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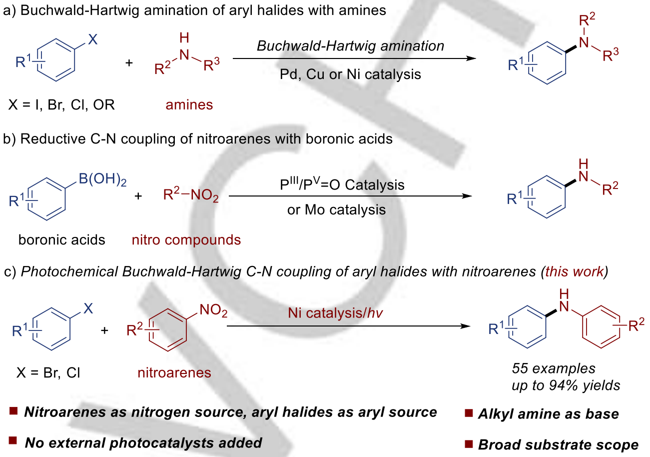
Light-Promoted C-N Coupling of Aryl Halides with Nitroarenes

Gang Li,[a] Liu Yang,[a] Jian-Jun Liu,[a] Wei Zhang,[a] Rui Cao,[a] Chao Wang,[a] Zunting Zhang,[a] Jianliang Xiao,[b] and Dong Xue*[a]

Abstract: A photochemical C-N coupling of aryl halides with nitroarenes is demonstrated for the first time. Catalyzed by a Ni(II) complex in the absence of any external photosensitizer, readily available nitroarenes undergo coupling with a variety of aryl halides, providing a step-economic extension to the widely used Buchwald-Hartwig C-N coupling reaction. The method tolerates coupling partners with steric-congestion and functional groups sensitive to bases and nucleophiles. Mechanistic studies suggest that the reaction proceeds via the addition of an aryl radical, generated from a Ni (I)/Ni (III) cycle, to a nitrosoarene intermediate.

The palladium-catalyzed Buchwald-Hartwig amination of aryl halides[1] and copper-catalyzed Ullmann coupling[2] have emerged as one of the most widely utilized reactions in modern organic chemistry, with the former ranked amongst one of the 20 most frequently used reactions in medicinal chemistry.[3] Since the first report in the 1950s,[4] the nickel-catalyzed C-N coupling of aryl halides with amines has been significantly improved (Scheme 1, a).[5-6] In particular, the last a few years have witnessed the advent of elegant ligand-control,[7] photochemical,[8] and electrochemical[9] strategies, greatly improving the efficacy and scope of the Ni-catalyzed C-N cross coupling. *Whilst these seminal works provide innovative ideas for further developing the Ni-catalyzed C-N coupling, all the thus-far reported amination reactions employ amines, especially anilines,[10] as the nitrogen source, which are usually obtained by reduction of nitroarenes*. The same is true with the regime of Pd and Cu catalysis. Could the nitroarenes be used as the nitrogen source instead? The ability to do so would widen the applicability of the C-N coupling, circumventing the need for the step of reduction of nitroarenes to amines while potentially improving the compatibility of functional groups in the coupling.

Nitroarenes are commercially widely available and are easily prepared building blocks in organic chemistry.[11] Since the early report on nucleophilic C-N addition of aryl magnesium reagents to nitroarenes by the Knochel group,[12] the following pioneering studies from the Baran[13] and Hu[14] groups have successfully demonstrated that nitroarenes are valuable precursor to anilines in organic synthesis. [15] Of particular note is the recent seminal work on organophosphorus[16] and molybdenum[17] catalyzed coupling of nitroarenes with boronic acids, which provides a new, effective process for the C-N bond formation (Scheme 1, b). However, there has been no report on the more economic, direct amination of aryl halides with nitroarenes. Note that aryl boronic acids are usually derived from the corresponding halides. Herein, we report a photochemical C-N coupling of aryl halides with nitroarenes catalyzed by a Ni (II)-aryl complex using a mild organic base, *N*,*N*-diisopropylethylamine (DIPEA) (Scheme 1, c). Starting from readily available nitroarenes as the nitrogen source and abundant aryl halides as the aryl source, this transformation provides a step-economic strategy for furthering the widely used Buchwald-Hartwig C-N coupling reaction.



Scheme 1. Methodologies for the formation of aryl C-N bonds.

