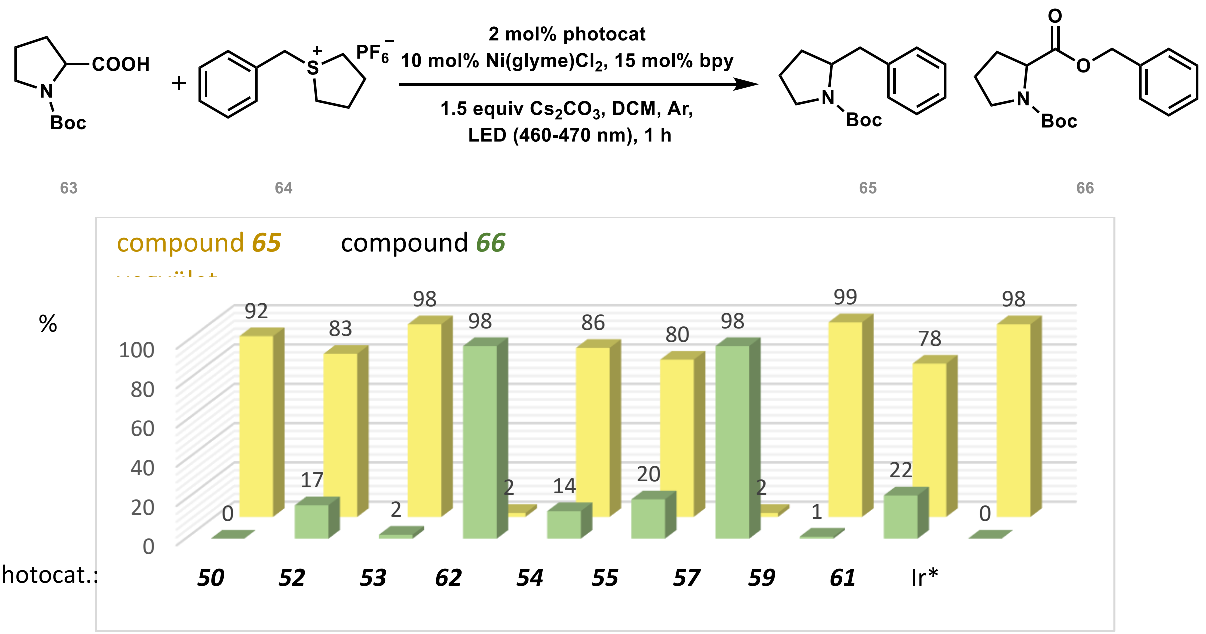
Development of novel photocatalytic dyes (unpublished results)

During the last period of the project we synthetized 13 differently substituted tetracarbazolyl-isophthalonitrile (CzIPN) dyes beyond the unsubstituted derivative. 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. After the purification by column chromatography and recrystallization the dyes were obtained in 6-91% yields (Scheme 16).



Scheme 16. *Collection of new CzIPN based organic photocatalysts*

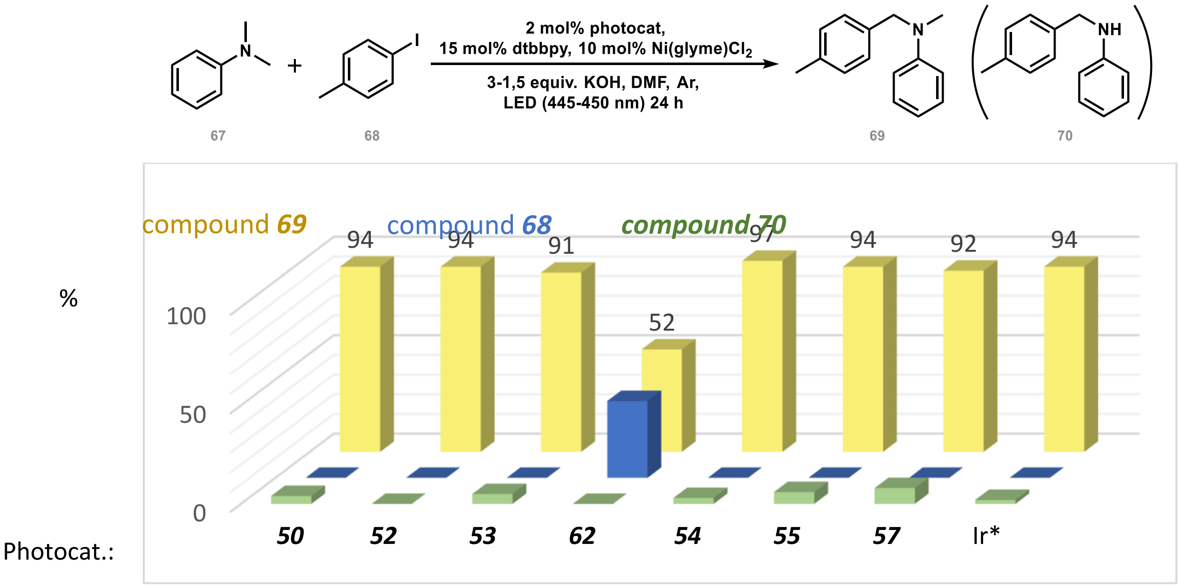
After the successful preparation of the catalyst kit we tested their photocatalytic activity in the nickel co-catalyzed coupling reaction of benzylsulfonium salt and Boc-proline in the presence of Cs_2CO_3 in DCM under argon atmosphere. We observed different selectivity as the outcome of the test reactions. Photocatalyst **50**, **53** and **59** proved to be selective to the formation of the desired bnzylpiperidine, while other gave its mixture with the appropriate ester. These catalysts showed similar activity to the Ir based catalyst.



*Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$

Scheme 17. *Reactivity study of new CzIPN fotocatalysts I.*

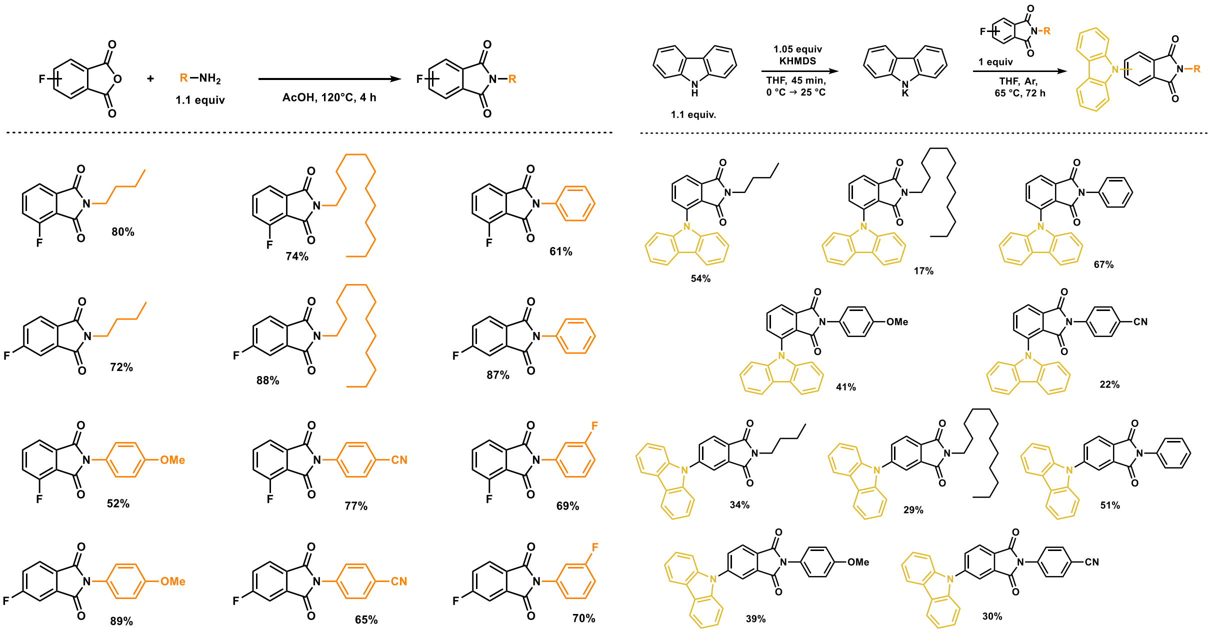
The catalyst kit was also tested in the C-arylation of *N*, *N*-dimethylaniline with 4-iodotoluene, and we found high activity of the catalyst in the photocatalytic transformation (Scheme 18).



*Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$

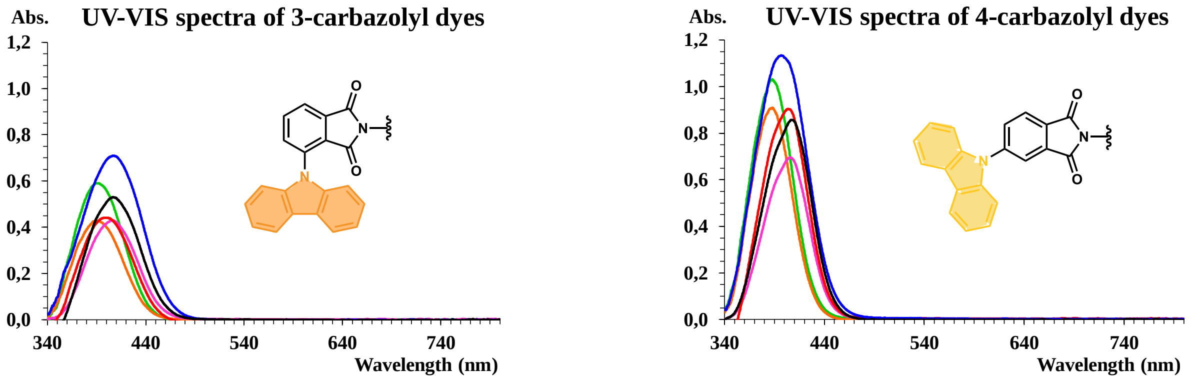
Scheme 18. *Reactivity study of new CzIPN photocatalysts II.*

Similar to CzIPN dyes we started another dyes family the carbazole substituted *N*-alkyl and *N*-aryl phthalimides synthesis. 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 19, left). The carbazolyl substitution was performed under similar conditions to the CzIPN derivatives, and we successfully prepared 10 new phthalimide based organic photocatalysts (Scheme 19, right).



Scheme 19. *Synthesis of novel phthalamide based photocatalysts*

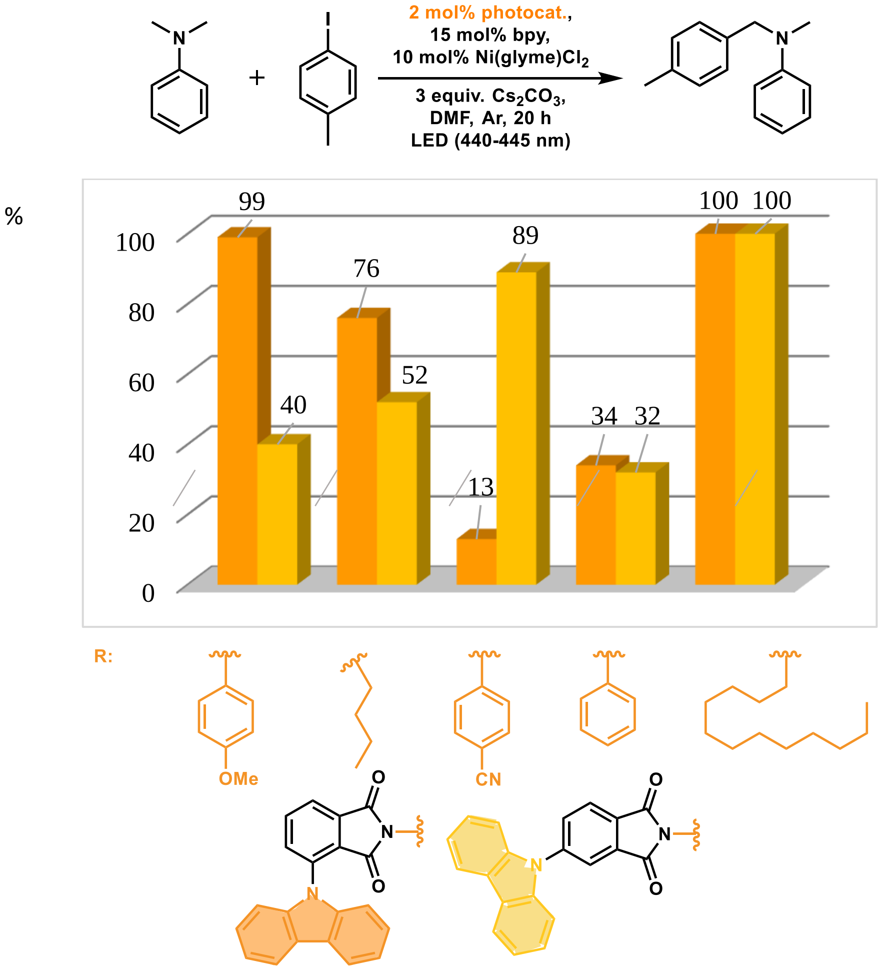
The UV-VIS spectra of the products show absorption in the visible light section, which will be eligible for excitation in photocatalytic transformations. Representative examples are indicated on Scheme 20.



