Sustainable, precious metal-free C-N cross coupling through photocatalysis

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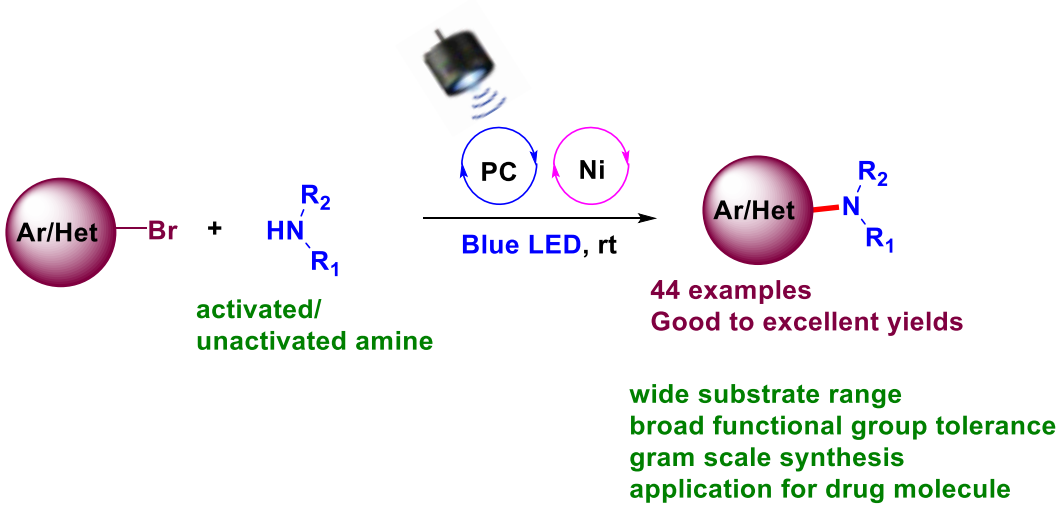


ABSTRACT: Photoredox catalysis has evolved out as one of the sustainable ways of constructing C-N bond. Herein, reported a visible-light organic photoredox catalyzed method that enables C-N cross coupling under mild and sustainable reaction condition. This catalytic system worked for both activated, unactivated amines and electron rich or deficient aryl bromides with broad range of functional group tolerance in good to excellent yields. The noteworthy aspects, milder reaction condition at room temperature without addition of any additional ligand make the procedure attractive.

The nitrogen-containing organic structure unit constitutes the basic building block of life, such as proteins, DNA, and RNA. Moreover, most natural products, pharmaceuticals and agrochemicals demand nitrogen-containing moiety for their particular activity (Figure 1).[1] Considering the widespread importance of arylated/aliphatic amines in pharmaceuticals, numerous metal mediated methodologies have been developed during the past three decades for C-N bond formation. Major development has been observed in Pd catalyzed C-N cross coupling of amines with aryl halides to form N-substituted anilines.[2] Recently, aminative Suzuki Miyaura coupling was reported which involved nitrene insertion for C-N bond formation.[3] In most cases Pd catalyzed methods depend on sterically hindered expensive ligand and elevated temperatures; sometimes these harsh conditions cause undesired outcomes such as deprotection of the protecting group, hydrolysis, charring and possibility of formation of color impurities.[4] In addition to these limitations, removal of trace Pd metal from active pharmaceutical ingredients is another challenge.[5] Development of greener and more convenient ways to form C-N bonds, has become one of the hottest research goals in synthetic chemistry to overcome these challenges.[6]

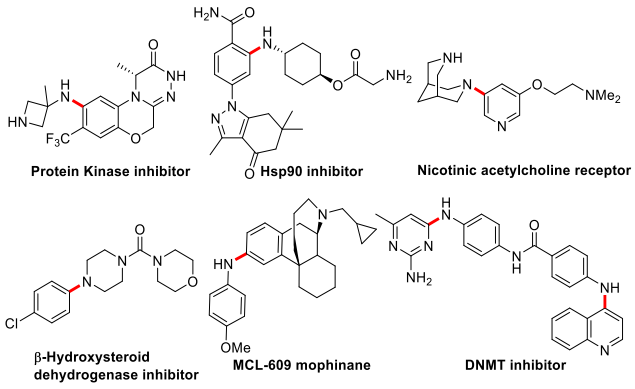


Figure 1: Pd mediated C-N cross coupling involvement in potential Pharmaceutical compound

