Photochemical Synthesis of Anilines via Ni-Catalyzed Coupling of Aryl Halides with Ammonium Salts

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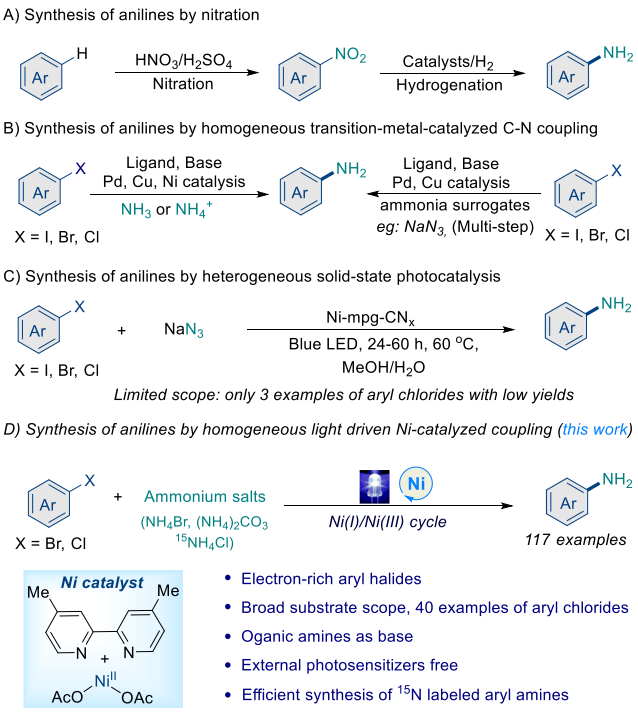
ABSTRACT: Easy, efficient and economic synthesis of anilines remains an important challenge in synthetic chemistry. In this study, a $Ni(OAc)_2$-bipyridine complex is shown to readily catalyze amination of aryl halides with ammonium salts under direct excitation of light, allowing a broad array of aryl chlorides and bromides to be converted into the corresponding primary (hetero)arylamines in the absence of an external photosensitizer. Late-stage modification of drug molecules and ^{15}N-labeling of primary aryl amines are also demonstrated with a number of examples. Photoinduced generation of Ni(I)-bipyridine species is believed to be the key step in the reaction, enabling a Ni(I)/Ni(III) cycle for catalytic turnover.

Introduction

Anilines are widely used fine chemicals for the synthesis of pharmaceuticals, agrochemicals, dyes and electronic materials.[1] To date, the most commonly used preparation method in industry is nitration of arenes followed by hydrogenation.[2] However, the environmental problems caused by the use of strong, corrosive acids HNO_3 and H_2SO_4 and the resulting functional group incompatibility challenge the continuing use of this method in practice (Scheme 1A).[3] Over the past one decade or so, the Pd[4] and Ni-catalyzed Buchwald-Hartwig[5,6] and Cu-catalyzed Ullmann-Ma[7, 8] amination of aryl halides with ammonia/ ammonium salts have become important methods for anilines synthesis (Scheme 1B). However, these methods often require the use of air-sensitive metal complexes, synthetically demanding ligands, or strong bases, and show a limited scope with aryl halides, particularly those that are functionalized, which hinders their wider application in organic synthesis.[4, 5, 7, 9] Whilst the direct utilization of ammonia would be preferred, it faces difficulties[6a] such as catalyst deactivation, loss of selectivity to monoarylation and the need for high-pressure reactors. To by-pass these limitations, ammonia surrogates such as silyl amines,[10] imines,[11] azides,[12] amides[13] and so on[14] have been employed (Scheme 1B). However, additional reaction steps are required to release the free anilines, while generating unwanted by-products. Hence, the development of efficient, selective and low-cost catalyst systems for the synthesis of anilines by C-N coupling of aryl halides, especially cheaper but less-reactive aryl chlorides, remains challenging. Recent progress in molecular nickel complexes-mediated photoredox catalysis[15] has addressed some major challenges facing cross-coupling reactions, expanding their scope under milder conditions.[16] In particular, photochemical C-C,[17] C-O[18] and C-N[19, 20] coupling reactions mediated by excited nickel complexes without external

Scheme 1. Methods for the synthesis of anilines

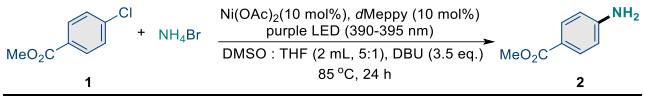


photocatalysts have been achieved. The strategy hinges on generating active Ni(I) species by light-induced homolysis of an excited Ni(II) complex, which initiates subsequent reactions[20, 21] However, the application of this strategy to the synthesis of anilines has not been reported. Herein, we disclose an efficient and general photochemical synthesis of anilines via $Ni(OAc)_2$-bipyridine complex-catalyzed C-N coupling of aryl halides with

ammonium salts (Scheme 1D). While this work was in progress, the Reisner group[22] reported a heterogeneous photocatalytic cross-coupling of aryl halides with sodium azide, in which the active Ni(I) species is generated via excitation of mesoporous carbon nitride (Scheme 1C). However, NaN_3 is shock sensitive, explosive and highly toxic[23] as nitrogen source, and the method is inefficient with aryl chlorides (<25% yields, incomplete with >60 h).

Results and Discussion

Table 1. Optimization of reaction conditions[a]



