Development of Ni-Ir Dual Photocatalytic Liebeskind-coupling of Sulfonium Salts for the Synthesis of 2-benzylpyrrolidines

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Abstract: A new method has been developed for the synthesis of 2-benzylpyrrolidines utilizing cross-coupling and photoredox catalysis. Using a well-established dual Ni-Ir system, we were able to successfully couple benzylsulfonium salts with a proline utilizing radical forming through CO_2 extrusion. This enabled the simple one step synthesis of 2-benzylpyrrolidines from stable inexpensive starting materials.

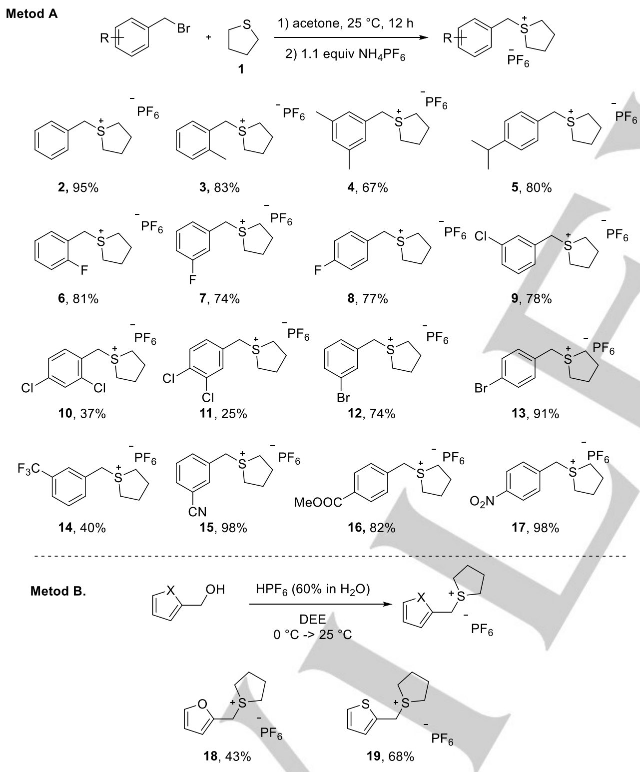
Introduction

2-Benzylpyrrolidines show biological activity as peripheral D-1 and D-2 dopamine agonist which can help the treatment of hypertension and heart disease.[1] Also, these compounds acts as dual orexin receptor antagonist, providing a useful strategy for treating sleep disorders,[2] furthermore they can be used as a calcium receptor antagonist, treating osteoporosis.[3]
Preparation of this moiety involves palladium catalyzed cyclization,[4,5] using sensitive organozinc reagent[6], and with a multistep process including ene-carbamate generation and their hydrogenation.[7]

As such powerful drug candidates their simple production from feedstock chemicals can be attractive. For this purpose, we were inspired by the available photoredox transformations,[8] which enables the functionalization of sp^3 carbon centers of saturated heterocyclic carboxylic acids.[9] In this scenario, a well-established methodology to exploit the opportunities is the merge of photoredox and nickel catalyzed cross-coupling reactions.[10] In our research we aimed to develop a method for the photocatalyzed coupling of sulfonium salts and *N*-protected proline to reach the desired target benzylpirrolidines, and demonstrates the applicability of these onium reagents as coupling partners for dual photoredox transformations.[11] Sulfonium salts are widely used versatile reagents in organic chemistry.[12] Among these compounds the tetrahydrothiophenium salts are capable of participating in cross-coupling via oxidative addition reaction to palladium or nickel center as it was demonstrated by Liebeskind.[13] However, the application of Umemoto's CF_3 reagent is already known,[14] the application of related alkyl sulfonium salts remained underdeveloped in photoredox transformations.[15] We envisioned that with the combination of nickel catalyzed cross-coupling of benzylsulfonium salts and the decarboxylative photocatalyzed transformation of Boc-protected prolines a novel synthetic approach could be developed for the synthesis of 2-benzylpyrrolidines in a one-step dual photoredox reaction.

Results and Discussion

For our study we prepared several structurally diverse 1-benzyltetrahydro-1*H*-thiophen-1-ium salts using the known literature procedures.[13] Reaction of substituted benzyl bromides with tetrahydrothiophene (THT) in acetone afforded the desired cyclic sulfoniums salts in good yields. In order to get sulfonium salts with higher stability, we performed the bromide anion exchange using NH_4PF_6 to obtain the hexafluorophosphate salts (Scheme 1. Method A). For the synthesis of heterocyclic THT salts **18**, **19** we used the appropriate alcohols as substrates for the nucleophilic replacement of the hydroxy group under acidic conditions (Scheme 1. Method B)



Scheme 1. The synthesized sulfonium salts made from benzylbromides (Method A) and heteroaryl methanol (Method B).