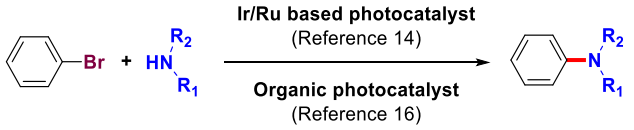
One of the prime requirements in chemical processes is reducing or eliminating the use or formation of hazardous substances. Methods based on green chemistry principles[7] are being embraced to meet this requirement. Photochemistry based applications, such as photoredox catalysis wherein redox reactions are accomplished in a catalytic manner, have become methodologies[8] of choice for achieving challenging carbon-heteroatom bond formations under mild conditions[9]

making this application more greener, cost effective and sustainable one. Photoredox catalysis, especially in the last decade, has become one of the trusted options to make new molecules by overcoming the limitations of the past and impressive methodologies have been developed. Photoredox catalysis, in recent times, has also emerged as a highly effcient and mild strategy for late stage diversification and access to syntheticalally challenging bioisosteres.[10] Asymmetric photoredox catalysis that enables enantioselective versions of useful methods for chemical synthesis, is gaining momentum to harness the stereoselectivity that is possible in this platform.[11] Appending flow chemistry to photoredox catalysis research efforts/explorations are in progress to adopt photoredox catalysis to achieve carbon-heteroatom couplings on a large scale.[12]

Metal-based photocatalysts, mainly the polypyridine complexes of Ru(II) and Ir(III) have been explored extensively as the visible-light photocatalysts with good success. However, the environmental issues related to these applications of rare metals led to consider alternatives to these metal-based photocatalysts. The organic dyes have been found to be cheap and effective visible light photoredox organocatalysts (PROC), wherein the photogenerated radical ion of the dye can promote a chemical reaction. The low cost and ease of preparation of these dyes have made them to be attractive alternatives to transition metal complexes; in some cases, even better photocatalytic performances with respect to their metal counterparts have been observed.[13]

Furthermore, the synergistic action of photoredox catalysis with another catalytic process has a profound impact on the reactivity profiles of many traditional synthetic routes.[14, 15] Numerous organic molecules such as methylene blue, rose bengal, eosin Y, acridinium salts, cyanoarenes have been reported as organic photocatalysts for organic transformations.[16] Application of organic photocatalysts such as phenoxazine, anthrazoline, dihydrophenazine for C-N cross coupling between aromatic halide with aromatic/aliphatic amines are also reported (Scheme 1).[17]

Earlier works:

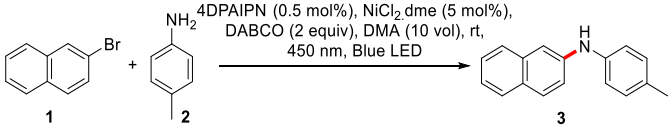


Scheme 1: Earlier photoredox approaches for C-N cross coupling

C–N bond formation under extremely mild conditions and high functional group tolerance is a need in pharmaceutical industry. To facilitate a library project on anilines under photoredox conditions, we wanted to have a photoredox catalyst that can work well, preferably in good yields, for a wider substrate scope with regards to both aryl halides and the amines-primary, secondary (both cyclic and acyclic).

