CHEMISTRY
A European Journal

Accepted Article

Title: A Unified and Practical Method for Carbon-Heteroatom Cross-Coupling via Nickel/Photo Dual Catalysis

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This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Chem. Eur. J.* 10.1002/chem.202000052

Link to VoR: http://dx.doi.org/10.1002/chem.202000052

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# A Unified and Practical Method for Carbon-Heteroatom Cross-Coupling *via* Nickel/Photo Dual Catalysis

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Abstract: *While carbon-heteroatom cross coupling reactions have been extensively studied, many methods are specific and limited to a particular set of substrates or functional groups. Reported here is a general method that allows for C-O, C-N and C-S cross coupling reactions under one general set of conditions. We propose that an energy transfer pathway, in which an iridium photosensitizer produces an excited nickel (II) complex, is responsible for the key reductive elimination step that couples aryl bromides, iodides, and chlorides to 1° and 2° alcohols, amines, thiols, carbamates, and sulfonamides, and is amenable to scale up via a flow apparatus.*
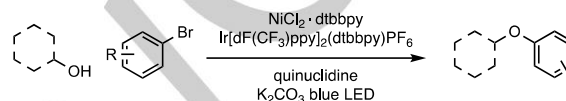
Carbon-heteroatom bond formation is a common disconnection in synthetic chemistry and the pharmaceutical industry.[1] Methods that furnish these bonds under mild conditions are appealing especially for late-stage cross coupling or functionalization of synthetic targets.[2] Transition-metal catalyzed cross-coupling reactions can facilitate C-O, C-S, and C-N bond formation and has been extensively investigated by numerous groups.[3] While the formation of these bonds have primarily involved the use of Pd and Cu catalysis, the advent of photocatalysis has added Ni as a viable option in the field.[4]

Nickel has the ability to access more oxidation states which allow for a wider range of chemical transformations.[5] However, the rate of carbon-heteroatom reductive elimination from Ni(II) in the ground state is known to be slow and several methods have successfully shown that this crucial mechanistic step could be achieved through manipulation of the oxidation states of the nickel (II) complex or the excitation of the nickel (II) complex *via* a dual transition metal catalytic manifold.[6] Our group at AstraZeneca have enabled C-S[7] and C-N[8] bond formation (Figure 1a) using the strongly oxidizing [Ir(dF(CF$_3$)ppy)$_3$(dtbbpy)]PF$_6$ photocatalyst which is proposed to directly oxidize the nucleophile to a radical that combines with a Ni(II) intermediate to generate the requisite Ni(III) species. Alternatively, the MacMillan group has employed the same [Ir(dF(CF$_3$)ppy)$_3$(dtbpy)]PF$_6$ photocatalyst to directly oxidize the Ni(II) complex to a higher energy Ni(III) complex to enable the reductive elimination step that couples alcohols with aryl halides to make C-O[9] bonds (Figure 1b).[9] They also employed the excitation of nickel (II) *via* energy transfer by an excited iridium photocatalyst to enable the reductive elimination step to couple carboxylic acids and sulfonamides with aryl halides to make C-O and C-N bonds (Figure 1c).[10] A number of groups have more recently described numerous elegant methodologies using this energy transfer transition-metal catalysis paradigm.[11] However, all of these methods have a limited substrate scope due to the reaction conditions and possibly due to the highly oxidizing redox potential of the photocatalyst. We believe there is still a need for a photoexcitation method that allows for a generalized substrate scope and the ability to readily access carbon-heteroatom bonds stemming from one method. Here we describe a method to form
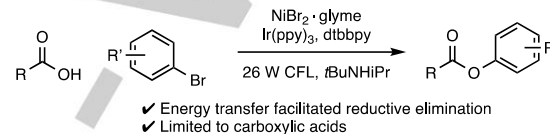

