Letter

Nickel-Catalyzed Photoredox-Mediated Cross-Coupling of Aryl Electrophiles and Aryl Azides

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Nickel-Catalyzed Photoredox-Mediated Cross-Coupling of Aryl Electrophiles and Aryl Azides

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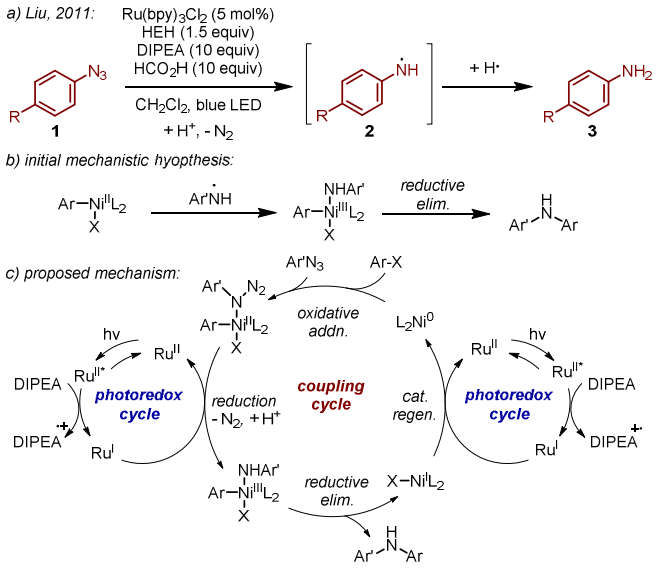
ABSTRACT: Medicinally-relevant diarylamines are prepared through a photoredox-mediated dual catalytic nickel/ruthenium system from aryl azides and aryl electrophiles. Photoreduction of the aryl azide is proposed to proceed through an arylnickel-azide complex, which upon reduction and loss of nitrogen, generates a nickel(III) species capable of facile reductive elimination to afford the desired C–N bond formation. A variety of functionalized (hetero)aryl electrophiles are shown to participate in the coupling, including iodides, bromides, chlorides, and triflates. The reactions are simple to set up and are run under ambient conditions without exclusion of oxygen or moisture.

Diarylamines are a ubiquitous and privileged scaffold in functional materials, agrochemicals, and pharmaceuticals.[1] For example, they act as a prominent hinge binding motif in the context of kinase inhibition.[2] While a variety of methods to access these manifolds exist,[3] many tend to be capricious, particularly when applied to complex substrates.[4] In an effort to improve the reliability of these transformations, recent interest in this area has focused on the development of alternative reaction manifolds which employ photoredox/transition metal dual catalysis for the generation and utilization of anilino radicals to achieve N-arylation of anilines.[5,6] While these methods provide good yields for a variety of substrates and are tolerant of various functionality, significant substrate dependence on coupling efficiency has been observed. For example, in our previously published protocol, *m*-toluidine coupled with 5-iodopyrimidine in high yields but the corresponding reaction using *p*-toluidine did not afford the desired product.[7] Additionally, employing more complex heterocycles results in either diminished yields or no formation of the desired product. Owing to the limitations of the currently available protocols, we sought to develop a mild, functional group tolerant, and mechanistically distinct method for the synthesis of diarylamines to expand the scope of these reactions to include complex substrates. Herein we report a nickel/photoredox dual catalytic system for the synthesis of diarylamines using aryl azides.

Inspired by recent work from the Liu group (Scheme 1, a),[8] we envisioned the generation of anilino radicals through a photoredox-mediated reduction of aryl azides could be utilized for our desired coupling. The proposed pathway begins with an initial photoexcitation of a $Ru^{II}(bpy)_3Cl_2$ catalyst which is subsequently reduced by a sacrificial amine additive to generate a highly reducing $Ru^{I}(bpy)_3Cl_2$ intermediate. This species can in turn reduce an aryl azide to the corresponding radical anion which upon protonation and loss of N_2 affords anilino radical **2**. Trapping of **2** by a nickel-oxidative addition complex and subsequent reductive elimination would yield the desired diarylamine (Scheme 1, b). In contrast to our previously published work, the hypothesized pathway relies on an initial reductive, rather than an oxidative, quenching mechanism to generate the anilino radical. As such, a less strongly oxidizing photocatalyst can be utilized, potentially further expanding the functional group and substrate compatibility of the reaction and allowing for selective N-arylation of azides over free anilines.