Herein, we report a general and attractive methodology for C-N cross coupling using inexpensive, easily synthesizable 4 DPAIPN as a photoredox catalyst. In order to realize the viability of the reaction, a model reaction employing 2-bromo naphthalene and *p*-toluidine was carried out using 450 nm blue light. Initially, we screened different organic dye at room temperature for 12 h; the dicyanoarene based, 4DPAIPN emerged out as the most prominent one for the coupling with an excellent yield of 82% (Table 1, entry 2). Other dicyanoarene based organic dyes (4CzPIN, 3DPA2FBN, dicyanoanthracene) were found to be next effective ones and yielded the product in good yield (Table 1, entry 1, 2, 4). Rest of the organic dyes were unable to generate any significant impact on product formation (Table 1, entry 5-8). Moreover, when the reaction was performed without 4DPAIPN there was no coupling, which showed the importance of DPAIPN in the C-N cross coupling (Table 1, entry 9). Delighted by this result, we next studied the impact of different Ni co-catalysts, such as $NiBr_2$.dme, $Ni(acac)_2$, $(Ni(OAc)_2.4H_2O$. In the absence of Ni catalyst, there was no product formation, indicating its involvement in catalytic cycle (Table 1, entry 10). $NiBr_2$.dme played a similar role, but the yield of the product was slightly lesser (Table 1, entry 11). While other Ni based co-catalysts showed the product formation to the extent of 52-60%. (Table 1, 12-13). After finding the suitable combination of photocatalyst and metal source, we next set to optimize equivalent of DPAIPN & $NiCl_2$ required for this C-N cross coupling. It was observed that 0.5 mol% of DPAIPN & 5 mol% $NiCl_2$ was best for the catalytic activity. A decrease in catalytic loading affected the product formation; even after longer durations the consumption of starting material was not complete (Supplementary, Table S1). We then monitored the photocatalysis reaction at different wavelengths; it was found that optimal yield was observed at 450 nm followed by 427 nm. There was no impact on product formation with 370 nm wavelength light (Supplementary, Table S2). Furthermore, we screened various solvents and found that DMA was most appropriate for catalysis (Supplementary, Table S3). MeCN is the next good solvent, which gave the product in 70% yield while in DMF the reaction is slow and product was isolated in 10% yield even after 24 h. Other common solvent such as EtOAc, DMSO, DCM, MeOH did not bring any significant impact on product formation. Among the different bases screened, DABCO gave the corresponding product in encouraging yields (Supplementary, Table S4).

Table-1: Optimization of reaction condition on photoredox C-N cross coupling[a]

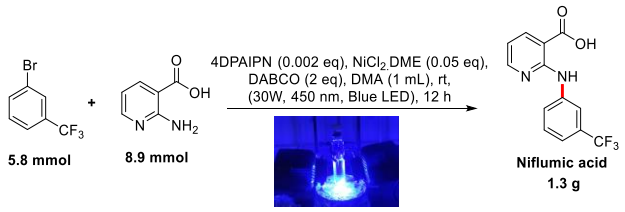


SN	Deviation from standard condition	Yield (%)
1	4CzPIN	49
2	None	82
3	3DPA2FBN	44
4	9,10-Anthracenedicarbonitrile	16
5	Methylene blue	NR
6	Eosin-Y	NR
7	Rose Bengal	NR
8	12-Phenyl-10H-phenothiazine	NR
9	No photocatalyst	NR
10	No $NiCl_2$.dme	NR
11	$NiBr_2$.dme	75
12	$Ni(acac)_2$	52
13	$Ni(OAc).4H_2O$	60

[a]Standard reaction conditions: 4DPAIPN (0.5 mmol%), $NiCl_2$.dme (5 mol%), DABCO (2 equiv), DMA (10 vol), 450 nm blue LED, ambient temperature, 12 h
[b]Isolated yield
NR: no reaction