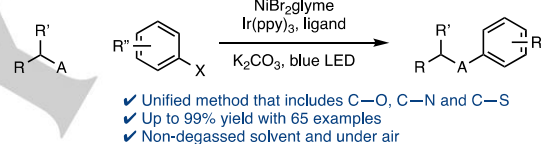a) *C-S* and *C-N* bond formation, our previous work (2016):
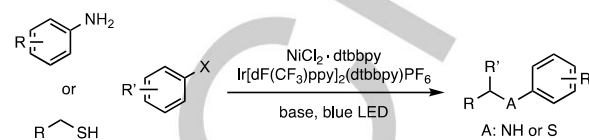
b) *C-O* bond formation from alcohols, MacMillan (2015):

c) *C-O* bond formation from carboxylic acids, MacMillan (2017):

✔ Energy transfer facilitated reductive elimination
✔ Limited to carboxylic acids

d) This work:

✔ Unified method that includes C—O, C—N and C—S
✔ Up to 99% yield with 65 examples
✔ Non-degassed solvent and under air

Figure 1. Cross coupling reactions *via* nickel/photo dual catalysis.

C-O, C-N, and C-S bonds under one catalytic manifold, without rigorous exclusion of oxygen, and under mild conditions (Figure 1d).

After an initial screen of conditions, (See Supporting Information) we started our investigation with benzyl alcohol **1a** (1.0 equiv.) and aryl halide **2a** (1.0 equiv.) as the model substrates; these were combined with 2 mol% of Ir(ppy)$_3$ as the photocatalyst, 5 mol% of NiBr$_2$•glyme, 10 mol% of dtbbpy **4a** as a ligand, and K$_2$CO$_3$ (2.0 equiv.) as a base in non-degassed DMF (0.3 M, 2.54 mL) under air. Irradiation with blue light for 18 hours at room temperature yielded the desired ether **3a** in 46% yield. (Table 1, entry 1) Further optimization was achieved by doing an extensive ligand screen. (See full ligand screen in the Supporting Information). When testing sterically demanding ligands, such as neocuprine, ferrocene ligands, or Buchwald ligands[12] **4b-4d** (Table 1, entries 2-4) no desired product was observed. When looking at the organic base TMEDA **4e** as a ligand, a diminished yield of 25% was observed (Table 1, entry 5). We next explored the electronics of the bipyridyl ligands *via* substitution on the 4-4' position (**4f-4h**). When going from the electron withdrawing group, CF$_3$ **4g**, to the nondonating H **4f** to the donating, OCH$_3$ **4h**, a dramatic increase in yield from 12% to >99% was observed (Table 1, entries 6-8). When the most donating N(CH$_3$)$_2$ **4i** was screened >99% yield was also observed (Table 1, entry 9). With the optimal conditions in hand (Table 1, entry 8) various control experiments were then performed.

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Table 1. Representative Ligand Screen.

Ligands:

R: *t*Bu **4a**, H **4f**, CF$_3$ **4g**, OCH$_3$ **4h**, N(CH$_3$)$_2$ **4i**

entry[a]	ligand	3a % yield[b]
1	4a	46%
2	4b	No Reaction
3	4c	No Reaction
4	4d	No Reaction
5	4e	25%
6	4f	27%
7	4g	12%
8	4h	>99%
9	4i	>99%

[a] Conditions: reactions were performed with **1a** (1 mmol, 1 equiv.), **2a** (1 mmol, 1 equiv.), NiBr$_2$•glyme (5 mol%), ligand (10 mol%), Ir(ppy)$_3$ (2 mol%) and K$_2$CO$_3$ (2 equiv.) in DMF (0.3 M) in a capped 1-dram vial under blue LED in a Hepato-chem reactor with a Kessil lamp with a fan (~50°C) and let stir for 18 hours. [b] Isolates yields.

