Carbon-Heteroatom Cross-Coupling *via* an Electronically Excited Nickel (II) Complex

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Supporting Information

ABSTRACT: While carbon-heteroatom cross coupling reactions have been extensively studied, many methods are specific and limited to a set of substrates or functional groups. Reported here is a method that allows for C-O, C-N and C-S cross coupling reactions under one general methodology. 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 halides to 1° and 2° alcohols, anilines, thiophenols, carbamates and sulfonamides.

Carbon-heteroatom bond formation is one of the most sought-after disconnections in synthetic chemistry and the pharmaceutical industry.¹ Methods that furnish these bonds under mild conditions are appealing especially for late-stage functionalization of synthetic targets.² Transition-metal-catalyzed cross-coupling reactions have been used to achieve C-O, C-S, and C-N bond formations famously displayed by Buchwald, MacMillan, Hartwig, and many other 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.

Nickel has the ability to access more oxidation states which allow for a wider range of chemical transformations.⁵ However,

a) C-O bond formation, MacMillan 2017:

b) C-N bond formation, MacMillan 2018:

c) This work:

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 or the excitation of the nickel (II) complex *via* a dual transition metal catalytic manifold.⁶ The Macmillan group employed 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 bonds⁷ (Figure 1a-b). A number of groups have more recently described numerous elegant methodologies using this energy transfer transition-metal catalysis paradigm.⁸ Nevertheless, 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 C-O, C-N, and C-S bonds under one catalyzed manifold, without rigorous exclusion of oxygen and under mild conditions (Figure 1c).

After doing 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 NiBr₂·glyme, 10 mol% of dtbbpy **4a** as a ligand, and K₂CO₃ (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 ligands⁹ **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). At this point, other 2-2'-bipyridine ligands were screened and a strong correlation to electronics was observed when varying the

Figure 1. Cross coupling reactions *via* an electronically excited nickel (II) complex.

Table 1. Representative Ligand Screen.

Ligands:

4b: 2,2'-bipyridine
 4c: 1,1'-bis(dicyclophosphino)ethane
 4d: (Ph)₂P(Ph)N(CH₃)₂
 4e: 1,1'-bis(dicyclophosphino)ethane
 4f: R: tBu
 4g: R: H
 4h: R: OCH₃

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%

^aConditions: reactions were performed with **1a** (1 mmol, 1 equiv.), **2a** (1 mmol, 1 equiv.), NiBr₂·glyme (5 mol%), ligand (10 mol%), Ir(ppy)₃ (2 mol%) and K₂CO₃ (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 and let stir for 18 hours.

^bIsolated yields.

Table 2. C-O coupling control experiments.

entry ^a	conditions ^b	3a (%) ^{c,d}
1	as shown	99%
2	no blue light	N.R.
3	no PC	N.R.
4	no PC, no light	N.R.
5	no PC, no light @ 70 °C	N.R.
6	no nickel	N.R.
7	no base	N.R.
8	no ligand	20%
9	TEA instead of K ₂ CO ₃	N.R.
10	DBU instead of K ₂ CO ₃	77%
11	NiBr ₂ ·3H ₂ O as Ni source	45%
12	Doyle's precatalyst as Ni source	75%
13	[Ir(dF(CF ₃)ppy) ₂ (dtbpy)] ⁺ as PC	NR
14	benzophenone as PC	10%

^aConditions: reactions were performed with **1a** (1 mmol, 1 equiv.), **2a** (1 mmol, 1 equiv.), Ni source (5 mol%), ligand **4d** (10 mol%), photocatalyst (2 mol%) and the base (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 and let stir for 18 hours.

^bPC = photocatalyst ^cIsolated yields. ^dN.R. = No Reaction

Figure 2. a) Reductive elimination readily occurs with blue LED and Ir(ppy)₃ alone. b) Proposed catalytic cycle for the coupling of alcohols and aryl halides.

substitution on the 4-4' position on the bipyridine **4f-4h**. When going from the electron withdrawing group, CF₃ **4g**, to the non-donating H **4f** to the most donating, OCH₃ **4h**, a dramatic increase in yield from 12% to >99% was observed (Table 1, entries 6-8). This trend could be attributed to the strong electron donating capabilities of ligand **4d** allowing for a stabilized nickel (II) complex in the ground or excited state. With the optimal conditions in hand (Table 1, entry 8) various control experiments were then performed to verify our proposed pathway.

At this point, we sought to evaluate our hypothesis that an energy-transfer pathway is the operative pathway in our proposed method. Control experiments showed that nickel, PC, blue light and base were critical in the formation of the expected ether **3a** (Table 2). Moreover, different sources of nickel such as NiBr₂·3H₂O and Doyle's precatalyst¹⁰ gave reduced yields (Table 2, entry 11-12). Additionally, organic bases such as TEA did not give any desired product, except DBU, which gave a 77% yield of the coupled product. Similar to a trend observed by MacMillan and coworkers⁸, the yield of product is inversely related to the oxidizing power of the photocatalyst, which suggests that the preferred pathway does not involve the Ni (II) to Ni (III) change in oxidation state that would be involved in a photoredox SET process (See full photocatalyst screen in the Supporting information).

In order to further explore the reductive elimination step of the transformation, 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%. It should be noted that a reaction without the prestir and ligand **4h** was attempted and a lower yield of 35%

Figure 3. Substrate 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, $\text{NiBr}_2 \cdot \text{glyme}$ (5 mol%), ligand **4d** (10 mol%), $\text{Ir}(\text{ppy})_3$ (2 mol%) and K_2CO_3 (2 equiv.) in DMF (0.3 M) in a capped 1-dram vial under blue LED in a Hepatochem reactor with a Hepatochem reactor with a Kessil lamp without a fan and let stir for 18 - 36 hours. All reported yields are isolated. ^aReactions were let stir for 36 hours.

was observed, which is consistent with the poor yield with lig- and **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**, (see our proposed Ni(II)-Ni(0) catalytic cycle in the Supplementary Information) 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 deprotonated 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 MacMillan's previously reported methods, 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 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 and this is attributed to the competing coupling pathways between the alcohol and the carboxylic acid, which is displayed as a substrate in MacMillan's method.^{7b} 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. Then secondary alcohols including isopropanol **1y** and cyclohexanol **1aa** yielded the desired product, albeit, longer stir periods were necessary. Additionally, coupling of water **1ab** was also observed which could explain the diminished yield when using the hydrated nickel source (Table 2, entry 11).

Other nucleophiles were attempted such as thiols and amines **1ac-1al** 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 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 sulfonamide **1am**, benzamide **1an**, and carbamates **1ao-1aq** allowing for the installment of protected amines that could be used for further functionalization.

The scope of the aryl bromides was explored with the intention of showing a tolerability to activated and non-activated halides. 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 **2o**. Electron-rich bromides yielded moderate amounts of the expected product only if let stir for 36 hours. It should be noted that if the bromide is switched to the iodide the reaction times are decreased significantly. However, when other electrophiles such as chlorides or triflates were attempted no reactivity was observed (See Supporting Information). To further demonstrate this halide selectivity, bis-halide **2e** gave 90% yield of product coupled through the bromide, while bis-halide **2f** gave 95% yield of product

coupled at the iodide. Selectivity towards the primary alcohol over aniline was also highlighted with bromoaniline **2k**, 70% yield of the product was isolated. Brominated hetero-arenes were also screened. Pyridine **2l** and pyrimidine **2m** coupled under the optimized conditions and furnished the respective product in moderate yields.

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

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

General experimental detail, procedures, and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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