Scheme 20. *Physicochemical properties of phthalamide based photocatalysts*

Finally, before the closing of the project we tested the photocatalytic activity of dyes in 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 dodecyl derivate has superior activity (Scheme 21), and reached the efficiency of the expensive, generally used $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ photocatalyst. The determination of the photophysical properties of the new catalyst and further exploration of their applicability in organic transformations will be continued in our laboratory.

In conclusion, we developed new organic dyes with promising catalytic activities, which could serve as non-metallic alternative of expensive iridium-based catalyst systems. The complete physical-chemical characterization of the new organic dyes is currently under investigation in our laboratory, and will be finished after the closing of the project.

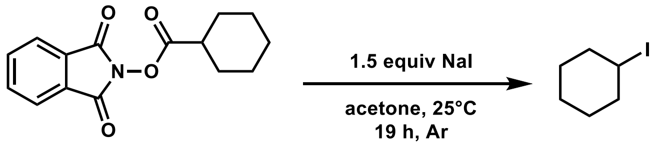


Scheme 21. *Reactivity studies of phthalamide based photocatalysts*

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-PPh3 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 grou 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 22).

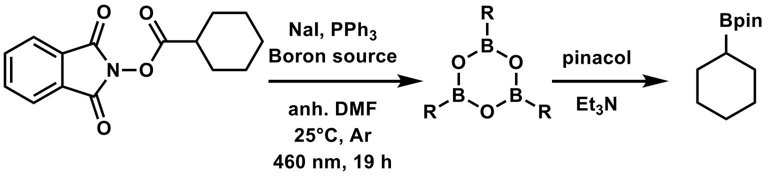
After the preparation of this representative example, we intend to continue the substrate scope considering the structural features of the carboxylic derivatives.



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

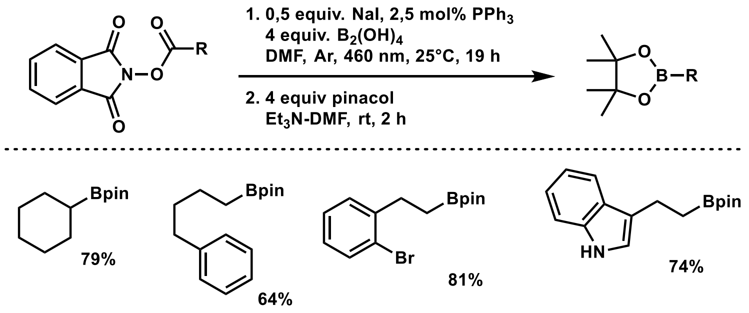
Parallel to the iodination reactions we examined the radical boronation of the esters with the utilization of the NaI-PPh_3 system. We found that the 3 or 4 equivalents of $B_2(OH)_2$ is an applicable boron source for the boronation, and followed by an esterification step we isolated the pinacolboronate in 79% yield.



Entry	**NaI (equiv)**	**PPh_3 (mol%)**	**Boron source (equiv)**	**boroxine (GC%)**	**cHexI (GC%)**	**prod. (%, isolated yield)**
1	1,5	2,5	$B_2(OH)_4$ (4)	100	-	-
2	1,5	2,5	B_2pin_2 (4)	0	54	-
3	1,5	2,5	$B_2(OH)_4$ (4)	n.a.	n.a.	78
4	1,5	2,5	$B_2(OH)_4$ (0,5)	16	83	n.a.
5	1,5	2,5	$B_2(OH)_4$ (2)	83	16	65
6	0,5	2,5	$B_2(OH)_4$ (4)	100	-	79
7	0,5	2,5	$B_2(OH)_4$ (3)	n.a.	n.a.	69
8	0,5	0	$B_2(OH)_4$ (4)	n.a.	n.a.	<5

Scheme 23. *Photocatalytic transformation of active esters to boronates with NaI-PPh3 system under visible light irradiation*

We have just started the extension of the reaction and prepared four primary alkyl pinacolboronate ester using the optimized reaction conditions in good yields (Scheme 23).



Scheme 24. *Photocatalytic transformation of active esters to boronates with NaI-PPh_3 system under visible light irradiation*