Control experiments showed that nickel, photocatalyst (PC), blue light, and base were critical for the formation of the expected ether **3a** (Table 2). Additionally, organic bases such as TEA did not give any desired product, except DBU, which gave a 77% yield of the coupled product. Surprisingly, for aryl chloride **2b** under the optimized conditions, no reactivity was observed when K$_2$CO$_3$ was used; however, when Na$_2$CO$_3$ was used instead a modest yield of 61% was realized. Moreover, when Ni(COD)$_2$ was used as the nickel source a yield of 90% was observed, while use of Doyle's precatalyst[13] gave reduced yields. Finally, a photocatalyst screen was performed, including those with high oxidation potentials at the excited state, compared to Ir(ppy)$_3$ (E$_{1/2}$^{red} Ir(III)*/Ir(II) = +0.31 V),[3e] such as [Ir(dF(CF$_3$)ppy)$_3$(dtbpy)]PF$_6$ (E$_{1/2}$^{red} Ir(III)*/Ir(II) = +1.21 V)[3e] and [Ru(bpy)$_3$]Cl$_2$ (E$_{1/2}$^{red} Ru(II)*/Ru(I) = +0.77 V)[3e], and it was observed that such catalysts yielded no product. This implies that the preferred pathway may not involve a Ni (II) to Ni (III) oxidation that would be involved in a photoredox SET process. We then screened other photocatalysts that are known photosensitizers, such as other homoleptic Ir(III) catalysts, benzophenone, and a phenoxazine based photocatalyst designed to mimic the redox and triplet energy of Ir(ppy)$_3$ (E$_T$ = 53.6 kcal/mol for Ir(ppy)$_3$; (E^0$_{ox}$ = +0.41 V, E$_T$ = 46.7 kcal/mol for phenoxazine).[14] All of these photocatalysts yielded the desired ether **3a**, notably, when phenoxazine was used as the photocatalyst quantitative yields

Table 2. C-O coupling control experiments.

entry[a]	conditions	3a (%)[b]
1	as shown	99%
2	no blue light	No Reaction
3	no photocatalyst	No Reaction
4	no photocatalyst, no light	No Reaction
5	no photocatalyst, no light @ 70 °C	No Reaction
6	no nickel	No Reaction
7	no base	No Reaction
8	no ligand	20%
9	TEA instead of K$_2$CO$_3$	No Reaction
10	DBU instead of K$_2$CO$_3$	77%
11	Halide **2b** instead of **2a**	No Reaction
12	Halide **2c** instead of **2a**	99%
13	Halide **2b** with Na$_2$CO$_3$ as base	61%
14	Ni(COD)$_2$ as Ni source	90%
15	Doyle's precatalyst as Ni source	75%
16	[Ir(dF(CF$_3$)ppy)$_2$(dtbpy)]$^+$ as PC	No Reaction
17	Benzophenone as PC	10%
18	Phenoxazine as PC	99%

[a] Conditions: reactions were performed with **1a** (1 mmol, 1 equiv.), **2a** (1 mmol, 1 equiv.), NiBr$_2$•glyme (5 mol%), ligand (10 mol%), Ir(ppy)$_3$ (2 mol%) and K$_2$CO$_3$ (2 equiv.) in DMF (0.3 M) in a capped 1-dram vial under blue LED in a Hepato-chem reactor with a Kessil lamp without a fan (~50°C) and let stir for 18 hours. [b] Isolates yields.

were also observed. (See full photocatalyst screen in the Supporting Information).

Based on our control experiments and ligand and photocatalyst screens, we hypothesize that an energy transfer pathway is responsible for the cross coupling reaction. Reductive elimination from an excited nickel (II) complex is essential for the efficiency of the catalytic cycle. With this in mind, we hypothesize that the strong electron donating capabilities of ligand **4h** and **4i**

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allows for a stabilized nickel (II) complex in the ground or excited state that may facilitate the energy transfer between the iridium PC and the nickel (II) complex. We believe that the donating ligand may improve the molecular orbital overlap between the ground state nickel (II) complex and excited iridium species allowing for facile energy transfer. Follow-up spectroscopic and computational studies are actively being performed exploring the effect the ligand has on the triplet energy and frontier molecular orbitals and mechanism of this transformation.