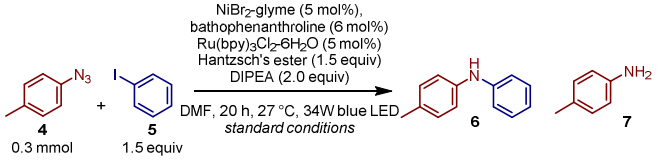
Scheme 1. a) Photoredox-mediated reduction of azides. b) Initial hypothesis of radical trapping by a nickel-oxidative addition complex. c) Current mechanistic hypothesis of photoredox aminations of aryl electrophiles with aryl azides or anilines.



With the envisioned pathway in mind, we began our investigation by employing reaction conditions analogous to

those reported by Liu. Gratifyingly, when using $Ru(bpy)_3Cl_2$ as a photocatalyst, diisopropylethylamine (DIPEA) as a stoichiometric reductant, $NiBr_2$•glyme as the nickel source, bathophenanthroline (Bphen) as a ligand, and Hantzsch ester, we observed complete conversion of the azide to the desired diarylamine product in near quantitative yield without the need of an inert environment or degassing of the reaction mixture (Table 1, entry 1).

Table 1. Control experiments for the desired coupling.



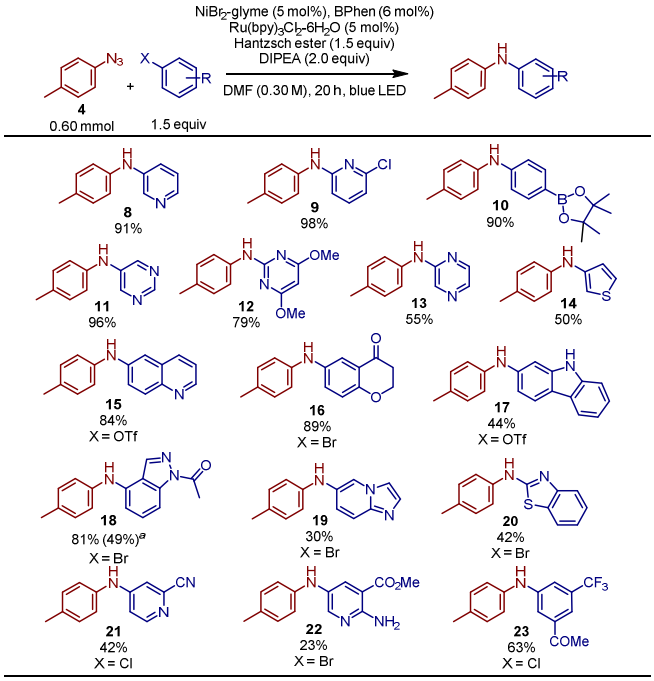
entry	variation from *standard conditions*	yield **6** (%)	yield **7** (%)
1	none	97	-
2	without light	-	-
3	without $NiBr_2$-glyme	-	44
4	without $Ru(bpy)_3Cl_2$-$6H_2O$	7	13
5	without DIPEA	7	-
6	without HEH	39	-
7	without BPhen	91	-
8	$Ni(cod)_2$ instead of $NiBr_2$-glyme	75 (84)[a]	11 (5)[a]
9	1 mol% $Ru(bpy)_3Cl_2$-$6H_2O$	93	-
10	1.0 equiv iodobenzene	78	-

[a]Reaction mixture sparged with N_2 for 5 minutes. Yields determined by ^1H NMR using PhTMS as an external standard.

As demonstrated by several control experiments, both light and nickel catalyst are essential for product formation (Table 1, entries 2 and 3). Interestingly, trace amount of product was observed in the absence of $Ru(bpy)_3Cl_2$ (entry 4), suggesting that the nickel complex itself can also serve as a photocatalyst,[9] albeit to a much lower extent. Although Hantzsch ester can act as a reducing agent for the catalyst, leading to small quantities of product (entry 5), the yield of the reaction is greatly improved in the presence of DIPEA as a sacrificial electron donor (entry 6). Hantzsch ester, however, was shown to be beneficial to the reaction, resulting in both higher yields and a cleaner reaction profile overall. Through extensive optimization, BPhen and DMF were determined to provide optimal yields, although several additional solvents and ligands are also well tolerated under the reaction conditions.[10] Similar to previous reports, in the absence of ligand, the reaction affords product in slightly diminished yield (entry 7).[5,6] A Ni(0) precatalyst proved to be competent in the reaction, suggesting the intermediacy of Ni(0) in the catalytic cycle (entry 8). Gratifyingly, good yields of product can also be obtained with a lower photocatalyst loading (entry 9), and with one equivalent of aryl electrophile for scenarios when it is a precious coupling partner (entry 10).