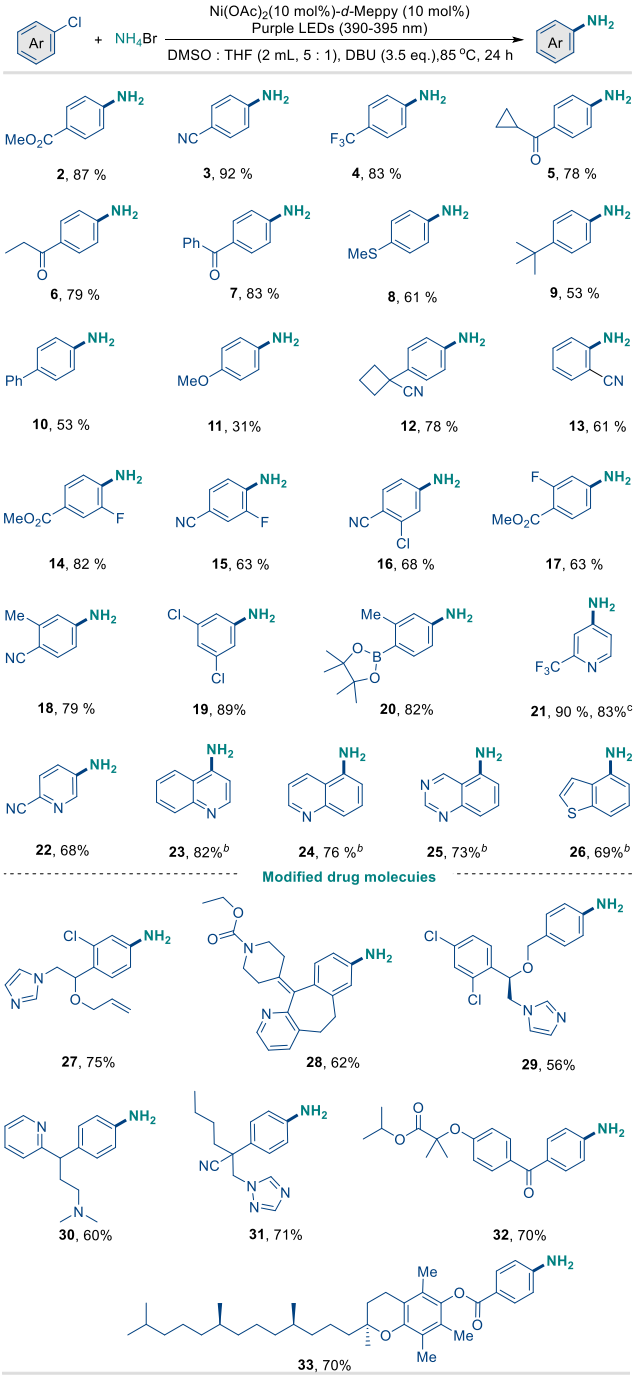
1 2

Entry	Variation from standard conditions	Yield (%)
1	Standard conditions	92，87[b]
2	Standard conditions, $Ni(COD)_2$ instead of $Ni(OAc)_2$	88
3	Standard conditions, NH_3 in H_2O	13
4	Standard conditions, NH_3 in THF or Dioxane	49/31
5	Standard conditions, NH_4Cl or NH_4I	71/59
6	Standard conditions, 380-385 nm	57
7	Standard conditions, 415-420 nm	32
8	Standard conditions, 460-465 nm	Trace
9	Standard conditions, Zn instead of light	32[c]
10	Standard conditions, light, 30 °C	Trace
11	Standard conditions, light, 40 °C	21
12	Standard conditions, light, 60 °C	47
13	Standard conditions, air instead of Ar	9
14	Standard conditions, no base	Trace
15	Standard conditions, no ligand	Trace
16	Standard conditions, no light, 85 °C	Trace

[a]Reaction conditions: 1 (0.2 mmol, 0.1 M), NH_4Br (0.4 mmol, 0.2 M), $Ni(OAc)_2$ (10.0 mol %), *d*-Mebpy (10.0 mol %), DBU (0.7 mmol, 0.35 M), DMSO : THF (2 mL, 5 : 1), 390-395 nm LEDs, 85 ℃, Ar, 24 h. [b]Isolated Yields. [c]Zn (0.1 equiv). Yields determined by ^1H NMR analysis using 1,3-benzodioxole as internal standard.

In continuing our study of nickel complexes-mediated photocatalytic coupling reactions,[20] we set out to examine conditions for the coupling of methyl 4-chlorobenzoate (1). As shown in Table 1, when the $Ni(OAc)_2$-*d*-Mebpy complex, prepared in situ from $Ni(OAc)_2$ and *d*-Mebpy (*d*-Mebpy: 4,4'-dimethybipyridine), was used as the catalyst, NH_4Br as ammonium source and DBU as the base, the desired aryl amine (2) was obtained with 87% isolated yield in a mixture solvent of DMSO and THF under the irradiation of purple light (390-395 nm) in the absence of an external photosensitizer (entry 1).[24] The bipyridine ligand and Ni salt play a crucial role (Table S1, S16 in SI). Among the investigated nickel catalysts, the $Ni(OAc)_2$-*d*-Mebpy complex exhibited the highest activity (Table S1, in SI). Meanwhile, the $Ni(0)(COD)_2$ complex as Ni source also afforded the coupling product in high yield, but it is very sensitive in air (entry 2). Notably, the ammonium source was also important for the

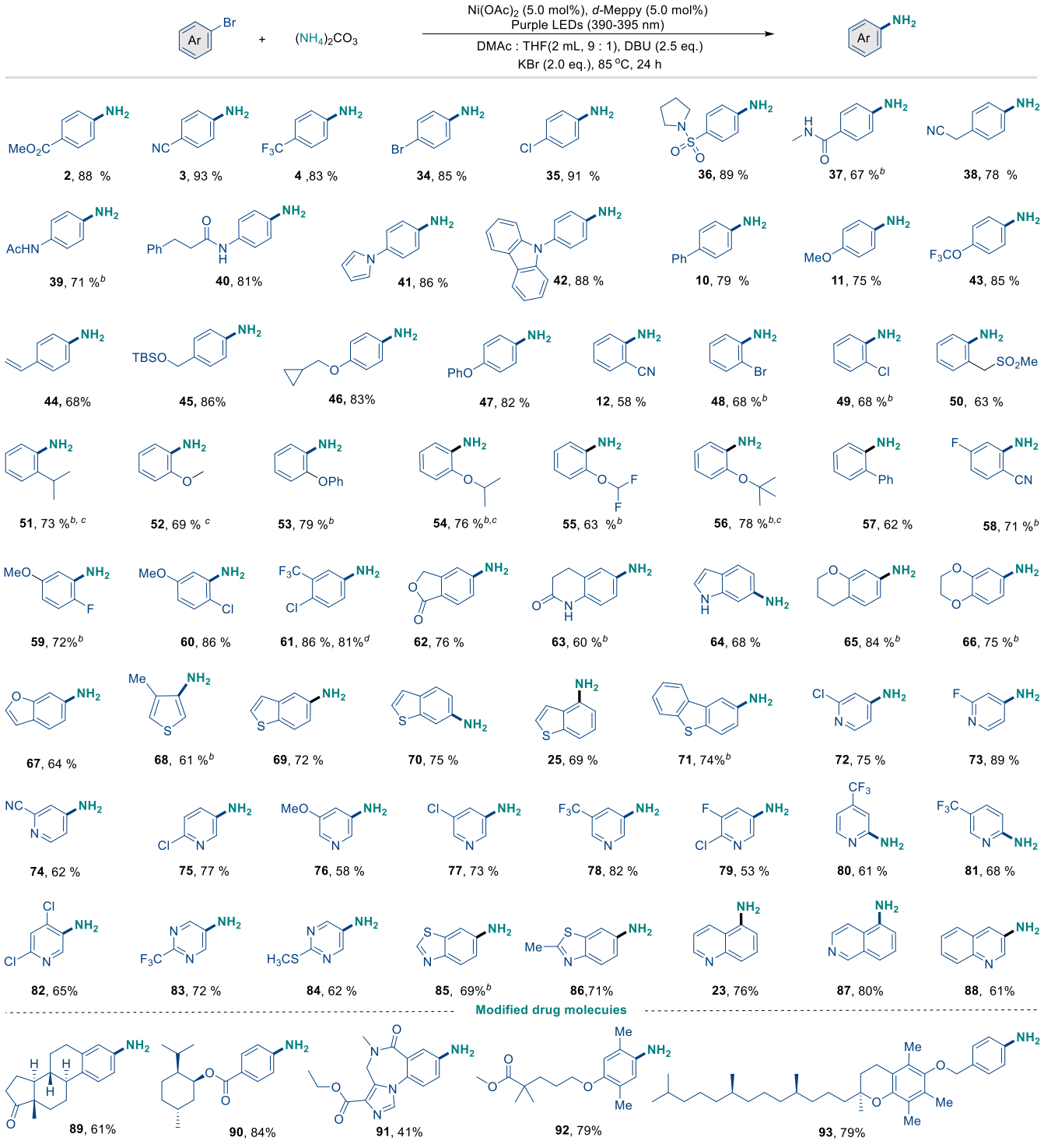
Table 2. Scope of aryl chlorides[a]