In order to further explore the proposed idea of a energy transfer facilitated reductive elimination step, a stoichiometric reaction was performed. (Figure 2a) Since the nickel (II) complex with benzyl alcohol **6** is not bench stable, the reaction was performed in a one-pot stepwise fashion. The reaction was started by dissolving Doyle's pre-catalyst **5** in DMF and left to stir for 4 hours at room temperature with ligand **4h.** After the pre-stir, benzyl alcohol **1a** was added along with Ir(ppy)$_3$ and irradiated with blue light for 18 hours to yield the expected ether **7** in a satisfactory yield of 60% without any stoichiometric oxidant. It should be noted that a reaction without the prestir and ligand **4h** was attempted and a lower yield of 35% was observed, which is consistent with the lower yield observed with ligand **4e** in our initial ligand screen (Table 1, entry 5).

Based on the control experiments and the stoichiometric reaction, we propose an energy transfer mechanism for this reaction. (Figure 2b) We believe the reaction starts with the generation of Ni(0) **8,** which then undergoes an oxidative addition with the aryl halide **9** to form the Ni(II)-aryl halide complex **10.** This complex performs a ligand exchange with the alcohol **11** to generate the Ni(II)-aryl alcohol complex **12** as the catalytic resting state. Irradiation of the iridium (III) photocatalyst with blue light produces a long-lived triplet photoexcited iridium (III). Based on our results and precedent set by MacMillan's previously reported methods[10], we propose that the excited iridium (III) will perform an energy transfer with the Ni(II)-aryl alcohol complex **12** to obtain the excited Ni(II)-aryl alcohol complex **13** and the ground state iridium (III)**.** The excited species **13** will readily undergo a reductive elimination to furnish the expected ether **14** and regenerate Ni(0) **8.**

With optimal conditions in hand and further understanding of the mechanism, we set out to explore the scope of the reaction. First, we decided to probe our photocatalytic method by varying the electronics of the benzyl alcohol (Figure 3). Gratifyingly, both the electron rich and electron poor benzyl alcohols gave satisfactory yields when coupled with the model aryl halide **2a.** However, the carboxylic acid substrate **1g** gave diminished yields, possibly due to the competing coupling pathways between the between the alcohol and the carboxylic acid.[3e] Heterocycles such as thiophene **1s** and furan **1t** were also tolerated under the established conditions. Aliphatic alcohols such as ethanol **1w** and trifluoroethanol **1x** were also screened and the expected ethers were isolated in moderate yields. Additionally, secondary alcohols including isopropanol **1y,** cyclohexanol **1z** and cyclobutanol **1ab** yielded the desired product, albeit, longer stir periods were necessary. Coupling of water **1af** was also observed which could explain the diminished yield when using the hydrated nickel source (See Supporting Information).

Other nucleophiles were attempted such as thiols and amines **1ag-1ap** and we were pleased to see that the respective products were observed using the same method without further optimization. Anilines functionalized at the 4-position were

a) Stoichiometric Reaction with ligand 4h:
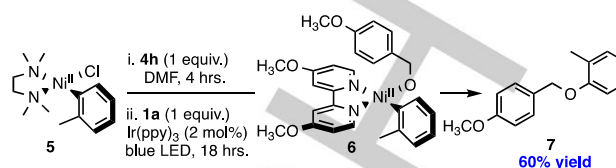

b) Proposed Energy Transfer Mechanism:
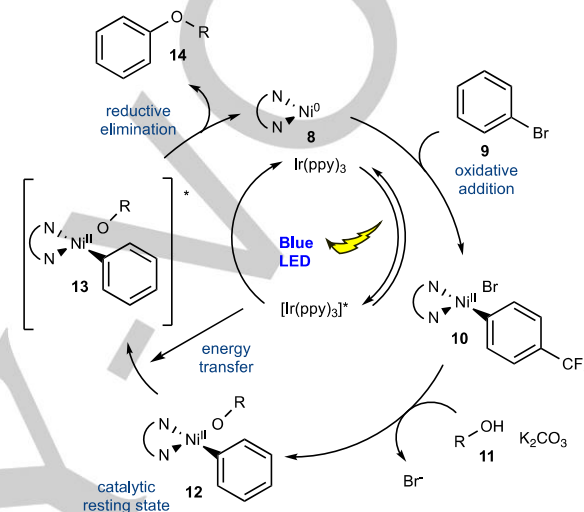
Figure 2. a) Reductive elimination readily occurs with blue LED and Ir(ppy)$_3$ alone without stoichiometric oxidant. **b)** Proposed catalytic cycle for the coupling of alcohols and aryl halides.