In our initial study, we discovered that a series of Ni complexes could catalyze the cross-coupling of 4-nitroanisole (**1**) with 4-bromobenzoate (**2**) under the irradiation of long-wave UV light (390-395 nm, purple LEDs) in the absence of any external photocatalyst. Notably, among all the surveyed Ni catalysts, the air-stable Ni-aryl complex **A**[18] afforded the best product yield (Table 1, entries 1-4). Light plays a crucial role in the reaction, with only the long-wave UV light affording high product yields (Table 1, entries 5–8). The choice of base also impacted the success of this reaction. Among the examined bases, DIPEA promoted the reaction significantly better than other organic amines (Table S1). This is delighting, as a mild organic base would enhance the compatibility of the reaction, as has been advocated in recent years.[7, 19] The subsequent investigation of solvent effect showed that toluene is the best solvent for this coupling reaction (Table S2). Further studies on the effects of additives and substrate concentration led to the optimized conditions (Table S3). Under the irradiation of long-wave UV light, with the Ni complex **A** as the catalyst, DIPEA as base and 4Å MS as the additive, the desired product **3** was obtained with 75% isolated yield at 70 °C for 12 h in toluene (4 mL) under argon. As revealed by the control experiments, the reaction did not proceed in the absence of nickel catalyst, light, or base (Table 1, entries 9-11, Table S6).

With the optimized reaction conditions in hands, the scope of nitroarenes and aryl halides for nitro version of the Buchwald-Hartwig C-N coupling reaction was investigated. First, the scope

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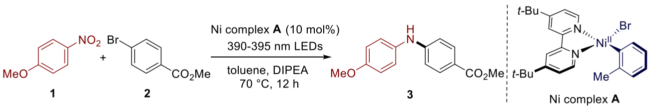
Table 1. Optimization of amination of aryl bromide with nitroarene.[a]

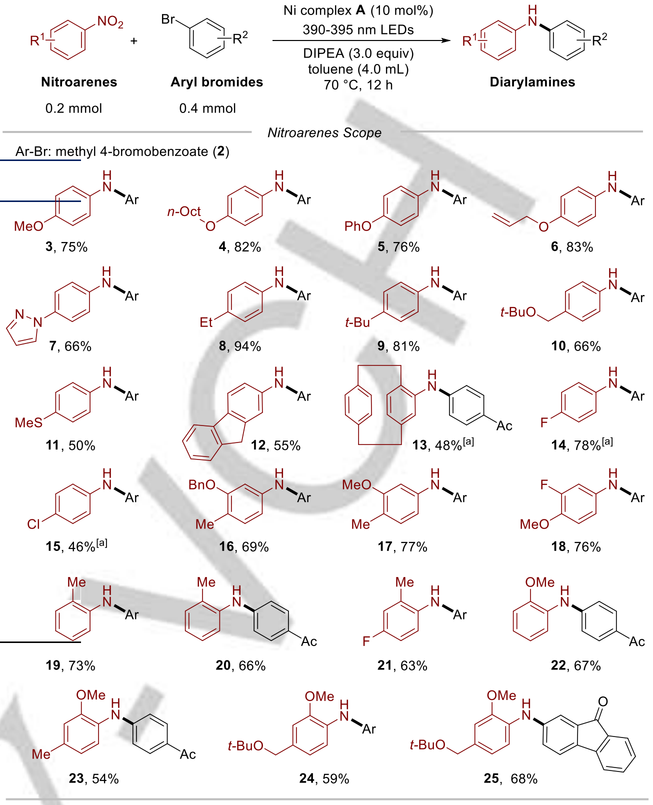


Entry	Variation from standard conditions	Yield (%)[b]
1	Standard conditions	75
2	Standard conditions, Ni(COD)$_2$-dtbbpy as catalyst	74
3	Standard conditions, NiBr$_2$(glyme)-dtbbpy as catalyst	54
4	Standard conditions, NiBr$_2$-dtbbpy as catalyst	16
5	Standard conditions, UV (360-365 nm)	16
6	Standard conditions, blue LEDs (460-465 nm)	0
7	Standard conditions, white LEDs	0
8	Standard conditions, green LEDs (530-535 nm)	0
9	Standard conditions, no light, heating to 70 °C	0
10	Standard conditions, no Ni catalyst	0
11	Standard conditions, no base	0

[a] Standard conditions: **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv), DIPEA (3.0 equiv), toluene (4.0 mL), 4Å MS (80 mg), 390-395 nm LEDs irradiation, 12 h, Ar. [b] Isolated yield. DIPEA = N,N-diisopropylethylamine.