[a]Aryl chloride (0.2 mmol, 0.1 M), NH_4Br (0.4 mmol, 0.2 M), $Ni(OAc)_2$ (10.0 mol %), *d*-Mebpy (10.0 mol %), DBU (0.7 mmol, 0.35 M), DMSO : THF (2 mL, 5 : 1), purple LEDs (390-395 nm), 85 ℃, Ar, 24 h. Isolated yields are shown. [b]36 h. [c]Gram scale.

success of this C-N coupling. A low yield was obtained using an ammonia solution (entry 3-4), while ammonium salts gave higher yields (entry 5). Light is essential for the reaction as well, with purple light (390-395 nm) promoting the C-N coupling with highest efficiency (entries 1 vs 6-8). When the light was replaced with Zn(0) as a reducing agent,[21h] the yield of the C-N coupling product was low, only at 32% (entry 9), and when the reaction was conducted in the dark, little coupling was

Table 3. Scope of aryl bromides[a]



[a]Aryl halides (0.2 mmol, 0.1 M), $(NH_4)_2CO_3$ (0.25 mmol, 0.125 M), KBr (0.4 mmol, 0.2 M), $Ni(OAc)_2$ (5.0 mol %), *d*-Mebpy (5.0 mol %), DBU (0.5 mmol, 0.25 M), DMAc : THF (2 mL, 9 : 1), purple LEDs (390-395 nm), 85 ℃, Ar, 24 h. Isolated yields are shown. [b]36 h. [c]DMSO : THF (2 mL, 5 : 1). [d] Gram scale.

observed (entry 9). Temperature is also important, as little product was obtained below 30 °C (entries 10-12). Heating may be required to facilitate the oxidative addition of Ni(I) with the aryl halide.[21] In addition, the light-on and off experiments[25] showed that continuous illumination is required throughout to sustain the catalytic turnover, presumably to generate active Ni(I) catalyst from off-cycle Ni(II) species (Table S9 in SI, and below). It is noted that the presence of oxygen dramatically decreased the reaction efficiency (entry 13). The choice of base also impacted considerably on the success of coupling (entry 14).

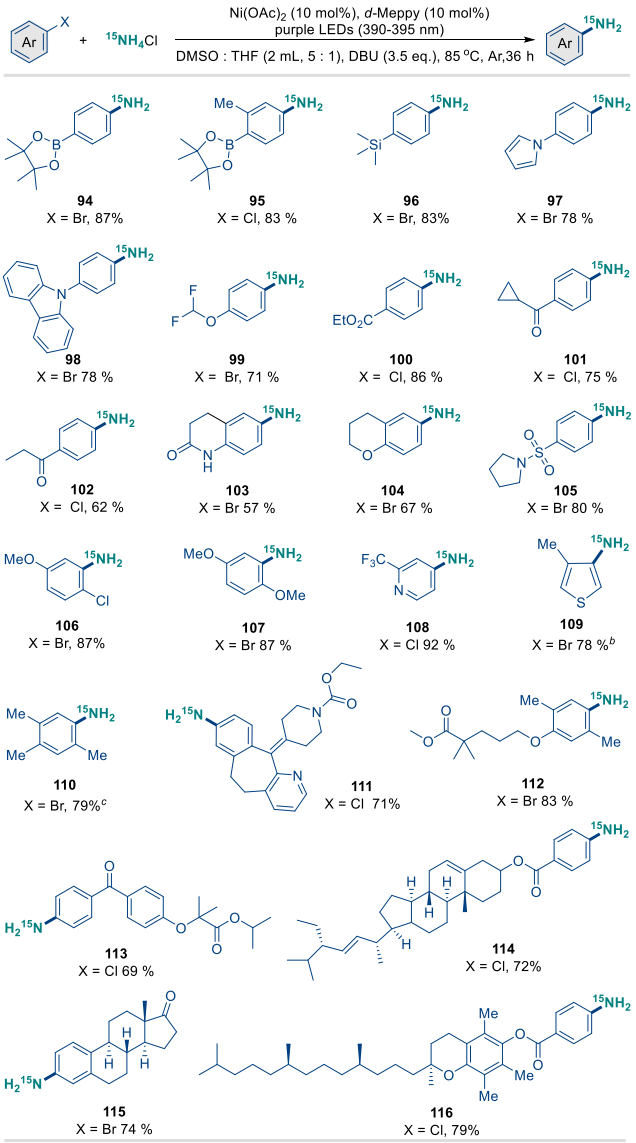
Among the investigated bases, inorganic bases were all ineffective, and only organic bases were shown to be effective, with the mild, soluble DBU promoting the reaction significantly better than other organic bases (Table S4, S12 in SI). Control experiments revealed that the reaction did not proceed in the absence of the organic base, ligand and light (entries 14-16).