screened with varying electron donating capabilities and the products were isolated in moderate to excellent yield. Furthermore, the coupling of thiols under standard reaction conditions gave the expected products in high yield. Protected anilines were also synthesized in excellent yields from sulfonamides **1aq**, benzamide **1ar**, and carbamates **1al-1au** allowing for the installment of protected amines that could be used for further functionalization. Aliphatic amines and thiols were also screened as nucleophiles and good to excellent yields were observed **1av-1az.** Coupling of ammonia **1ba** was also noted to have synthetically useful yields to make functionalized anilines.

The scope of the aryl bromides was explored with the intention of showing a tolerability to activated and non-activated halides (Figure 4). We were able to show that, in general, most activated halides yielded 90% or above even when the substitution was at the meta- position on the aryl ring **2r**. It should be noted that if the bromide is switched to the iodide the reaction times are decreased significantly. Inversely, when the bromide is switched to the chloride we see a dramatic decrease in reactivity. To further demonstrate this halide selectivity, bis-halide **2o** gave 90% yield of product coupled through the bromide, while bis-halide **2p** gave 95% yield of product coupled at the iodide. Electron-rich bromides yielded moderate amounts of the expected product only if let stir for 36 hours. Selectivity towards the primary alcohol over aniline was also highlighted with bromoaniline **2t,** 70% yield of the product was isolated. Halogenated hetero-arenes were also screened. Pyridine **2v,** pyrimidine **2w**, and thiazole **2z** coupled under the optimized conditions and furnished the respective product in moderate