Upon identifying suitable reaction conditions for the parent system, we investigated the scope of aryl electrophiles for this transformation (Table 2). In addition to simple arene systems, a variety of polyfunctional heteroaryl electrophiles perform well under the developed conditions. Pyridines bearing the electrophile in any position afforded coupling products in good yields (entries **8**, **9**, **21**, **22**). Various diazines participated well in the coupling including pyrazine **13**, and both 2- and 5-substituted pyrimidines (entries **11** and **12**). More electron-rich azole- and thiazole-derived electrophiles were competent coupling partners, including carbazole **17**, indazole **18**, imidazopyridine **19**, thiophene **14**, and benzothiazole **20**. Halides bearing synthetically useful functional groups such as ketone, ether, ester, cyano, trifluoromethyl, and boronate ester were all well tolerated. Gratifyingly, unprotected N-H groups remained unreactive towards N-arylation, tolerating free carbazole **17** and unprotected primary aniline **22**. In addition to aryl iodides as electrophiles, aryl bromides, chlorides, and triflates all participate well in the reaction. Aryl iodides served as the preferential site of oxidative addition in substrates which possess multiple sites of reactivity (entry **9**), allowing for site selective couplings to be carried out on functionally dense substrates.

Table 2. Scope of aryl electrophile coupling partner.

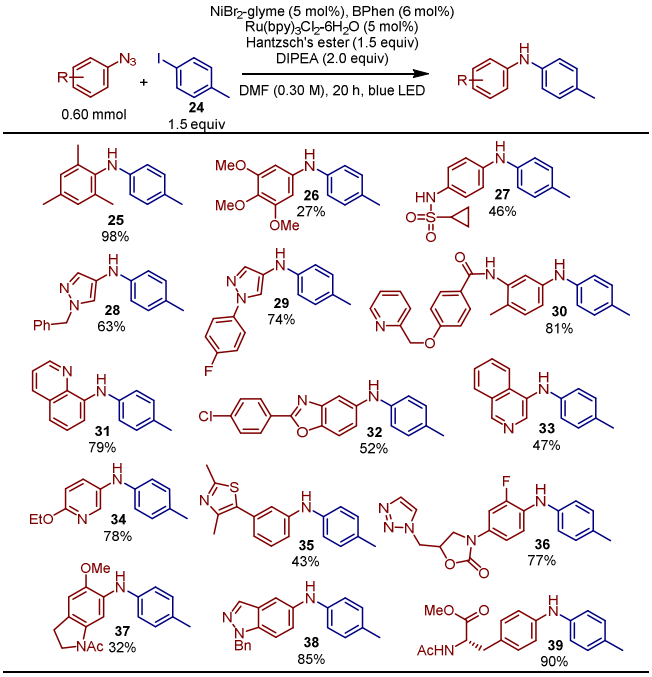


[a]Reaction performed without BPhen. X = I, unless otherwise noted.

The reaction is similarly tolerant of a wide array of arenes and substitution patterns on the azide coupling partner. Both electron-neutral and electron-rich azides participate in the coupling, affording simple phenyl-derived diarylamines in good yields (entries **25**-**27**). Steric hinderance around the azide was not detrimental to the reaction, affording mesityl-derived product **25** in high yield. Delightfully, a range of azido-substituted heterocycles are also competent coupling partners. Both N-alkyl and N-aryl azidopyrazoles are efficiently coupled (entries **28** and **29**),[11] and related 5-azidoindazole reacted well to afforded product **38** in high yield. Azine substrates including 3-azidopyridine, 8-azidoquinoline, and 4-azidoisoquinoline also afforded the desired products in good yields (entries **34**, **31**, **33**). Distal heterocycles including pyridine-containing **31**, thiazole **35**, and triazole and oxazolidinone **36** did not diminish yields of the coupling. Furthermore, substrates containing synthetically useful

functional groups including sulfonamide, aryl fluoride, aryl chloride, aryl ether, and amides, were well tolerated. Additionally, a phenylalanine derived azide performed well in the reaction affording product **39** in high yield, potentially providing a new straightforward method for the functionalization of peptides.

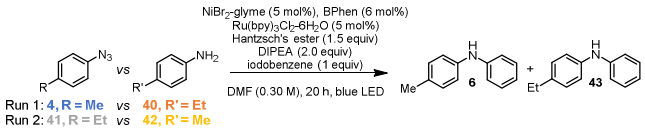
Table 3. Scope of aryl azide coupling partner.