With the optimized conditions in hand, the reaction scopewas explored. As summarized in Table 2, a wide range of electron-neutral, -rich, and -deficient aryl chlorides could couple efficiently with NH_4Br, delivering the desired aryl amines with high yields generally (**2-19**). Aryl chlorides with electron-withdrawing substituents such as -CO_2Me, -CN, -CF_3, and -COR (R = Me, cyclopropyl and Ph) in the para position of the phenyl ring coupled with NH_4Br, affording the desired products with excellent yields (**2-7**). Except trifluoromethyl, these functional groups provide an opportunity for subsequent transformations. Due to the use of a weak amine base, all electrophiles containing the ester and cyano group are tolerated, affording the anilines in good yields (**2-3**, **12-18**). In contrast, the use of strong bases could lead to the formation of transesterification products and impurities in the coupling reactions.[26] Unactivated aryl chlorides containing substituents such as -SMe, -t-Bu and -Ph are compatible in this protocol (**8-10**). However, the yield of the substrate (**11**) containing the more electron-donating -OMe substituent was low.[9] Meanwhile, sterically hindered aryl chlorides were also adaptable, delivering the desired aryl amines with good yields (**13-15**). Disubstituted aryl chlorides with sensitive functional groups could also participate in the reaction efficiently (**14-20**), and no further reaction was observed with the dichloro (**19**) and BPin (**20**) groups. (Hetero)aryl chlorides containing pyridine (**21-22**), quinolines (**23-24**), quinazoline (**25**) and thianaphthene (**26**) are also compatible, which are important in medicinal chemistry.[27]

The utility of the method is also demonstrated in the late-stage modification of drug molecules and derivatives. As shown in Scheme 2, Imazalil (**27**, fungicide),[28a] Loratadine (**28**, antihistamines),[28b] Econazole (**29**, antifungal agents),[28c] Chlorpheniramine (**30**, antihistamines), Myclobutanil (**31**, fungicide),[28d] Fenofibrate (**32**, for mixed dyslipidemia or primary hypercholesterolemia)[28e] and chloride diversified Tocopherol (**33**) were adaptable to this catalyst system, affording the aminated derivatives with high efficiency. Considering the prevalence of amino moieties in drug molecules, this method thus provides an attractive approach to late-stage functionalization of Csp^2-X (X = Cl, Br, also see below) bonds to Csp^2-NH_2 analogues in drug and other bioactive molecules, aiding in drug development.

Next, the scope of aryl bromides was examined. As summarized in Table 3, regardless of the electronic properties of the aryl bromides, the reaction proceeded efficiently with ammonium carbonate, affording the desired anilines in high yields in general. Compared with ammonium bromide, the use of ammonium carbonate reduces the amount of organic base, while affording a similar product yield. Thus, aryl bromides bearing electron-withdrawing substituents, such as -CO_2Me, -F, -Cl, -Br, -CF_3, -CN, -CH_2CN, pyrrole, sulfonamide and amide in the para or meta position, all delivered the products with good to excellent yields (**2-4**, **34-38**). In particular, for aryl bromides bearing electron-neutral and -rich substituent, the corresponding amines were obtained also with high yields (**39-42**, **10-11**, **43-48**). Such substrates are usually difficult to undergo photoredox C-N cross-coupling reactions. Furthermore, the vinyl unit in 44 remained intact during the coupling reaction. It is gratifying that the sterically more-demanding ortho- substituted aryl

Table 4. Amination of aryl halides with ^{15}N-labeled ammonium salt[a]



[a]Aryl halide (0.2 mmol, 0.1 M), $^{15}NH_4Cl$ (0.4 mmol, 0.2 M), $Ni(OAc)_2$ (5.0 mol%), *d*-Mebpy (5.0 mol %), DBU (0.75 mmol, 0.35 M), DMSO : THF (2 mL, 5 : 1), purple LEDs (390-395 nm), 85 ℃, Ar, 24 h. [b] $^{15}NH_4Cl$ (0.24 mmol, 0.12 M). [c]36 h. Isolated yields.

bromides also afforded the desired products in high yields (**12, 49-61**). Disubstituted aryl bromides also worked successfully (**59-63**), highlighting the wide scope of aryl electrophiles in this C-N coupling reaction. Of further interest is that a range of (hetero)aryl bromides are compatible, delivering aryl amines containing indole (**64**), isobenzo-furan-1(3H)-one (**65**), benzofuran (**67**), thiophene (**68**), benzothiophene (**69-71**), pyridine (**72-82**), pyrimidine (**83-84**), benzothiazole (**85-86**), quino-lone (**23, 88**), and isoquinoline (**87**). As in the case of aryl chlorides, this methodology could also be applied to the late-stage modification of drug-like molecules bearing an aryl bromide unit. Examples are seen in the synthesis of estrone (**89**), gemfibrozil methyl ester (**92**), flumazenil (**91**) and other complex molecules (**90, 93**) with good yields. Together with the examples of aryl chlorides, the results obtained with aryl bromides demonstrate

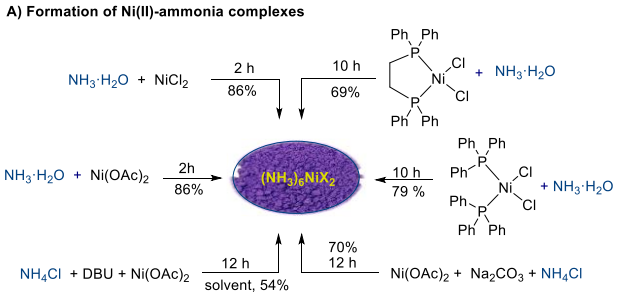
the great potential of this light-driven Ni(II)-catalysis protocol for the synthesis of various anilines.

The facile synthesis of ^{15}N-labeled anilines further demonstrates the utility of this method. ^{15}N-labeled compounds are of significance in studying the pharmacokinetics and metabolism of bioactive compounds.[29] ^{15}N-labeled anilines, key precursors for the synthesis of ^{15}N-labeled aromatic heterocycles,[30] are usually prepared by a nitration-reduction process with ^{15}N-labeled nitric acid as nitrogen source.[31, 32] Using this light-driven Ni(II)-catalyzed C-N coupling reaction, ^{15}N-labeled anilines could be readily accessed with commercially available $^{15}NH_4Cl$, a cheaper and more conveniently handled nitrogen-15 source. Note that there has been only one liter-ature example of ^{15}N-labeled anilines being prepared via C-N coupling reaction.[4k] As shown in Table 4, aryl halides containing boron ester (**94-95**), silane (**96**), pyrrole (**97**), carbazole (**98**), ketone (**101-102**), amide (**103**), sulfonamidec (**105**), multisubstituents (**104, 106-107, 110**), pyridine (**108**) and thiophene (**109**) all coupled efficiently, requiring only 2 equivalents of $^{15}NH_4Cl$ while delivering important ^{15}N-labeled aryl amines in good yields. Notably, ^{15}N-labeling of bioactive and drug molecules can also be readily performed. Examples are seen in the synthesis of ^{15}N-labeled Loratadine (**111**), Gemfibrozil methyl ester (**112**), Fenofibrate (**113**), Estrone (**115**), Tocopherol (**116**) and a halogenated complex molecule (**114**). Thus, this methodology provides a handy tool for the synthesis of ^{15}N-labeled anilines and drug-like molecules.

