Dual Catalysis

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Highly Chemoselective Iridium Photoredox and Nickel Catalysis for the Cross-Coupling of Primary Aryl Amines with Aryl Halides

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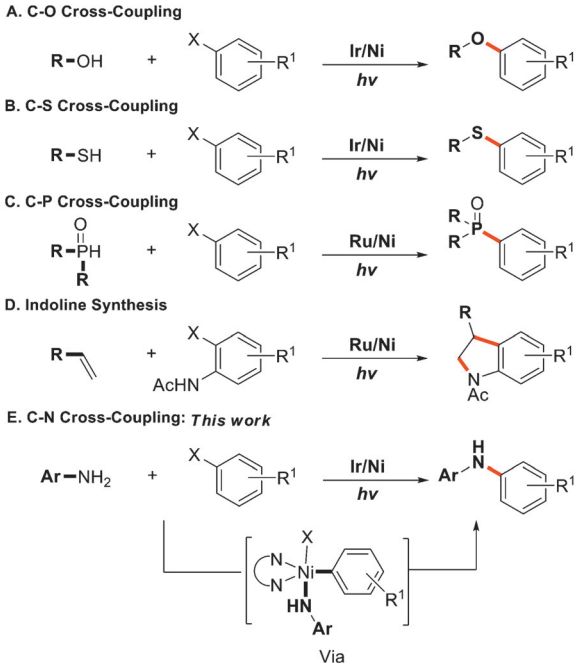
Abstract: *A visible-light-promoted iridium photoredox and nickel dual-catalyzed cross-coupling procedure for the formation C–N bonds has been developed. With this method, various aryl amines were chemoselectively cross-coupled with electronically and sterically diverse aryl iodides and bromides to forge the corresponding C–N bonds, which are of high interest to the pharmaceutical industries. Aryl iodides were found to be a more efficient electrophilic coupling partner. The coupling reactions were carried out at room temperature without the rigorous exclusion of molecular oxygen, thus making this newly developed Ir-photoredox/Ni dual-catalyzed procedure very mild and operationally simple.*

The strategic combination of a photoredox catalyst with a transition-metal cross-coupling catalyst in chemical synthesis has seen a remarkable "renaissance" in recent years.[1] The hallmark of this dual-catalytic platform is the systematic modulation of transition-metal oxidation states by a photoredox catalyst through single-electron-transfer (SET) processes.[2] This redox-controlled strategy has not only enabled easy access to previously elusive reaction mechanisms, but also enhanced the efficiency of known chemical transformations.[1–3] Cross-coupling conditions employed under dual catalysis are generally very mild and bond formation proceeds with exceptionally high chemoselectivity and remarkable functional group tolerance,[1–3] thus inspiring our continued interest in this new approach to cross-coupling.

Aryl amines are highly valued motifs with important structural, electronic, and mechanical properties in drug molecules.[4] Transition-metal-catalyzed coupling of amines with aryl halides (and pseudohalides) remains the most versatile and direct method of synthesizing aryl amines, with Pd catalysis as the most developed synthetic approach.[5] Despite the tremendous advances that have been made in Pd-catalyzed C–N cross-coupling reactions, forging C–N bonds in a general fashion through Ni catalysis has proven challenging. Decreased cost, highly chemoselective mediation of radical reactions, and modular redox properties are key advantages of Ni catalysis over Pd catalysis. By exploring the modular redox properties of Ni, MacMillan and co-workers developed an Ir-photoredox/Ni dual-catalyzed C–O cross-coupling method for the synthesis of aryl ethers (Scheme 1 A).[3] Our group has also developed an Ir-photoredox/Ni dual-catalyzed C–S cross-coupling method, which gave access to a large library of thioethers (Scheme 1 B).[6] A remarkable photoredox/Ni dual-catalyzed C–P cross-coupling method has also been developed by Xiao and co-workers (Scheme 1 C).[2f] Similarly, Jamison and Tasker reported an elegant photoredox/Ni dual-catalyzed annulation approach for the synthesis of indolines (Scheme 1 D).[2c]



Scheme 1. Photoredox/Ni dual-catalyzed coupling reactions involving heteroatoms and aryl halides.