of nitroarenes was explored. As shown in Scheme 2, the electron-donating (**3**-**7**) and electron-neutral (**8**-**10**) nitroarenes worked well in coupling with 4-bromobenzoate, affording the desired products with good to excellent yields. In addition, a nitroarene with a pyrazolo substituent and polycyclic nitroarenes were also compatible substrates (**7, 12, 13**). Notably, nitroarenes bearing halogen could tolerate this reaction, giving the corresponding halogen-substituted product (**14**, **15**, **18**), albeit at a higher catalyst loading (15 mol%). Disubstituted nitroarenes also worked successfully with this protocol (**16**-**18**), showcasing the wide scope of nitroarenes in this C-N coupling reaction. In particular, it is noted that nitroarenes with substitutes at the *ortho* position successfully delivered the desired diarylamines with high yields (**19**-**25**), revealing the good adaptability of the protocol to steric hindrance of substrates. Furthermore, this Ni-catalyzed C-N coupling reaction provides a convenient method for the synthesis of chiral ligands useful in asymmetric catalysis (**13**) and a step-economy route for the efficient synthesis of key intermediates of carbazole alkaloids (**19-25**).[20] However, nitroarenes with electron-withdrawing groups, such as -CO$_2$Me and -CN, could not provide the desired diarylamines.[21]

Next, a wide range of aryl halides were examined. As summarized in Scheme 3, aryl bromides bearing electron-withdrawing substituents, such as -CO$_2$Me, -Ac, -CHO, -COPh, -F, -Cl, -Br, -CF$_3$, -OCF$_3$ and -CN in the *para* or *meta* position were employed, and they delivered the desired products with good to excellent yields (**26**-**34**, **38**-**42**). These important functional groups provide the possibility for subsequent transformations. It is worth noting that all the ester and cyano-containing electrophiles are compatible in this protocol due to the use of a weak amine base. This contrasts with the formation of transesterification products and impurities in traditional coupling reactions where strong bases are common place.[22] As in the case of nitroarenes, for the *ortho*-substituted aryl bromides, the C-N coupling product was obtained with moderate yield (**43**), again showcasing the good adaptability to steric hindrance in substrates. The disubstituted aryl bromides bearing either electron-donating or withdrawing groups were well tolerated (**44**-**49**). In general, electron-deficient aryl halides exhibit higher reaction efficiency in this reaction, somewhat compensating the lack of reactivity of electron-deficient nitroaromatics, while providing a new synthetic strategy for the preparation of this type of diarylamines.