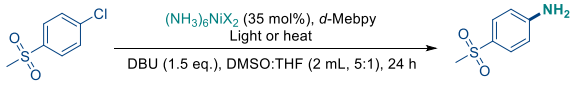
Preliminary studies were carried out to gain understanding of the possible reaction mechanism. Firstly, the possibility of ammonia coordination to nickel and the effect of the resulting complexes on the reaction were investigated. As shown in Scheme 2, ammonia or ammonium salts can readily convert various Ni(II) compounds to ammonia-ligated $[(NH_3)_6Ni(II)]X_2$ with high yields (Scheme 2 A, and Section 4 in SI).[24, 33] However, the nickel complexes $[(NH_3)_6Ni(II)]X_2$ could not participate in the C-N coupling reactions under either thermal or photocatalytic conditions (Section 7.3 in SI). In contrast, upon introduction of the *d*-Mebpy ligand light irradiation, the desired product was obtained in high yields (Scheme 2 B, and Section 7.3 in SI), highlighting the critical role of ligand and light in this coupling reaction.

UV-Vis and HRMS spectroscopy shed light on the nickel-bipyridine complexes formed. The complex $[(NH_3)_6Ni(II)](OAc)_2$ displays absorption features similar to those of octahedral Ni(II)-ammonia complexes (Scheme 2 C, and Fig12 in SI).[24, 33] When the bipyridine ligand was introduced, the absorption band of the Ni(II)-ammonia complex disappeared, being replaced by a new absorption band at 340 nm with a shoulder at 392 nm which falls within the light used in this study. The same absorptions are seen when $Ni(II)(OAc)_2$ is reacted with *d*-Mebpy (Scheme 2 E, and Fig13 in SI), indicating the formation of $[Ni(OAc)_2(d\text{-Mebpy})]$ and complete displacement of NH_3 by *d*-Mebpy in the case of $[(NH_3)_6Ni(II)](OAc)_2$.[20c] In support of this surmise, ammonia gas was detected by GC analysis (SI, Section 6). The HRMS of the mixture of $[(NH_3)_6Ni(II)](OAc)_2$ and *d*-Mebpy revealed a m/z peak at 301.0483, which is consistent with the formation of $[Ni(II)(OAc)(d\text{-Mebpy})]^+$ or $[Ni(OAc)_2(d\text{-Mebpy})]$ (Fig 13 in SI). Thus, it appears that the active catalyst of this C-N coupling reaction is derived from a Ni(II)-bipyridine precatalyst that bears no coordinated NH_3. Additional probe reactions were also conducted. When the premade $[Ni(OAc)_2(d\text{-Mebpy})]$ complex was irradiated at 390-395 nm for 5 h in the absence of substrates

Scheme 2. Mechanistic investigations[a]

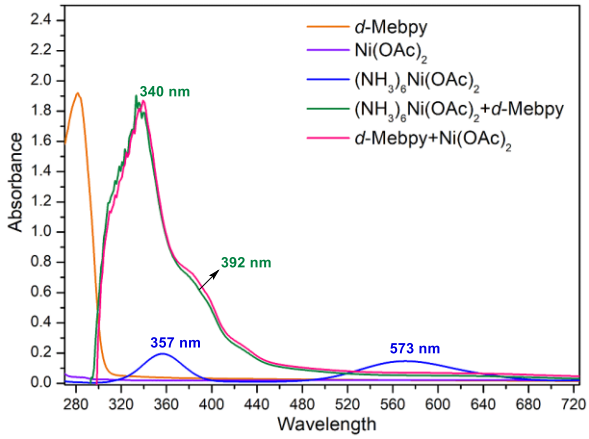


B) Amination of aryl chloride with Ni-ammonia complexes

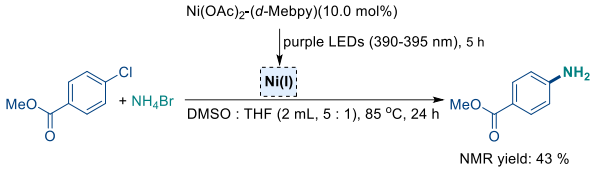


Entry	Conditions				
	Ni-amine-complex	Light (or Heat)	Ligand	Base	Yield (%)[a]
1	$(NH_3)_6Ni(OAc)_2$	Heat	*d*-Mebpy	DBU	N.R.
2	$(NH_3)_6NiCl_2$	Light	*d*-Mebpy	DBU	95
3	$(NH_3)_6Ni(OAc)_2$	Light	*d*-Mebpy	DBU	96
4	$(NH_3)_6Ni(OAc)_2$	Light	–	–	N.R.

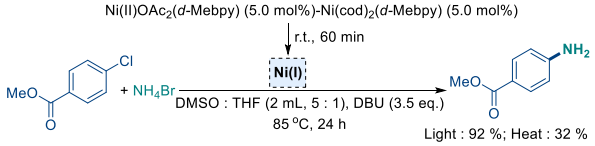
C) UV-Vis absorption spectra



D) Amination of aryl chloride with Ni(I)-*d*-Mebpy complex generated via irradiation



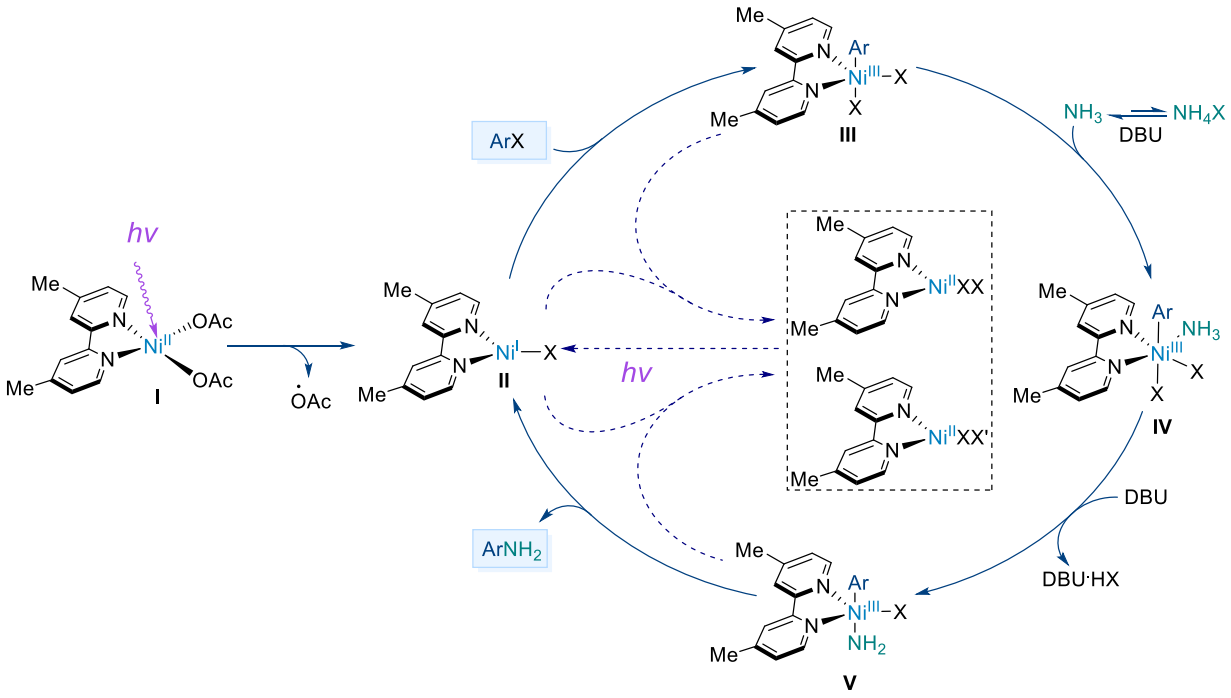
E) Amination of aryl chloride with Ni(I) complex generated via comproportionation