To examine the scope of the reaction, we have subjected various aryl bromo partners with varying functional groups. Substrates bearing electron donating (**5**) or withdrawing group (**7-8**) on bromo arene gave their corresponding product in good to excellent yields. Substrates bearing electron withdrawing group on aryl amine (**15-18**) coupled efficiently with bromo arene. Chiral aliphatic amines yielded the corresponding product without loss of the chirality (**22-23**). Heterocyclic bromides, such as pyridine, thiophene, quinoline, isoquinoline, benzothiophene (**9-15**) under the developed reaction condition gave corresponding anilines in 49-56% yield. To our delight, the present protocol is also effective for coupling unreactive primary, secondary aliphatic amine such as cyclohexyl amine, cyclopentyl amine, benzyl amine, phenyl ethyl amine, phenyl propyl amine, octyl amine, azetidine, pyrrolidine, piperidine, morphine, piperazine (**24-37**) which gave their corresponding arylalkylamines in modest to good yields (Figure 2).

The simplicity of the reaction condition tempted us to check for the scalability of this reaction condition; a gram-scale reaction on 2-bromo-1-trifluromethyl benzene was attempted to get niflumic acid, a nonsteroidal anti-inflammatory drug (NSAID). The reaction proceeded smoothly using just 0.002 mol% of 4DPAIPN, affording niflumic acid in 80% isolated yield at room temperature (Scheme 2).



Scheme 2: Gram scale synthesis of niflumic acid

After successfully establishing the methodology for various C-N coupled product formation, we extended this protocol for the synthesis of active pharmaceutical ingredients by treating respective aryl halides and aryl/aliphatic amines; the products such as mefenamic acid, meclofena acid, niflumic acid, brexipiprazole, melatonin receptor ligand, β-hyroxysteroid degydrogenase inhibitor and BRAF inhibitors were isolated in 43-80% yields (Figure 3).