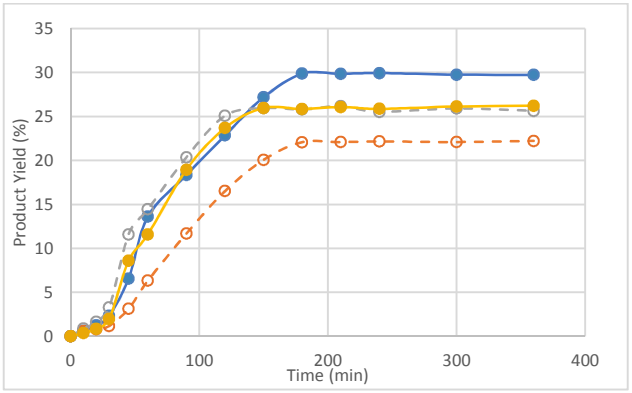


Under the developed conditions, both aryl electrophiles and azides exhibit broad functional group tolerance. In particular, functional groups amenable for orthogonal functionalization performed well. An additional hallmark of the reaction is the range of heterocycle containing substrates which provide synthetically useful yields of a diverse array of complex diarylamines. Indeed, when directly compared with previous methods, the developed conditions provided superior yields, displaying the increased tolerability of the developed reaction.

Furthermore, we performed preliminary studies to elucidate the reaction mechanism and rule out alternative pathways. One alternative to the proposed mechanism involves full reduction of the aryl azide to the corresponding aniline and subsequent oxidation/deprotonation to the anilino radical intermediate. In order to investigate this possibility further, a direct competition study was performed to compare the relative reactivities of azides and anilines. Interestingly, when equimolar amounts of 4-azidotoluene and *p*-ethylaniline are used in the reaction, the azide coupling product is formed preferentially (Scheme 2). When employing the switched substrates (1-azido-4-ethylbenzene **41** and *p*-methylaniline **42**), **41** reacted slightly faster than **42**, although yields of the products were similar. While it appears that *p*-methylaniline reacts faster than *p*-ethylaniline, the obtained data suggests that direct coupling of the azide is more efficient than the coupling of the analogous aniline. For an individual substrate, however, product could arise from either substrate presuming the *in situ* formed aniline is able to be oxidized by the photocatalyst as is observed in the competition experiments. Although selectivity in this example is moderate, enhanced azide coupling selectivity would be expected for electronically differentiated substrates in which the competitive aniline is unable to be oxidized by the photocatalyst.

Scheme 2. Competition study.

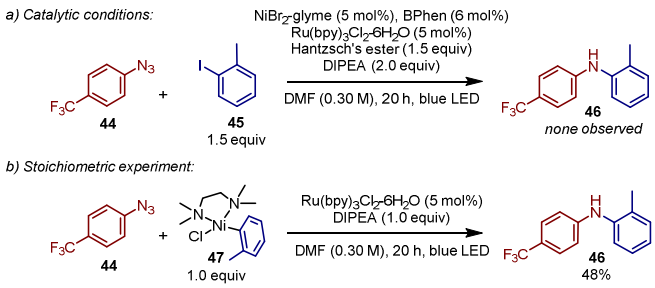




Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an external standard. Dotted curves indicate product arising from ethylated starting material.

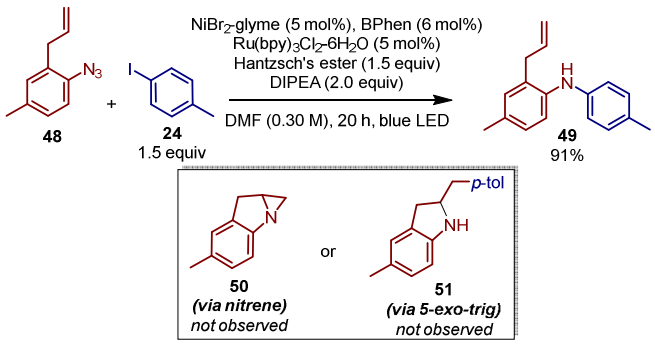
In the envisioned pathway (Scheme 1, b), initial azide reduction and subsequent fragmentation must occur to generate the desired anilino radical which must be of sufficient lifetime to be trapped by a Ni(II) oxidative addition complex. Particularly electron deficient azides, such as **44**, are rapidly reduced and the resulting highly unstable anilino radical is quickly quenched by an H-atom donor leading to formation of the corresponding aniline which does not undergo further reaction (Scheme 3, a).[12] Consistent with this hypothesis, when a stoichiometric quantity of a preformed Ni(II) oxidative addition complex was utilized,[13] thereby increasing the effective molarity of the catalyst species, the desired product was formed in modest yield (Scheme 3, b), suggesting direct reaction of the azide with complex **47** is necessary for product formation.