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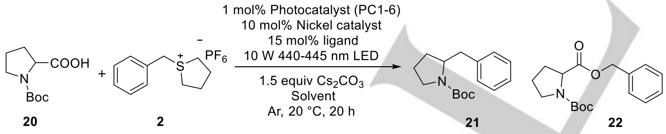
For the optimization of the dual photocatalytic coupling we examined the reaction of *N*-Boc-proline and simple benzyltetrahydrotiophenium hexafluorophosphate under various reaction conditions. First, we examined the effect of transition metal based photocatalysts on the nickel catalyzed coupling.

Entry	**PC**[a]	**Ni catalyst, Ligand**	**Solvent**	**21 (%)**[b], [c]	**22 (%)**[b]
1[d]	PC1	Ni(glyme)Cl$_2$, bpy	DMF	0	100
2[e]	PC1	Ni(glyme)Cl$_2$, bpy	DMF	0	100
3	PC2	Ni(glyme)Cl$_2$, bpy	DMF	11	17
4	PC3	Ni(glyme)Cl$_2$, bpy	DMF	30	10
5	PC4	Ni(glyme)Cl$_2$, bpy	DMF	59	6
6	PC5	Ni(glyme)Cl$_2$, bpy	DMF	69	3

7	PC6	Ni(glyme)Cl$_2$, bpy	DMF	91	1
8[d]	PC6	Ni(glyme)Cl$_2$, bpy	DMF	71	0
9[f]	PC6	Ni(glyme)Cl$_2$, bpy	DMF	0	100
10	PC6	-	DMF	0	100
11	-	Ni(glyme)Cl$_2$, bpy	DMF	0	100
12	-	-	DMF	0	100
13[d], [g]	PC6	Ni(glyme)Cl$_2$, bpy	DMF	36	55
14	PC6	Ni(glyme)Cl$_2$, bpy	Dioxane	16	16
15	PC6	Ni(glyme)Cl$_2$, bpy	DME	85	1
16	**PC6**	**Ni(glyme)Cl$_2$, bpy**	**MeCN**	**100 (69)**	**0**

Table 1. Optimization of reaction conditions

17	PC6	Ni(dtBubpy)Cl$_2$	MeCN	63 (36)	15
18	PC6	Ni(dMeObpy)Cl$_2$	MeCN	41 (28)	16
19	PC6	Ni(bpy)Cl$_2$	MeCN	100 (68)	0
20	PC6	Ni(glyme)Cl$_2$, dtbbpy	MeCN	93 (50)	1
21	PC6	Ni(glyme)Cl$_2$, d(MeO)bpy	MeCN	68 (40)	8
22	**PC6**	**Ni(glyme)Cl$_2$, bpy**	**MeCN**	**100 (74)** [h]	**0**

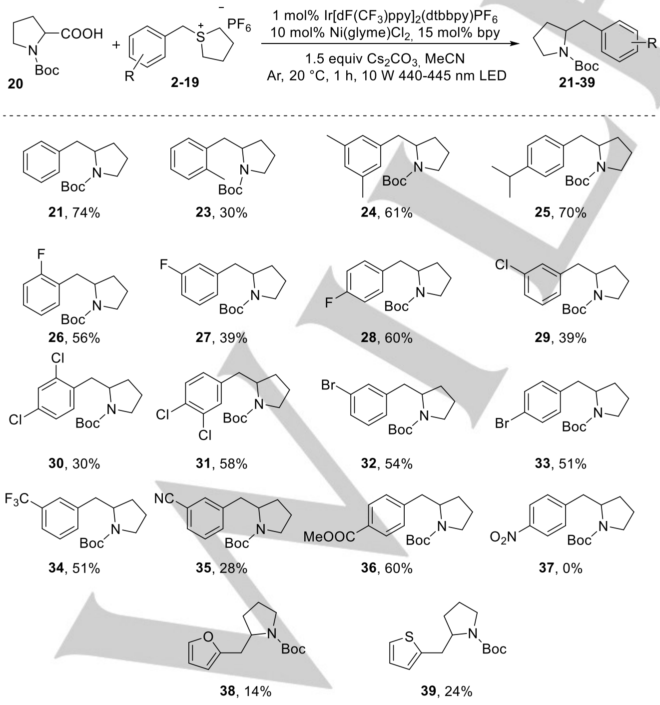


[a] PC: photocatalysts: PC 1: Ru(bpy)$_2$PF$_6$, PC 2: Ir(ppy)$_3$, PC 3: Ir[dtbppy]$_2$(dtbbpy)PF$_6$, PC 4: Ir(Fppy)$_3$, PC 5: Ir[dtbbpy](ppy)$_2$PF$_6$, PC 6: Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ [b] Conversions determined by GC-MS based on the consumption of proline [c] Preparative yields are in brackets [d] LED emission maximum: 460-470 nm [e] LED emission maximum: 520-525 nm [f] No LED irradtiation [g] Benzyl bromide was used instead of sulfonium salt [h] 1 hour reaction time instead of 20 hours