Although there are existing reports on Ni-catalyzed methods for the amination of aryl halides, those conditions often require high temperatures and either air-sensitive Ni^0 sources or expensive Ni^{II} precursors with external reducing agents, such as zinc dust, NaH, *n*-BuLi, or MeMgBr, which are incompatible with many functional groups.[7] In addition, the mechanism of Ni-catalyzed C–N coupling is poorly under-

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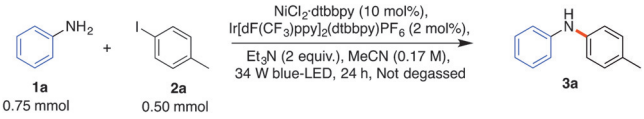
stood compared to its Pd counterpart. However, it is believed that the C–N bond-forming step involves the reductive elimination of a Ni^{III} species.[8] This mechanistic viewpoint stems from a seminal report by Koo and Hillhouse in which they showed that Ni^{II} aryl amido complexes do not undergo reductive elimination, even at elevated temperatures, and that oxidation of the Ni^{II} species into a higher energy Ni^{III} species by a stoichiometric oxidant is necessary to produce C–N bonds.[8] We therefore recognized that it should be possible to utilize Ir-photoredox/Ni dual catalysis to access the Ni^{III} amido aryl halide species that will undergo facile reductive elimination to form C–N bonds (Scheme 1 E). This strategy eliminates the stoichiometric oxidant and facilitates chemoselective C–N coupling reactions under mild conditions.

Herein, we demonstrate that Ir-photoredox/Ni dual catalysis can chemoselectively promote the cross-coupling of primary aromatic amines with aryl iodides and bromides to afford C–N bonds with broad functional group compatibility under very mild conditions.

Our initial efforts focused on the development and optimization of the catalysts and reaction conditions to effect the coupling of aniline (**1a**) and 4-iodotoluene (**2a**) (Table 1). To our delight, the desired coupled product 4-methyl-*N*-phenylaniline (**3a**) was obtained in 80% yield in the presence of $NiCl_2$·dtbbpy (10 mol%), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol%), and Et_3N (200 mol%) in MeCN (0.17 M) under blue LED irradiation at room temperature for 24 h (Table 1, entry 1; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl, $dF(CF_3)ppy$ = 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-*C*). A series of control experiments established the importance of light, the Ir catalyst, the Ni complex, and Et_3N for the success of the reaction (Table 1, entries 1–9). Surprisingly, the coupling proceeded with good conversion in the absence of the dtbbpy ligand, which suggests that the aniline can also serve as a ligand (Table 1, entry 10). Interestingly, unlike in our previously developed Ir-photoredox/Ni dual-catalyzed C–S cross-coupling method, aryl bromides and the Ni^0 precatalyst, which is generated in situ from $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene) and dtbbpy, are competent in this C–N coupling (Table 1, entries 11–12). Blue LEDs are the optimal visible-light source for the C–N coupling and no coupling was observed under white-light (26 W CF lamp) irradiation (entry 13).[9] Although no cross-coupling occurred under green-LED irradiation (entry 14), irradiation with violet LEDs delivered the C–N coupled product (entry 15). Remarkably, the presence of molecular oxygen does not affect the efficiency of the C–N cross-coupling (Table 1, entries 1 and 16).[6,9] Efficient coupling without rigorous degassing further underscores the practical utility of this newly developed C–N bond-forming method.

Having identified the optimal reaction conditions, we explored the substrate scope of the C–N cross-coupling procedure (Table 2). Sterically hindered aryl iodides bearing methoxy, fluoro, and methyl groups at the *ortho* position underwent cross-coupling to form C–N bonds in good yields (**3b–3d**). Impressively, electron-rich and electron-poor aryl iodides delivered C–N bonds with nearly identical yields (**3e–3h**). The high efficiency of C–N coupling in the presence of synthetically useful functional groups, such as fluoride (**3g**), chloride (**3h**), ketone (**3i**), carbamate (**3j**), ester (**3k**), aldehyde (**3l**), trifluoromethyl (**3m**), cyano (**3n**), and thio-