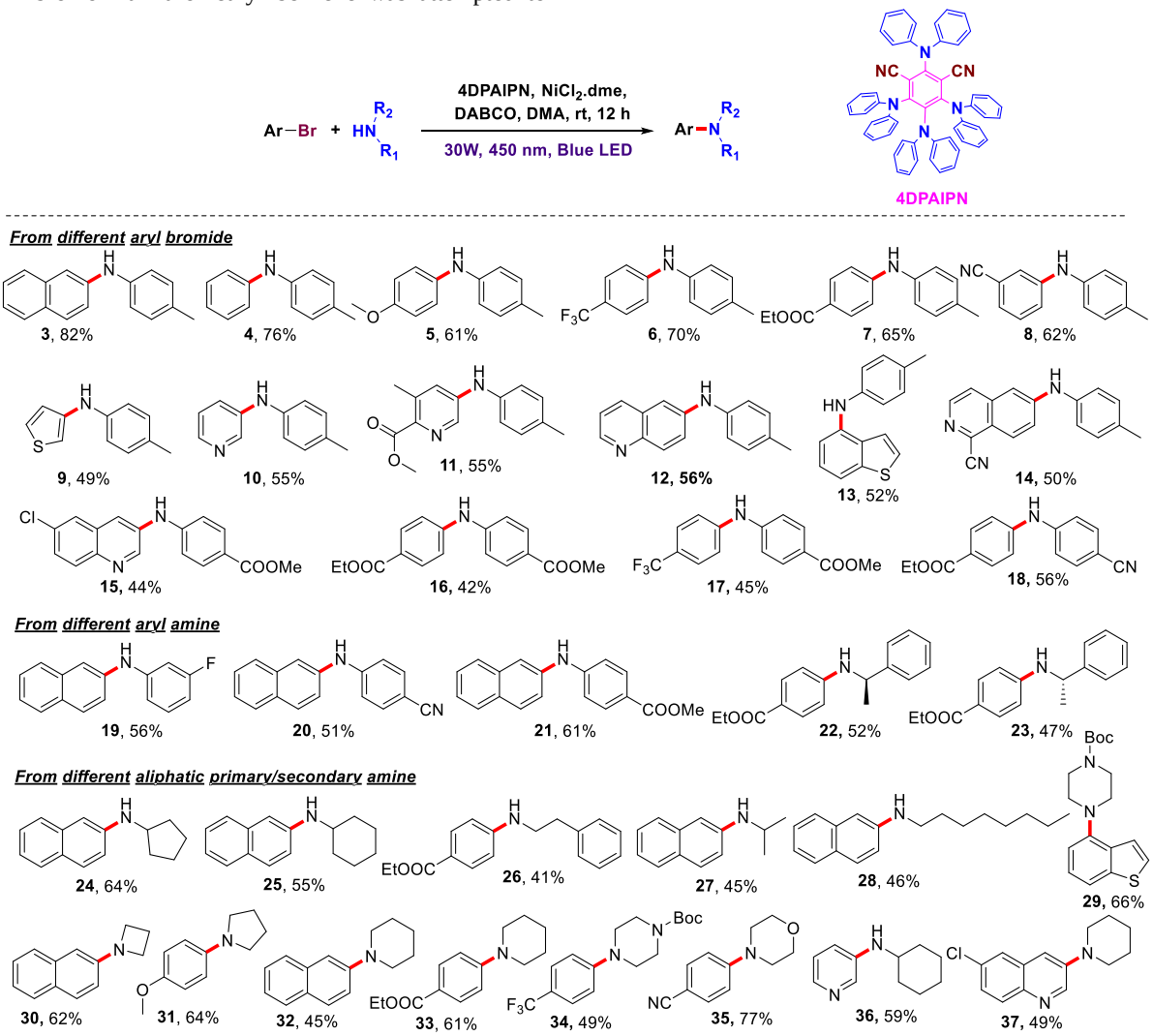


Figure 2: Scope of different substrate under photoredox C-N cross coupling

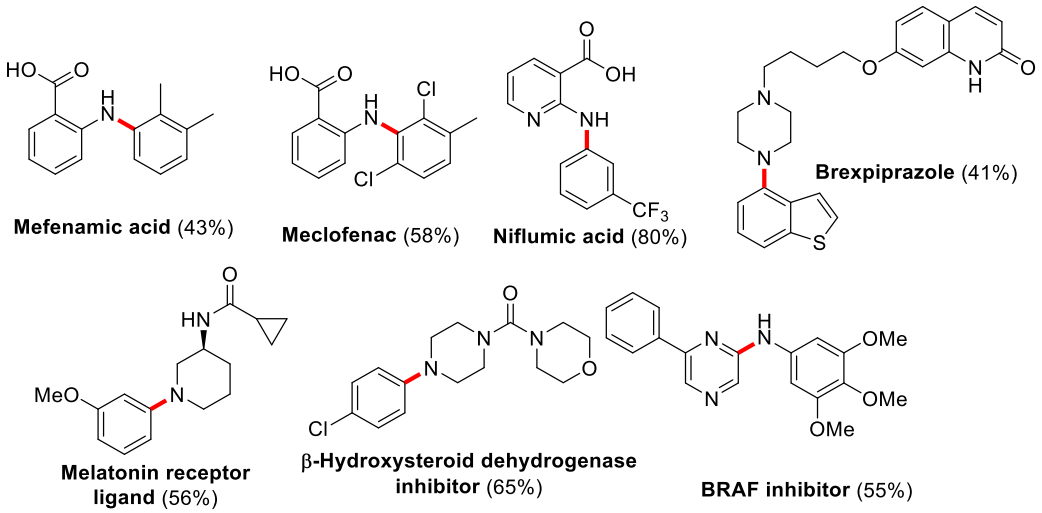


Figure 3: Synthetic application of 4DPAIPN in the synthesis of drug molecule/active pharmaceutical ingredients

In conclusion, a sustainable, milder, step economic, photocatalytic C-N cross coupling procedure was developed using cost effective organic dye. The 4DPAIPN based catalytic system has showed broad applicability to wide range of aryl bromides bearing different functional groups such as electron donating, withdrawing, heterocyclic that coupled efficiently with aryl amines, primary as well as secondary amines. Hope, this methodology will be helpful as an alternative to palladium catalyzed C-N cross coupling in drug discovery efforts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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