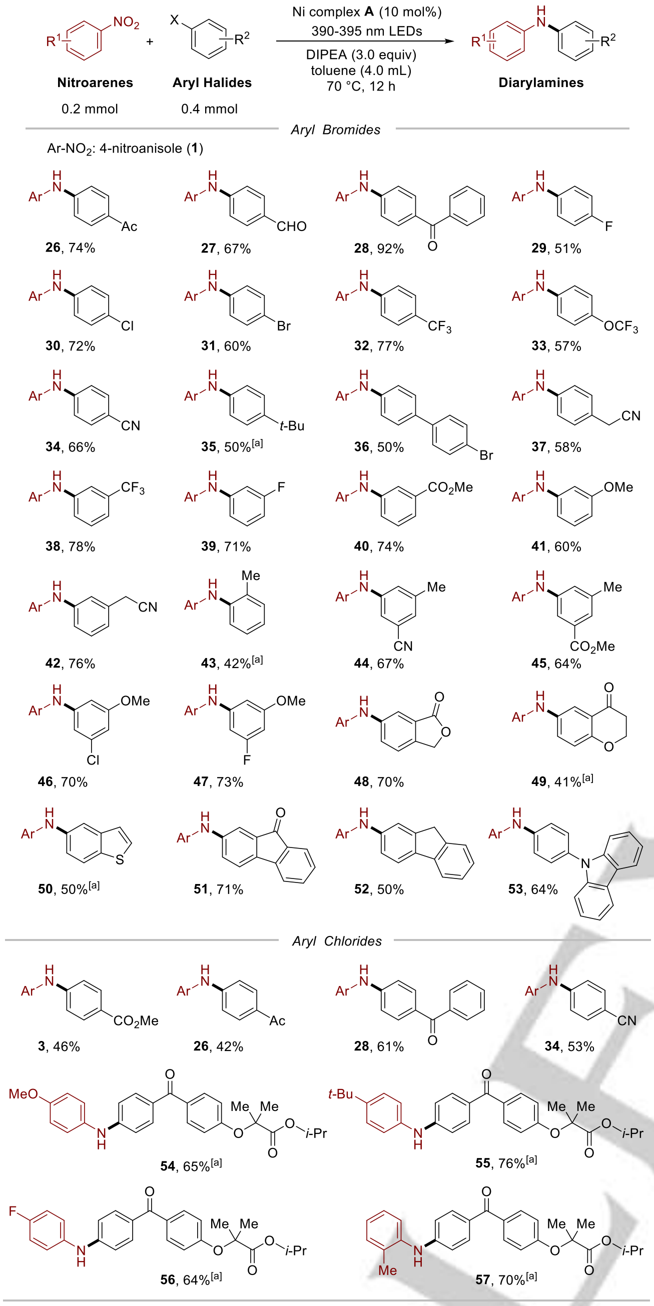


Scheme 2. Scope of nitroarenes. Isolated yields are shown. [a] Ni complex **A** (15 mol%).

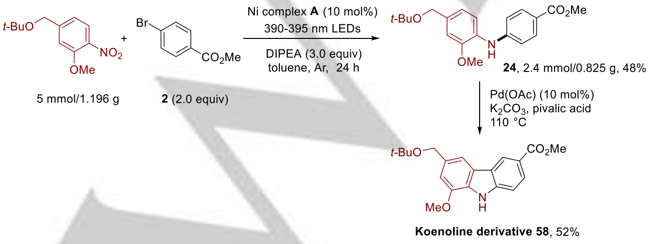
Notably, as shown in Scheme 3, cheaper but more challenging aryl chlorides are also suitable for this reaction. Aryl chlorides containing ester (**3**) ketone (**26**, **28**, **54**-**57**) or nitrile (**34**) units afforded the desired products with good yields. Of particular note is that Fenofibrate, a biologically relevant and more complex substrate, is also tolerated in this transformation, yielding the amination products with nitroarenes containing substitutes in the *para* or *ortho* position (**54**-**57**).

To further investigate the potential application of this protocol in synthetic chemistry, the synthesis of a key precursor to koenoline derivative **58,** a methyl ester of a known natural product, was explored at gram scale. As shown in Scheme 4, the desired diarylamine (**24**) was obtained with 48% isolated yield; by extending the reaction time to 24 h. The following known cyclization of the diarylamine intermediate led to the formation of **58**. Using commercially available nitroarene as staring material, this protocol avoids the challenging reduction of nitroarenes to aromatic amine, providing a green and effective process for the synthesis of **58**.[20]

To gain understanding of the reaction mechanism, a series of probing experiments were carried out. Firstly, when 2, 2, 6, 6-



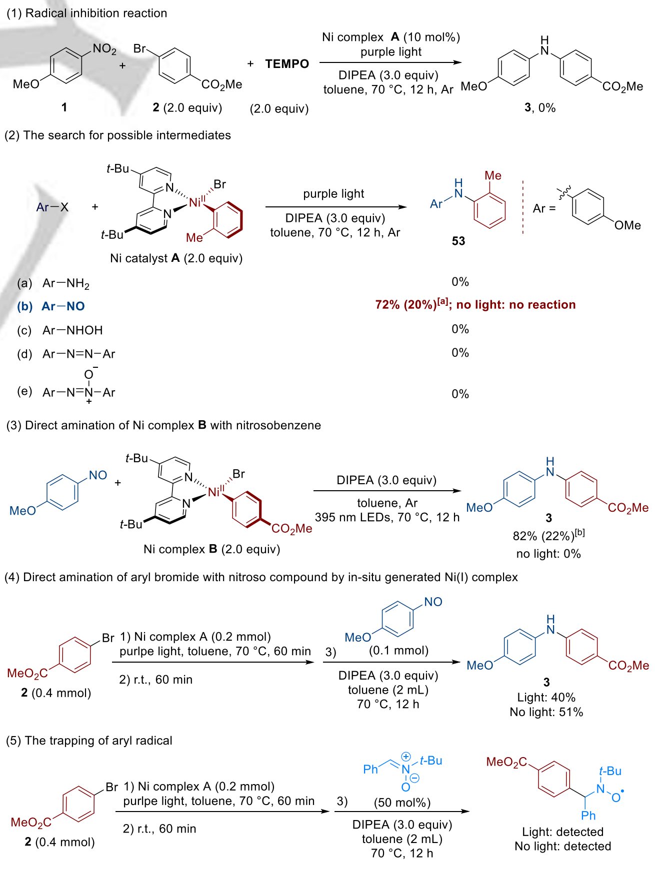
Scheme 3. Scope of aryl halides. Isolated yields are shown. [a] Ni complex **A** (15 mol%).