[a]UV-Vis absorption spectra were recorded at $1.0x0^{-3}$ M (1 mm pathlength quartz cuvette). For details, see Supporting Information.

and followed by reacting with 4-chlorobenzoate methyl ester and ammonium bromide in the dark, the desired product was obtained in 43% yield in 24 h (Scheme 2 D).[24] In our previous studies,[20c, e] $Ni(OAc)_2$-bipyridine complexes were shown to generate Ni(I) species via light-induced homolytic cleavage of

Scheme 3. A tentative mechanism for the amination under light-promoted nickel catalysis (X = Cl, Br or OAc; X'= NH_2)



the Ni-OAc bond, which then undergoes oxidative addition with an aryl halide. In line with the hypothesis of Ni(I) species being the active catalyst, a similar yield was observed when the same coupling was conducted under thermal conditions, in which a Ni(I) complex was generated in situ from the comproportionation of [Ni(OAc)$_2$(*d*-Mebpy)] and [Ni(0)(*d*-Mebpy)(cod)] complexes (Scheme 2, E).[20, 24, 34] It is noted, however, that the yields of these thermal reactions are significantly lower than those obtained under the photocatalytic conditions, highlighting the need for light during the catalysis.

On the basis of these observations and the recent mechanistic studies on light-promoted Ni-catalyzed C-O and C-N coupling reactions by several groups,[16, 19, 20, 21] a simplified mechanistic pathway for the amination is suggested in Scheme 3. Irradiation of the Ni(OAc)$_2$-*d*-Mebpy complex at 390-395 nm excites the Ni(II) complex **I**, generating a Ni(I) species **II** by light-induced homolytic cleavage of the Ni-OAc bond. The Ni(I) species then reacts with the aryl halide to generate a Ni(III)-Ar intermediate **III**, ligation of which with ammonia leads to Ar-Ni(III)-NH_3 **IV**. Deprotonation of the coordinated NH_3 by DBU yields Ar-Ni(III)-NH_2 **V**, which undergoes reductive elimination to afford the C-N coupled product while regenerating the Ni(I) species. Continuous lighting is necessary. This is probably due to the formation of off-cycle, catalytically inactive Ni(II) species from the comproportionation of Ni(III) and Ni(I) or the homolysis of Ni(III)-Ar intermediate, which requires continuous irradiation to convert to the active Ni(I) and thus sustain catalytic turnover.[21a, e]

Conclusion

In summary, we have developed a highly efficient photochemical C-N coupling reaction of aryl halides with ammonium salts. The reaction is catalyzed by the easily available Ni(OAc)$_2$-*d*-Mebpy complex under direct excitation of light without the need for any external photosensitizer. With a diverse range of more than 110 examples reported, this coupling protocol demonstrates the practical applicability in the synthesis of anilines, late-stage modification of drug molecules and ^{15}N-labeling of primary aryl amines. Mechanistic probing points to a Ni(I)/Ni(III) cycle that drives the catalytic turnover.

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Notes

Any additional relevant notes should be placed here.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at https://pubs.acs.org/.

Experimental detailed and spectroscopic data (PDF).

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REFERENCES

(1) For Selected Reviews, See: (a) Lawrence, S. A. *Amines: Synthesis Properties and Applications*, Cambridge University Press, Cambridge, **2004**, p1-384. (b) Roundhill, D. M. Transition Metal and Enzyme Catalyzed Reactions Involving Reactions with Ammonia and Amines. *Chem. Rev.* **1992**, *92*, 1-27.

(2) Downing, R. S.; Kunkeler, P. J.; Bekkum H. van. Catalytic Syntheses of Aromatic Amines. *Catal. Today*, **1997**, *37*, 121-136.

(3) (a) Formenti, D.; Ferretti, F.; Scharnagl, F. K.; Beller, M. Reduction of Nitro Compounds Using ^{3}d-Non-Noble Metal Catalysts. *Chem. Rev.* **2019**, *119*, 2611-2680. (b) Orlandi, M.; Brenna, D.; Harms, R.; Jost, S.; Benaglia, M. Recent Developments in the Reduction of Aromatic and Aliphatic Nitro Compounds to Amines. *Org. Process Res. Dev.* **2018,** *22*, 430-445.

(4) For Selected Examples of Pd-Catalyzed Buchwald-Hartwig Amination Using Ammonia/Ammonium Salts, See: (a) Shen, Q. Hartwig, J. F. Palladium-Catalyzed Coupling of Ammonia and Lithium Amide with Aryl Halides. *J. Am. Chem. Soc.* **2006**, *128*, 10028-10029. (b) Surry, D. S. Buchwald, S. L. Selective Palladium-Catalyzed Arylation of Ammonia: Synthesis of Anilines as Well as Symmetrical and Unsymmetrical Di- and Triarylamines. *J. Am. Chem. Soc.* **2007**, *129*, 10354-10355. (c) Vo, G. D.; Hartwig, J. F. Palladium-Catalyzed Coupling of Ammonia with Aryl Chlorides, Bromides, Iodides, and Sulfonates: A General Method for the Preparation of Primary Aryl amines. *J. Am. Chem. Soc.* **2009**, *131*, 11049-11061. (d) Schulz, T.; Torborg, C.; Enthaler, S.; Schäffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Börner, A.; Beller, M. A General Palladium-Catalyzed Amination of Aryl Halides with Ammonia. *Chem. Eur. J.* **2009**, *15*, 4528-4533. (e) Klinkenberg, J. L.; Hartwig, J. F.; Slow Reductive Elimination from Arylpalladium Parent Amido Complexes. *J. Am. Chem. Soc.* **2010**, *132*, 11830-11833. (f) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem. Eur. J.* **2010**, *16*, 1983-1991. (g) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. A P,N-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl Chlorides, Chemoselective Arylations, and Room Temperature Reactions. *Angew. Chem. Int. Ed*. **2010**, *49*, 4071-4074. (h) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. Recyclable Catalysts for Palladium-Catalyzed Aminations of Aryl Halides. *Chem. Eur. J.* **2011**, *17*, 9599-9604. (i) Cheung, C. W.; Surry, D. S.; Buchwald, S. L. Mild and Highly Selective Palladium-Catalyzed Monoarylation of Ammonia Enabled by the Use of Bulky Biarylphosphine Ligands and Palladacycle Precatalysts. *Org. Lett.* **2013**, *15*, 3734-3737. (j) Alsabeh, P. G.; Lundgren, R. J.; McDonald, R.; Johansson Seechurn, C. C. C.; Colacot, T. J.; Stradiotto, M. An Examination of the Palladium/Mor-DalPhos Catalyst System in the Context of Selective Ammonia Monoarylation at Room Temperature. *Chem. Eur. J.* **2013**, *19*, 2131-2141. (k) Green, R. A.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Chlorides and Bromides with Ammonium Salts. *Org. Lett.* **2014**, *16*, 4388-4391. (l) Lombardi, C.; Day, J.; Chandrasoma, N.; Mitchell, Rodriguez, D. M.; Farmer, J. J. L.; Organ, M. G. Selective Cross-Coupling of (Hetero)aryl Halides with Ammonia to Produce Primary Arylamines using Pd-NHC Complexes. *Organometallics* **2017**, 36, 251-254.