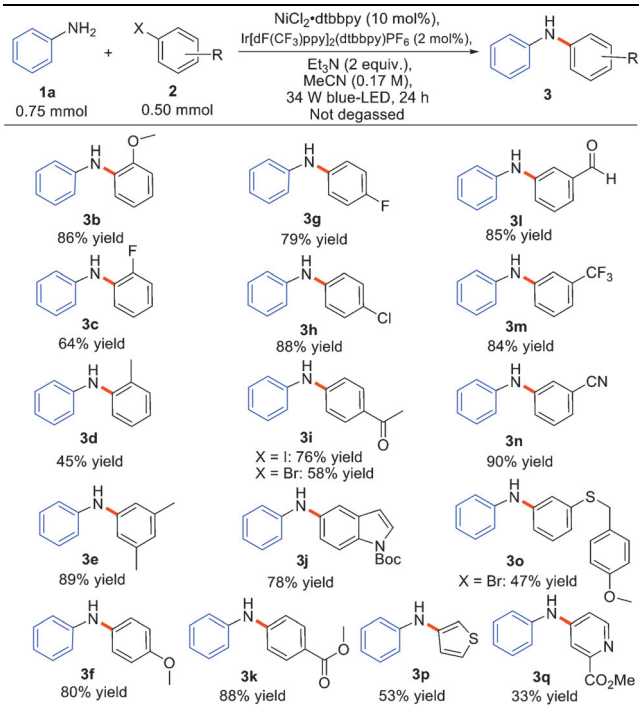
Table 1: Effect of variation of the reaction parameters and conditions on the reaction efficiency.



Entry	Variation from the standard conditions[a]	Conversion [%][b]
1	none	>95 (80%)
2	no light (dark)	0
3	no Ir^{III} catalyst	0
4	no $NiCl_2$·glyme and no dtbbpy	0
5	no Et_3N	0
6	KO*t*Bu instead of Et_3N	0
7	$KN(TMS)_2$ instead of Et_3N	0
8	1.5 equiv KO*t*Bu and 0.10 equiv Et_3N	<5
9	iPr_2EtN instead of Et_3N	80
10	no dtbbpy	80-85
11	4-bromotoluene instead of 4-iodotoluene	50
12	Ni^0·dtbbpy[c] instead of $NiCl_2$·dtbbpy	90
13	with a 26 W CF lamp	0
14	with 34 W green LEDs	0
15	with 34 W violet LEDs	70
16	degassed	>95 (80%)

[a] Reactions carried out in 3 mL of 99.8% MeCN (0.17 M). [b] Conversion % was determined by ^1H NMR spectroscopy with the aid of an internal standard. The yield of the isolated product after purification by column chromatography is given in parenthesis. [c] Generated in situ from $[Ni(cod)_2]$ and dtbbpy. TMS = trimethylsilyl.

Table 2: Scope of aryl halide coupling partner.[a]

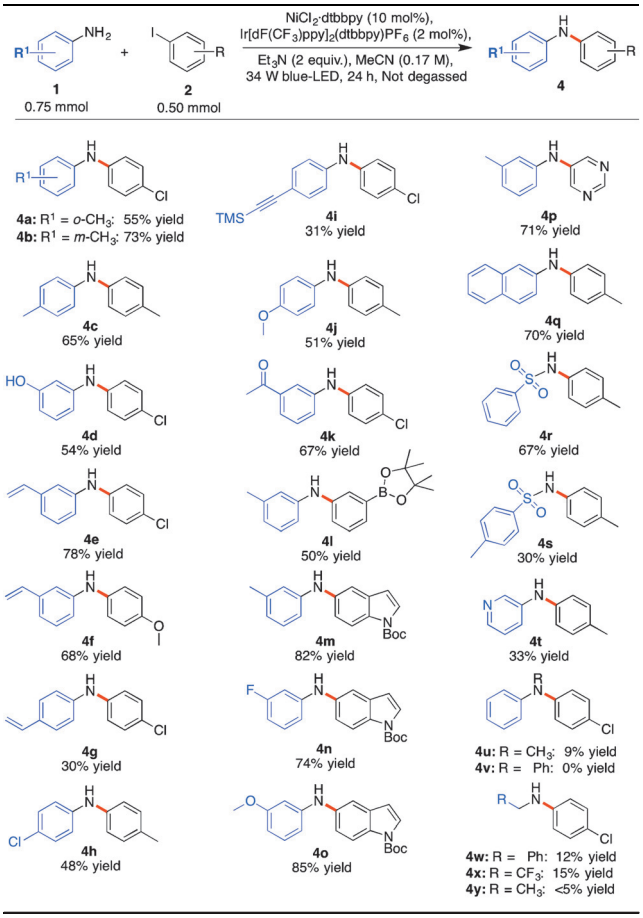


[a] Unless otherwise stated the aryl iodide was used. Boc = *tert*-butoxycarbonyl.

ether (**3o**) groups, demonstrates mild reaction conditions and high chemoselectivity. In addition, heteroaryl iodides underwent cross-coupling with aniline under these conditions (**3j**, **3p**, and **3q**). It is noteworthy that no subsequent coupling of secondary aryl amine products was detected in any of the reactions. However, the aryl iodides were fully consumed in all reactions and the mass balance is the reduced arenes (hydrodehalogenation reaction). Trace amounts of biaryl products were also detected in some of the reactions. The reduced and biaryl side-products indicate a mechanism involving aryl radicals (see below).