We carried out the coupling in the presence of 10 mol% Ni(glyme)Cl$_2$, 15 mol% 2,2'-bipyridyl ligand and 1.5 equiv Cs$_2$CO$_3$ base in DMF solvent under argon atmosphere using LEDs with different wavelength (Table 1.). In case of Ru(bpy)$_3$PF$_6$ we did not observe the formation of the desired benzylpyrrolidine (**21**), only the benzyl ester of *N*-Boc-proline (**22**) was formed, demonstrating the lack of photocatalytic decarboxylation step and the formation of the heterocyclic radical (Entries 1-2). Based on the potentials and stability, it was expected, that the iridium based photocatalyst proved to be more applicable in this transformation. However the ligands connected to the metal center had a great impact on the conversion rate. Among the tested five different iridium complexes the most successful photocatalyst was Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ complex, which ensured 91% conversion of **21** after 20 hours reaction time, and the reaction mixture contained only 1% of the benzyl ester side product (**22,** Entry 7). The utilization of other iridium photocatalysts showed lower photocatalytic activity and provided the desired coupled product in lower efficiency. In parallel, the lower conversion resulted the formation of ester **22** in higher amount (entries 3-6). Changing royal blue (440-445 nm) LED to the blue (460-470 nm) chip we observed 71% conversion after 20 hours reaction time (Entry 8). Next, we examined the dual photocatalytic nature of the transformation, and we found that the reaction did not take place in the absence of photocatalyst, nickel complex or light irradiation (Entries 9-12). In each case only the appropriate ester formation occurred, demonstrating the lack of photocatalytic activity and coupling cycle. When the reaction was performed with benzyl bromide instead of the sulfonium salt (**2**), we observed that the esterification of proline is faster and **22** formed in greater amount (91:1 vs. 36:55, Entries 7 and 13).

The results were very promising, and we continued the optimization study with the screening of different solvents. While dimethylformamide (DMF) seemed like a good solvent for the reaction, we did not reach full conversion. Among the tested solvents (1,4-dioxane, 1,2-dimethoxyethane and acetonitrile) acetonitrile proved to the best reaction media. The conversion of proline in MeCN after 20 hours was 100% and we did not observe the formation of ester **22.** After the workup of the reaction mixture 2-benzylpyrrolidine was isolated in 69% yield (Entry 16). In order to improve further the efficiency of the optimized reaction we studied the effect of the Ni catalyst on the photocatalytic coupling. In our comparative study different ligands and nickel sources were examined. Among the nickel-bipyridyl complexes the simple unsubstituted bipyridyl-nickel complex provided the higher conversion and yield (Entry 19, 68% isolated yield). The similar reactivity trend was observed when we generated the nickel complex *in situ* from Ni(glyme)Cl$_2$ and the appropriate bipyridyl ligand (Entries 20 and 21). Finally, the best catalytic condition was applied in a shorter reaction time in the presence of 2,2’-bipyridyl ligand, the Ni-Ir dual system provided the highest yield of the desired product **21** (74%) in reduced, 1 hour reaction time (Entry 22).

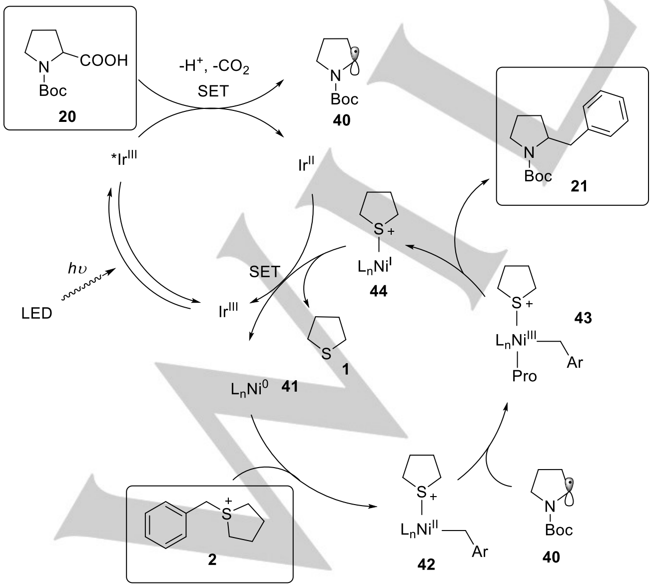
With the optimized reaction conditions in hand, and after the first successful isolation of product **21** with 74% yield, we begun to explore the scope of the decarboxylative benzylation reactions. Benzylsulfonium salts having alkyl substituents in the aromatic core reacted smoothly with *N*-Boc-proline under the optimized reaction conditions and provided the appropriate products **23**, **24** and **25** in 30%, 61% and 70% yield respectively. The reactivity pattern revealed that the steric factors determines the efficiency of the reaction, and the *ortho* substituted benzyl derivative gave lower yield compared to the other reagents. Next, halogenated benzylsulfonium salts were used for the photocatalyzed transformation of *N*-Boc-proline. The coupling of these substrates could be challenging due to the tendency of oxidative addition reaction between the aryl halide and the nickel catalyst. We demonstrated that F, Cl, and Br function are compatible with the reaction conditions and the desired benzylpyrrolidines (**26**-**33**) were isolated in 30-60% yield when the appropriate sulfonium salts were subjected to photocatalyzed transformation. The lowest yield (30%) was observed when the large chloro atom was in the *ortho* position in the benzylsulfonium salt. Some of the halogenated products are ready for further transformation via transition metal catalyzed cross-coupling reactions.