Scheme 4. Gram-scale nitro C-N coupling.

tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction under the standard conditions, no desired diarylamine product **3** was obtained, suggesting that this C-N coupling may undergo a radical pathway (Scheme 5, 1). We next searched for possible intermediates. Inspired by Hu's reports,[14] we studied the reactions between five possibly existing intermediates in the reduction of nitroarenes with two equivalents of Ni complex **A**. Notably, only the nitroso compound could afford the desired diarylamine **43** in 72% isolated yield along with the generation of *o*-dimethylbiphenyl (Scheme 5, 2b). In addition, the following reaction of Ni complex **B** with *p*-nitrosoanisole also delivered the diarylamine **3** in 82% yield under the irradiation of light (Scheme 5, 3), which supports the nitroso compound to be a possible intermediate in this light-promoted C-N coupling,[23] while indicating that Ni(II) species are inactive without light irradiation.

Considering the recent, studies of the photochemistry of Ni(II)-aryl complex by Doyle,[18a-b] Scholes [18c] and our group,[18e] the results gave us a hint that aryl radicals and Ni(I) species, generated in situ under the irradiation of light, could be key intermediates or active catalyst species for this C-N coupling. Therefore, we next studied the oxidative addition of Ni(I) complex with aryl halide and the following reaction with a nitrosoanisole. In the absence of substrates, the Ni (II) complex **A** was irradiated under the purple light for 60 min, which was expected to generate a Ni(I) complex. Then the irradiation was stopped, and the aryl substrate was added to the mixture. The subsequent, expected



Scheme 5. Preliminary mechanistic studies. [a] The yield of biphenyl was determined by ^{1}H NMR (parenthesises). [b] Isolated yield of biphenyl (parenthesises).

oxidative addition reaction was run for 60 min in the dark. Following addition of nitrosoanisole to the reaction solution and stirring for 12 h without irradiation, the corresponding diarylamine was obtained with 51% yield (Scheme 5, 4). These results support a sequence involving oxidative addition of aryl halides to a photo-generated Ni(I). Next, the formation of aryl radicals was probed. A spin-trapping experiment was carried out by replacing nitrosoanisole with N-*tert*-butyl-α-phenylnitrone (PBN) as a radical trap under the identical reaction and operational conditions as above (Scheme 5, 5). The spin adduct of aryl radical was indeed observed by electron paramagnetic resonance (EPR) spectroscopy (Figure S5) and is characterized by the hyperfine coupling constants, which is in agreement with the literature data.[24] These observations suggest that the nitro C-N coupling involves a Ni(I)/N(III) cycle, with light required to generate the Ni(I) species and the Ni(III) being responsible for the formation of aryl radicals.

In conclusion, we have developed a new protocol that allows for the amination of aryl halides with nitroarenes. The amination is catalyzed by a Ni(II)-aryl complex under purple light irradiation with a trialkyl amine as the base, requiring no external photosensitizers. Starting with commercially available nitroarenes as the amines source, this reaction avoids the pre-reduction of nitroarenes to anilines, providing a step-economic strategy for further developing the Buchwald-Hartwig C-N coupling reaction.

Acknowledgements

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Keywords: amination • aryl halides • nitroarenes • nickel catalysis • aryl radicals

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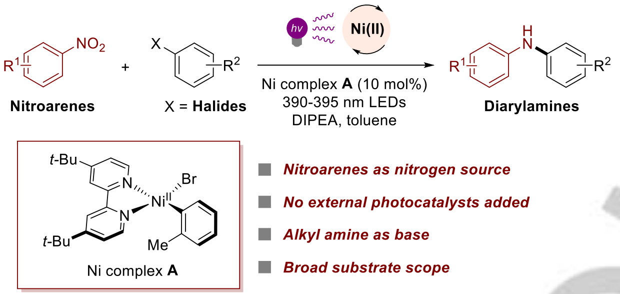

C-N coupling of aryl halides with nitroarenes is achieved by nickel catalysis under light irradiation and mild basic conditions, with no need for any external photosensitizers, offering a nitro version for the Buchwald-Hartwig C-N coupling reaction.