The aryl amine scope was also explored to gain further insight into this coupling reaction (Table 3). *Ortho*-, *meta*-, and *para*-methylanilines all coupled with both electron-poor and electron-rich aryl iodides to form new C–N bonds in

Table 3: Scope of aryl amine coupling partner.



moderate to good yields (**4a**–**4c**). Satisfactorily, anilines bearing synthetically versatile functional groups, such as hydroxy, vinyl, acetylene, chloro, methoxy, and acetyl groups, all engaged in chemoselective C–N cross-coupling with electronically diverse aryl iodides to deliver synthetically useful scaffolds (**4d**–**4k**). In addition, substituted anilines were cross-coupled with aryl iodides bearing useful functional groups, such as organoboronate (**4l**) and heteroaryl iodides (**4m**–**4p**), to give the desired products in good yields. A naphthylamine (**4q**) also competently engaged in the C–N cross-coupling reaction. Most importantly, the remarkable chemoselectivity demonstrated under this Ir-photoredox/Ni dual-catalysis will allow the orthogonal elaboration of the reactive functional groups as well as the subsequent cross-coupling of chloride, alkene, and organoboronate by means of conventional Pd or Ni catalysis.[5,7]

The exploration of primary aryl amines other than anilines that can efficiently cross-couple with aryl iodides under our optimized photoredox-mediated conditions revealed that sulfonamides (**4r**, **4s**) and 3-aminopyridine (**4t**) are competent amines.

The preference for primary over secondary amines under our conditions was further demonstrated by conducting the cross-coupling of 1-chloro-4-iodobenzene with both *N*-methylaniline and diphenylamine. In those reactions, little to no C–N coupling was detected (Table 3, **4u** and **4v**). We attribute the poor efficiency of secondary amines in this reaction to steric hindrance.

That being said, we observed that the electronic properties of aryl amines influenced the reaction efficiency. Specifically, *para*-substituted anilines and sulfonamides gave lower yields of C–N coupled products (**4g**–**4j**, **4s**).

Although additional mechanistic studies are ongoing in our laboratories, we propose the mechanism depicted in Figure 1. Visible-light irradiation of the heteroleptic $\mathbf{Ir^{III}}$ photocatalyst generates a long-lived excited $\mathbf{*Ir^{III}}$ species (lifetime $\tau = 2.35\ \mu s$).[6] Kinetic oxidation of the aniline

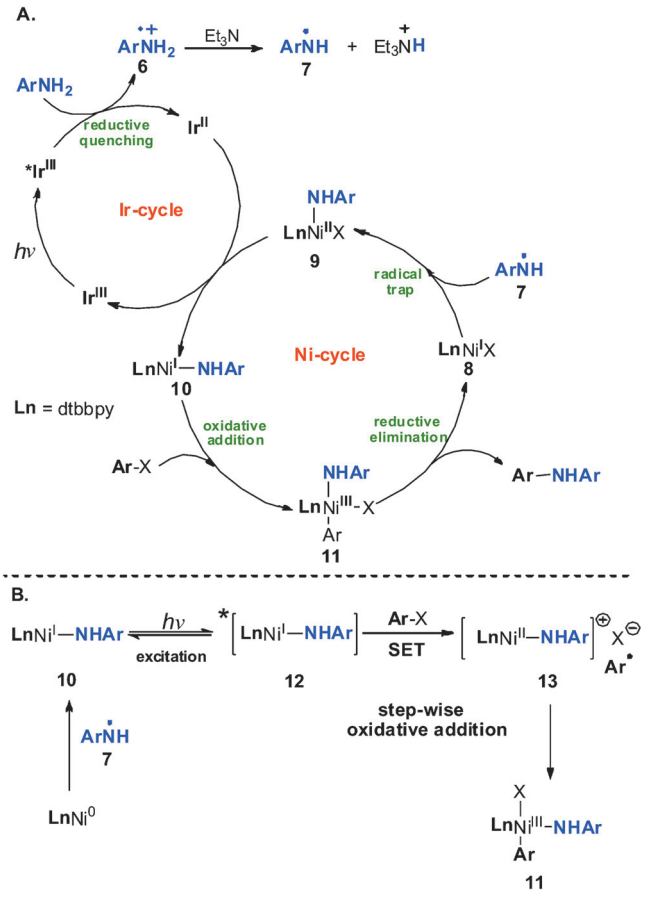


Figure 1. Proposed C–N coupling mechanism.