Scheme 3. Reactions with electron deficient azide.



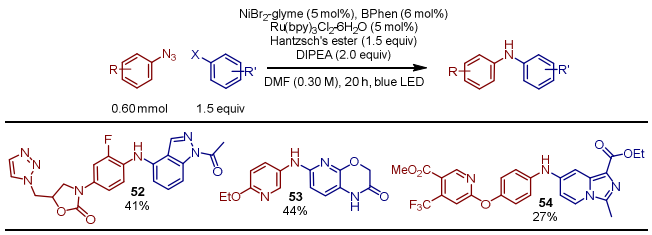
Based on previous reports, another mechanism involving energy transfer to generate an aryl nitrene can also be envisoned.[14] If such a mechanism were operative, subjection of substrate **48** to the reaction conditions would be expected to form product **50** through initial nitrene formation and subsequent C=C insertion (Scheme 4). Moreover, if an anilino radical of sufficient lifetime to combine with a nickel species was generated, products originating from a radical 5-exo-trig cyclization would be expected (e.g. **51**).[15] Surprisingly, however, only the corresponding diarylamine product **49** was observed. Furthermore, when subjecting the corresponding aniline to the standard conditions, a complex mixture of products were observed with only a trace amount of the desired diarylamine (see SI for details). Although further studies are necessary to elucidate additional mechanistic details, these results, in concert with the competition and stoichiometric experiments, suggest a mechanism in which the azide is coordinated to the nickel oxidative addition complex as the key intermediate.[16] Subsequent single electron reduction and loss of N_2 generates a nickel (III) intermediate poised for reductive elimination as shown in the proposed mechanism outlined above (Scheme 1, c).

Scheme 4. Experiment to rule out nitrene and radical pathway.



Finally, to further demonstrate the utility of this transformation, substrates representative of those encountered in a medicinal chemistry program were tested under the reaction conditions (Table 4). Gratifyingly, several drug-like diarylamines were synthesized in modest yields, including N-arylated linezolid derived product **52**, diheteroarylamine **53**, and imidazopyridine-containing diarylether **54**.

Table 4. Preparation of medicinally-relevant diarylamines.



In conclusion, we have developed an efficient method for the cross-coupling of aryl azides and aryl electrophiles for the synthesis of functionally diverse diarylamines, enabled by a dual catalytic Ni/Ru photoredox system. Benefits of the reaction include an operationally simple protocol, mild reaction conditions, and a significant improvement of substrate and functional group tolerance compared to previously published methods. Finally, this protocol appears to proceed through an alternative reaction manifold which allows for selective N-arylation of azides over free N-H bonds.

ASSOCIATED CONTENT

Supporting Information. General experimental details, procedures, and characterization data for all products are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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10. A variety of alternative solvents and ligands were tolerated under the reaction conditions, albeit with lower yields of product. Other competent solvents include: DCM, MeOH, DMA, and MeCN. Preformed Ni(II) catalysts including $NiCl_2$dppf, $NiCl_2(PCy_3)_2$, $NiCl_2$dppe, $NiCl_2$dppp afforded modest yields of product. Additionally, a variety of aromatic nitrogen-containing ligands including bipyridyl and phenanthroline derivatives were tolerated.

11. While pyrazole derived product **28** is formed in good yields from the 4-azido-1-benzylpyrazole starting material, switching of coupling partners (using 4-iodo-1-benzylpyrazole and 4-azidotoluene) did not yield any of the desired product (see SI for details).

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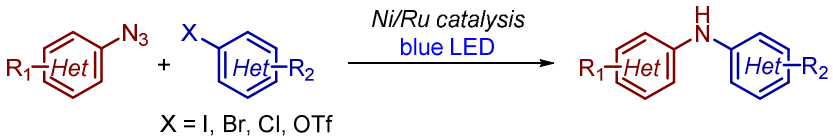
N3
R1
Het
+
X
Het
R2
X = I, Br, Cl, OTf
Ni/Ru catalysis
blue LED
H
N
R1
Het
Het
R2