Scheme 2. The scope of the photochemical reaction

Among the electron withdrawing groups CF$_3$, CN, and COOMe was tolerated, and products **34**, **35**, **36** were isolated in 51%, 28%, 60% yield respectively. In contrast, the presence of strong electron withdrawing NO$_2$ group in the benzyl part completely shut down the reaction. Additionally, the coupling with heteroaryl sulfonium salts were successful, but products **38**, **39** were isolated only in 14% and 24% yield, probably due to the sensitivity and instability of the molecules.

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 3). It is established that the photoexcited Ir bearing high reducing potential (Ir(III) {$E_{1/2}^{red}$ [*Ir(III)/Ir(II)] = +1.21 V vs SCE in CH$_3$CN}[16] and initiates a SET reaction with the deprotonated Boc-proline [(Boc)-Pro-OCs, $E_{1/2}^{red}$ = +0.95 V vs. SCE in CH$_3$CN][17] 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**)[18] and participates in oxidative addition producing Ni(II) (**42**)[19]. 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**)[20]. Then another SET event occurs, simultaneously reducing the Ni(I) to Ni(0) ($E_{1/2}^{red}$[Ni(II)/Ni(0)] = −1.2 V vs SCE in DMF)[11] and oxidizing Ir(II) to Ir(III) {$E_{1/2}^{red}$ [Ir(III)/Ir(II)] = –1.37 V versus SCE in CH$_3$CN}[16] closing both catalytic circles at the same time.



Scheme 3. The proposed mechanism of the reaction

Conclusions

In summary, we developed a novel dual Ni-Ir photocatalyzed reaction for the synthesis of benzylpirrolidine derivatives from simple *N*-Boc-proline. We demonstrated for the first time that benzylsulfonium derivatives are applicable substrates of the photocatalyzed coupling. This finding could open new synthetic approaches to the construction of C(sp^3)-C(sp^3) bonds, and broaden the collection of available photoredox procedures. The optimized reaction conditions ensured the novel synthesis of versatile benzylpirrolidine compounds, which have high interest in the field of medicinal chemistry research.

Experimental Section

A 20 mL glass vial equipped with a magnetic stir bar and *N*-Boc-proline (86 mg, 0.40 mmol, 1.00 equiv), then the Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.5 mg, 0.004 mmol, 1 mol%), Ni(glyme)Cl$_2$ (8.8 mg, 0.04 mmol, 10 mol%), bpy (9.4 mg, 0.06 mmol, 15 mol%), the sulfonium salt (0.40 mmol, 1.00 equiv) and Cs$_2$CO$_3$ (200 mg, 0.60 mmol, 1.50 equiv) was measured in. The vial was sealed, evacuated and refilled with Ar three times. Then 20mL degassed anh. acetonitrile was added. The reaction vial was put into our photoreactor and stirred at 20 °C (for photoreactor setup see SI). After 1 hour the mixture was removed from the reactor. Ethyl acetate was added (20 ml) and the mixture was washed with sat. NaHCO$_3$ once then with brine. The organic phase was dried over anhydrous Na$_2$SO$_4$ then concentrated. The crude product was purified with column chromatography using silica gel, with a gradient of hexanes and ethyl acetate.

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Keywords: photoredox • sulfonium-salt • benzylpyrrolidine • cross-coupling • nickel• nickel

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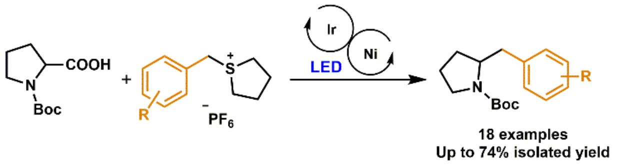
COMMUNICATION



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Photoredox catalysis

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Page No. – Page No.