($E_{1/2}^{ox} = +0.80$ V versus the saturated calomel electrode (SCE))[10a] by the photoexcited *$\mathbf{Ir^{III}}$ species ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.21 V versus SCE)[11] produces both the aniline radical cation **6** and $\mathbf{Ir^{II}}$ (see the Supporting Information for emission quenching studies). Deprotonation of the aniline radical cation **6** ($pK_a = 7.1$)[10a] by Et_3N ($pK_a = 11$)[10b] then produces the aniline radical **7**. SET reduction of $NiCl_2$·dtbbpy ($E_{1/2}^{red}$ [Ni^{II}/Ni^{I}] = −1.34 V versus SCE)[6] by $\mathbf{Ir^{II}}$ ($E_{1/2}^{red}$ [Ir^{III}/Ir^{II}] = −1.37 V versus SCE)[11] will initially regenerate the $\mathbf{Ir^{III}}$ photocatalyst and deliver the Ni^{I}–halide complex **8**. At this juncture, **8** rapidly intercepts the aniline radical **7** to form Ni^{II} species **9**, which is then reduced to Ni^{I}–amido derivative **10** by $\mathbf{Ir^{II}}$. Oxidative addition of the aryl halide to Ni^{I}–amido species **10** delivers the Ni^{III} complex **11**, which undergoes facile reductive elimination to form the C–N coupled product with concomitant regeneration of the Ni^{I}–halide complex **8**.

The observed reduction of the aryl halide is indicative of a step-wise oxidative addition involving a SET process (Figure 1 B).[12] The oxidation potential of a similar Ni^{I}–amido complex ($E_{1/2}^{oxi}$ [Ni^{I}/Ni^{II}] = −0.90 V versus Fc/Fc^+ or −0.52 V versus SCE),[13] indicates that the reduction of iodobenzene ($E_{1/2}^{red}$ = −1.59 V versus SCE)[14] by Ni^{I}–amido species **10** in its ground state is thermodynamically unfavorable (endergonic). However, visible-light excitation of Ni^{I}–amido **10** should produce a long-lived and highly reducing excited *Ni^{I}–amido species **12**.[15] Subsequent SET reduction of aryl iodides and bromides by *Ni^{I}–amido species **12** will give an ionic Ni^{II} complex **13** together with an aryl radical. We recognized here that the amine's electronic properties will have a strong influence on the efficiency of the excitation of **10**, the resulting lifetime of **12**, and the rate at which **13** reacts with the aryl radical. To this end, the aryl radical can either be trapped by **13** to give Ni^{III}–amido aryl halide **11** or undergo hydrogen atom abstraction from an aminium radical cation[12] to give the reduced product. Should the hydrogen atom abstraction reaction be favored, a single electron reduction of the ionic Ni^{II} complex **13** by $\mathbf{Ir^{II}}$ will reproduce Ni^{I}–amido species **10**.

The high efficiency of the coupling conducted with the Ni^0 precatalyst (Table 1, entry 12) suggests that a rapid trap of the Ni^0 complex by the aniline radical **7** can also produce the Ni^{I}–amido species **10** (Figure 1 B).[9] Finally, we attribute the low coupling efficiency of amines containing an α-C_{sp3}-H group, such as benzyl amines and alkyl amines (Table 3, **4w**–**4y**), to competitive deprotonation of their corresponding aminium radical cation at the α position. Ni^{I}–amido complexes generated from such amines may also be susceptible to undesirable β-hydride elimination reactions.[16]

In conclusion, we have developed a mild, highly chemoselective photoinduced Ir/Ni dual-catalyzed procedure for the cross-coupling of primary aryl amines with aryl and heteroaryl halides, which, to the best of our knowledge, is the first method of its kind. In terms of practical utility, this dual-catalyzed C–N coupling procedure operates with high efficiency in the presence of molecular oxygen using a simple and readily available Ni-based catalyst. We also demonstrate the tolerance of synthetically useful functional groups, including alcohol, fluoride, chloride, aldehyde, organoboronate, vinyl, ketone, carbamate, ester, cyano, methyl, methoxy, thioether, and acetylene, using this mild procedure. Mechanistic studies and experimental evidence suggest that the reaction proceeds through an aminyl radical and a stepwise oxidative addition process. This synthetic method should find use in the synthesis of nitrogen-containing drug molecules and the mechanistic insights provided should promote interest and further development.

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[16] It is possible that Et_3N plays an additional role in the reaction. We are currently studying the mechanism of this reaction in more detail.

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