(5) For Selected Examples of Ni-catalyzed Buchwald-Hartwig Amination Using Ammonia/Ammonium Salts, See: (a) Borzenko, A.; Rotta-Loria, N. L.; Macqueen, P. M.; Lavoie, C. M.; McDonald, R.; Stradiotto, M. Nickel-Catalyzed Monoarylation of Ammonia. *Angew. Chem. Int. Ed.* **2015**, *54*, 3773-3777. (b) Green, R. A.; Hartwig, J. F.; Nickel-Catalyzed Amination of Aryl Chlorides with Ammonia or Ammonium Salts. *Angew. Chem. Int. Ed.* **2015**, *54*, 3768-3772. (c) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm,A. J.; Hargreaves,B. K. V.; McDonald, R.; Ferguson,M. J.; Stradiotto, M. Challenging Nickel-Catalysed Amine Arylations Enabled by Tailored Ancillary Ligand Design. *Nat. Commun.* **2016**, *7*, 11073. (d) MacQueen, P. M.; Stradiotto, M.; Nickel-Catalyzed Cross-Coupling of Ammonia or Primary Alkylamines with (Hetero)aryl Sulfamates, Carbamates, or Pivalates. *Synlett* **2017**, *28*, 1652-1656. (e) Schranck, J.; Furer, P.; Hartmann, V.; Tlili, A. Nickel-Catalyzed Amination of Aryl Carbamates with Ammonia. *Eur. J. Org. Chem.* **2017**, 3496-3500. (f) Lavoie, C. M.; Tassone, J. P.; Ferguson, M. l J.; Zhou, Y.; Johnson, E. R.; Stradiotto, M. Probing the Influence of PAd-DalPhos Ancillary Ligand Structure on Nickel-Catalyzed Ammonia Cross-Coupling. *Organometallics* **2018**, *37*, 4015-4023.

(6) For Selected Reviews on Buchwald-Hartwig Amination, See: (a) Schranck, J.; Tlili, A. Transition-Metal-Catalyzed Monoarylation of Ammonia. *ACS Catal.* **2018**, *8*, 405-418. (b) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald–Hartwig Amination After 25 Years. *Angew. Chem. Int. Ed.* **2019**, *58*, 17118-17129. (c) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564-12649. (d) Forero-Cortés, P. A.; Haydl, A. M. The 25th Anniversary of the Buchwald–Hartwig Amination: Development, Applications, and Outlook. *Org. Process Res. Dev*. **2019**, *23*, 1478-1483. (e) Beletskaya, I. P.; Cheprakov, A. V. The Complementary Competitors: Palladium and Copper in C–N Cross-Coupling Reactions. *Organometallics*, **2012**, *31*, 7753-7808.

(7) For Selected Examples of Cu-Catalyzed Ullmann Cross-Coupling Using Ammonia/Ammonium Salts, See: (a) Kim, J.; Chang, S. Ammonium Salts as an Inexpensive and Convenient Nitrogen Source in the Cu-Catalyzed Amination of Aryl Halides at Room Temperature. *Chem. Commun.* **2008**, 3052-3054. (b) Xia, N.; Taillefer, M. A Very Simple

Copper-Catalyzed Synthesis of Anilines by Employing Aqueous Ammonia. *Angew. Chem. Int. Ed*. **2009**, 48, 337-339. (c) Jiang, L.; Lu, X.; Zhang, H.; Jiang, Y.; Ma, D. CuI/4-Hydro-l-proline as a More Effective Catalytic System for Coupling of Aryl Bromides with *N*-Boc Hydrazine and Aqueous Ammonia. *J. Org. Chem.* **2009**, *74*, 4542-4546. (d) Xu, H.; Wolf, C. Efficient Copper-Catalyzed Coupling of Aryl Chlorides, Bromides and Iodides with Aqueous Ammonia. *Chem. Comm.* **2009**, 3035-3037. (e) Elmkaddem, M. K.; Fischmeister, C.; Thomas, C. M.; Renaud, J. -L. Efficient Synthesis of Aminopyridine Derivatives by Copper Catalyzed Amination Reactions. *Chem. Commun.* **2010**, *46*, 925-927. (f) Thakur, K. G.; Ganapathy, D.; Sekar, G. *d*-Glucosamine as a Green Ligand for Copper Catalyzed Synthesis of Primary Aryl Amines from Aryl Halides and Ammonia. *Chem. Commun.* **2011**, *47*, 5076-5078. (g) Fan, M.; Zhou, W.; Jiang, Y.; Ma, D. Assembly of Primary (Hetero)Arylamines via CuI/Oxalic Diamide-Catalyzed Coupling of Aryl Chlorides and Ammonia. *Org. Lett.* **2015**, *17*, 5934-5937. (h) Gao, J.; Bhunia, S.; Wang, K.; Gan, L.; Xia, S.; Ma, D. Discovery of *N*-(Naphthalen-1-yl)-*N*′-alkyl Oxalamide Ligands Enables Cu-Catalyzed Aryl Amination with High Turnovers. *Org. Lett.* **2017**, *19*, 2809-2812.