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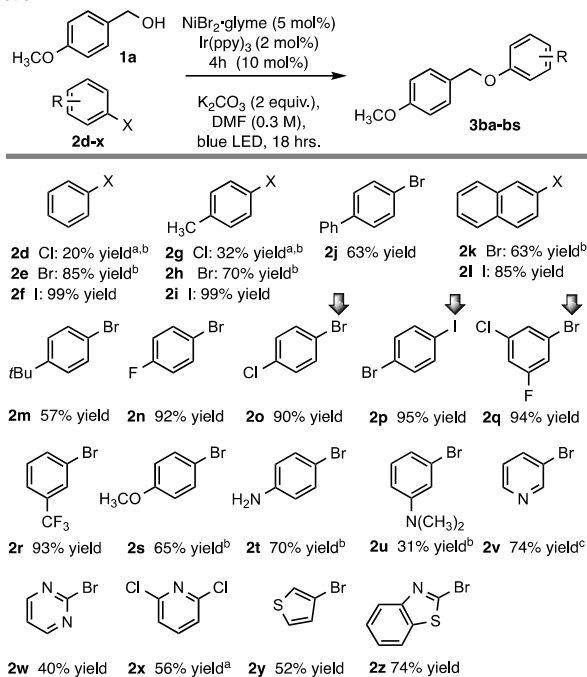**Figure 3.** Nucleophile scope for the nickel/iridium dual catalyzed cross-coupling reaction.
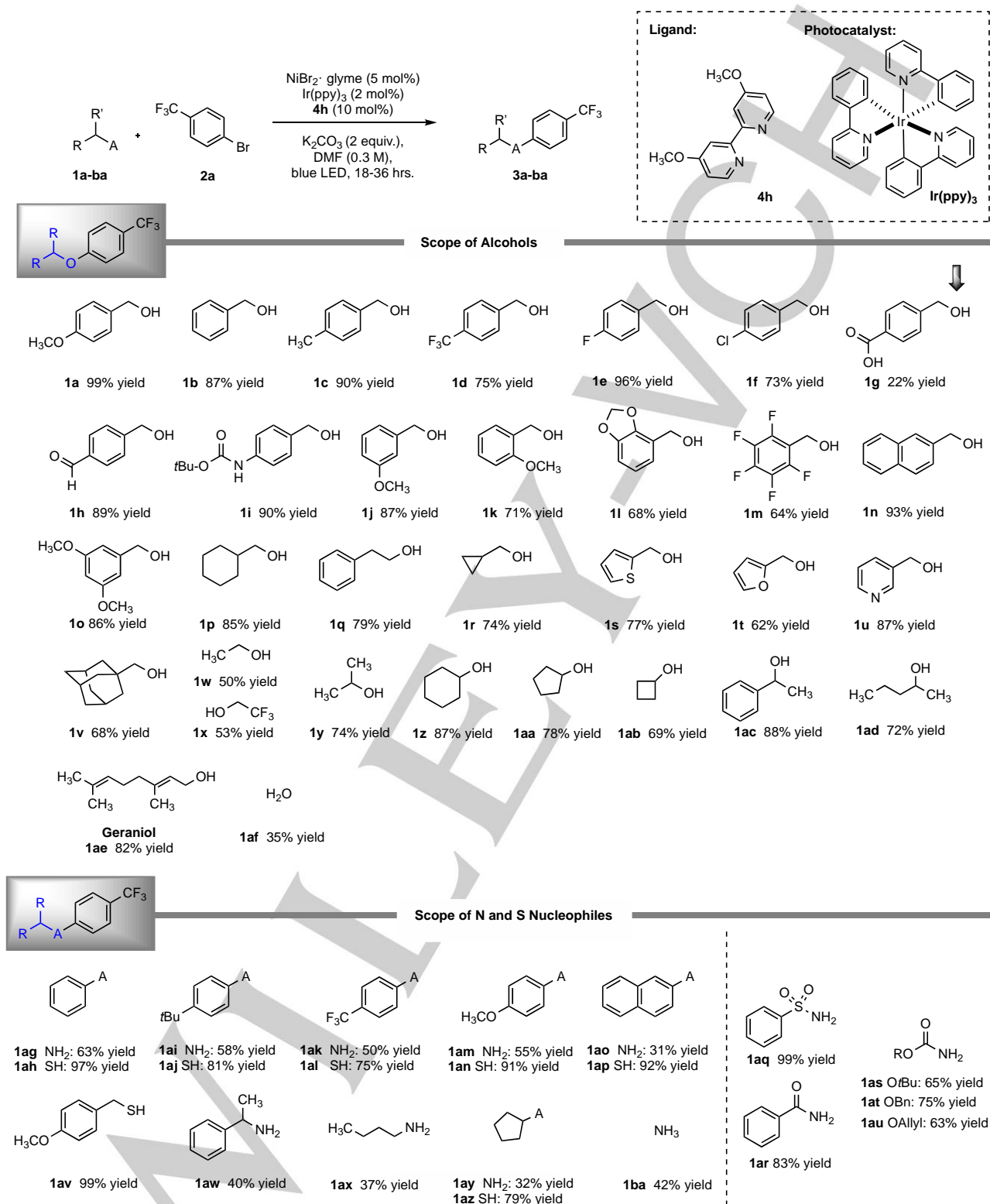
Conditions: reactions were performed with (1 mmol, 1 equiv.) of the nucleophile, (1 mmol, 1 equiv.) of the aryl halide, NiBr$_2$•glyme (5 mol%), ligand **4h** (10 mol%), Ir(ppy)$_3$ (2 mol%) and K$_2$CO$_3$ (2 equiv.) in DMF (0.3 M) in a capped 1-dram *vial* under blue LED in a Hepatochem reactor with a Kessil lamp without a fan (~50°C) and let stir for 18 - 36 hours. All reported yields are isolated.

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re 4. Electrophile scope for the nickel/iridium dual catalyzed cross-coupling reaction.

2d Cl: 20% yield[a,b]
2e Br: 85% yield[b]
2f I: 99% yield

2g Cl: 32% yield[a,b]
2h Br: 70% yield[b]
2i I: 99% yield

2j 63% yield

2k Br: 63% yield[b]
2l I: 85% yield

2m 57% yield   **2n** 92% yield   **2o** 90% yield   **2p** 95% yield   **2q** 94% yield

2r 93% yield   **2s** 65% yield[b]   **2t** 70% yield[b]   **2u** 31% yield[b]   **2v** 74% yield[c]

2w 40% yield   **2x** 56% yield[a]   **2y** 52% yield   **2z** 74% yield

Conditions: reactions were performed with (1 mmol, 1 equiv.) of nucleophile **1a**, (1 mmol, 1 equiv.) of the aryl halide, NiBr$_2$•glyme (5 mol%), ligand **4h** (10 mol%), Ir(ppy)$_3$ (2 mol%) and K$_2$CO$_3$ (2 equiv.) in DMF (0.3 M) in a capped 1-dram *vial* under blue LED in a Hepatochem reactor with a Kessil lamp without a fan (~50°C) and let stir for 18 - 36 hours. All reported yields are isolated. [a] Na$_2$CO$_3$ was used as the base. [b] Reactions were let stir for 36 hours. [c] Ligand **4i** was used instead of **4h**.

yields. Interestingly, when the ligand 4i was used with the pyridine **2v** a significant increase in yield is observed.

Then we turned our attention towards the scalability of the reaction. Unfortunately, when scaling up a photochemical reaction in batch, the light penetration in a round-bottom flask is of concern. It was then decided to attempt optimization of our model reaction in flow using a Vaportech flow apparatus (See Supporting Information). Due to the heterogeneity of the optimized conditions caused by the K$_2$CO$_3$, it was decided to use the DBU as the base, which afforded a batch reaction yield of 77% at 1 mmol scale (Table 2, entry 10) and a complete homogenized solution under the reaction conditions when using our model substrates **1a** and **2a**. After doing some preliminary optimization, it was noted that when using a retention time (t$_R$) of 15 min, with a flow rate of 0.33 mL/min and a reactor temperature of 45 °C, the reaction could be successfully scaled up to 5 mmol with a synthetically useful yield of 45% (Table 3, entry 3). It should also be noted that the catalyst loading was decreased for both the Ir(ppy)$_3$ and NiBr$_2$•glyme from 2 mol% and 5 mol% to 1 mol% and 2 mol%. Due to the volume capabilities of our photoreactor, we could not increase the residence time to allow for higher yields but nevertheless these preliminary results indicate that with the proper flow apparatus, this reaction could be further scaled.

Herein, we described an optimized method in which a carbon-alcohol coupling was achieved *via* excitation of a nickel (II) complex by a commercially available iridium (III) photocatalyst. The method was also able to successfully furnish

Table 3. Optimization of the nickel/iridium dual catalyzed cross-coupling reaction in flow for scalability studies.

entry	temp (°C)	t$_R$ (min)	flow rate (mL/min)	scale (mmol)	yield (%)
1	35	15	0.33	2.5	37
2	50	10	0.50	2.5	NR
3	45	15	0.33	5.0	45

C-N, and C-S bonds without the need for any further optimization or modification to the reaction conditions and allows for activated and non-activated aryl halides as coupling partners. These results along with the control experiments and the stoichiometric reaction supports our proposed mechanism in which the iridium performs a triplet-triplet energy transfer to facilitate the otherwise disfavored reductive elimination to furnish the desired product. We envision this method could be widely applied for a variety of synthetic targets in total synthesis or in the pharmaceutical industry due to its robustness, mild conditions and its ability to scale when used in a flow platform.

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