(8) For Selected Reviews on Cu-Catalyzed Ullmann Cross-Coupling, See: (a) Cai, Q.; Zhou, W. Ullmann-Ma Reaction: Development, Scope and Applications in Organic Synthesis. *Chin. J. Chem.* **2020**, *38*, 879-893. (b) Chen, J.; Li, J.; Dong, Z. A Review on the Latest Progress of Chan-Lam Coupling Reaction. *Adv. Synth. Catal.* **2020**, *362*, 3311-3331. (c) Bhunia, S; Goroba Pawar, G.; VijayKumar, S.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C−N, C−O, C−S, and C−C Bond Formation. *Angew. Chem. Int. Ed.* **2017**, *56*, 16136-16179. (d) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. Copper Catalysed Ullmann Type Chemistry: From Mechanistic Aspects to Modern Development. *Chem. Soc. Rev.* **2014**, *43*, 3525-3550.

(9) (a) Harris, M. C.; Huang, X.; Buchwald, S. L. Improved Functional Group Compatibility in the Palladium-Catalyzed Synthesis of Aryl Amines. *Org. Lett.* **2002**, *4*, 2885-2888. (b) Sperry, J. B.; Wiglesworth, K. E. P.; Edmonds, I.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Chekler, E. L. P.; Langille, J.; Coe, J. W. Kiloscale Buchwald–Hartwig Amination: Optimized Coupling of Base-Sensitive 6-Bromoisoquinoline-1-carbonitrile with (*S*)-3-Amino-2-methylpropan-1-ol. *Org. Process Res. Dev.* **2014**, *18*, 1752-1758. (c) Chen, Z.; Jiang, Y.; Zhang, L.; Guo, Y.; Ma, D. Oxalic Diamides and tert-Butoxide: Two Types of Ligands Enabling Practical Access to Alkyl Aryl Ethers via Cu-Catalyzed Coupling Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 3541-3549. (d) Liu, R. Y.; J. Dennis, M.; Buchwald, S. L. The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C–N Cross-Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 4500-4507.

(10) (a) Lee, S.; Jorgensen, M.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides and Lithium Bis(trimethylsilyl)amide as an Ammonia Equivalent. *Org. Lett.* **2001**, *3*, 2729-2732. (b) Huang, X. H.; Buchwald, S. L. New Ammonia Equivalents for the Pd-Catalyzed Amination of Aryl Halides. *Org. Lett.* **2001**, *3*, 3417-3419. (c) Lee ,D. Y.; Hartwig, J. F. Zinc Trimethylsilylamide as a Mild Ammonia Equivalent and Base for the Amination of Aryl Halides and Triflates. *Org. Lett.* **2005**, *7*, 1169-1172.

(11) (a) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates. *Tetrahedron Lett.* **1997**, *38*, 6367-6370. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. Amination Reactions of Aryl Halides with Nitrogen-Containing Reagents Mediated by Palladium/Imidazolium Salt Systems. *J. Org. Chem.* **2001**, *66*, 7729-7737.

(12) (a) Messaoudi, S.; Brion, J. D.; Alami, M. An Expeditious Copper-Catalyzed Access to 3-Aminoquinolinones, 3-Aminocoumarins and Anilines using Sodium Azide. *Adv. Synth. Catal.* **2010**, *352*, 1677-1687. (b) Georgiádes, Á.; Ötvös, S. B.; Fülöp, F. Controlled Transformations of Aryl Halides in a Flow System: Selective Synthesis of Aryl Azides and Aniline Derivatives. *Adv. Synth. Catal.* **2018**, *360*, 1841-1849. (c) Thakur, K. G.; Srinivas, K. S.; Chiranjeevi, K.; Sekar, G. *d*-Glucosamine as an Efficient Ligand For the Copper-Catalyzed Selective Synthesis of Anilines From Aryl Halides and NaN_3. *Green Chem.* **2011**, *13*, 2326-2329.

(13) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational, and Synthetic Investigation. *J. Am. Chem. Soc*. **2007**, *129*, 13001-13007.

(14) (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G.; Allyl Amines as Ammonia Equivalents in the Preparation of Anilines and Heteroarylamines. *Tetrahedron Lett*. **1998**, *39*, 1313-1316. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M.; Room-Temperature Palladium-Catalyzed Amination of Aryl Bromides and Chlorides and Extended Scope of Aromatic C−N Bond Formation with a Commercial Ligand. *J. Org. Chem.* **1999**, *64*, 5575-5580. (c) Yin, J.; Buchwald, S. L. Palladium-Catalyzed Intermolecular Coupling of Aryl Halides and Amides. *Org. Lett.* **2000**, *2*, 1101-1104. (d) Weigand, K.; Pelka, S. Palladium-Catalyzed Amination of Aryl Halides on Solid Support Klaus Weigand and Sylvie Pelka. *Org. Lett*. **2002**, *4*, 4689-4692. (e) Weigand, K.; Pelka, S.; Microwave-Assisted Pd(0)-Catalyzed Amination of Aryl Halides on Solid Support. *Mol. Diversity* **2003**, *7*, 181-184. (f) Trabanco, A. A.; Vega, J. A.; Fernµndez, M. A. Fluorous-Tagged Carbamates for the Pd-Catalyzed Amination of Aryl Halides. *J. Org. Chem.* **2007**, *72*, 8146-8148. (g) Gao, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. Copper-Catalyzed Synthesis of Primary Arylamines via Cascade Reactions of Aryl Halides with Amidine Hydrochlorides. *J. Org. Chem.* **2008**, *73*, 6864-6866.

(15) (a) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102-113. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322-5363. (c) Koike, T.; Akita, M. Visible-Light Radical Reaction Designed by Ru- and Ir-Based Photoredox Catalysis. *Inorg. Chem. Front.* **2014**, *1*, 562-576. (d) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The Merger of Transition Metal and Photocatalysis. *Nat. Rev. Chem.* **2017**, *1*, 0052. (e) Milligan, J. A.; Phelan, J. P.; Badir, S. O.; Molander, G. A. Alkyl Carbon–Carbon Bond Formation by Nickel/Photoredox Cross-Coupling. *Angew. Chem. Int. Ed.* **2019**, *58*, 6152-6163. (f) Wenger, O. S. Photoactive Nickel Complexes in Cross-Coupling Catalysis. *Chem. Eur. J.* **2021**, *27*, 2270-2278.

(16) (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-Electron Transmetalation in Organoboron Cross-Coupling by Photoredox/Nickel Dual Catalysis. *Science* **2014**, *345*, 433-436. (b) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437-440. (c) Heitz, D. R.; Tellis, J. C.; Molander, G. A. Photochemical Nickel-Catalyzed C–H Arylation: Synthetic Scope and Mechanistic Investigations. *J. Am. Chem. Soc.* **2016**, *138*, 12715-12718. (d) Shields, B. J.; Doyle, A. G.; Direct $C(sp^3)$–H Cross Coupling Enabled by Catalytic Generation of Chlorine Radicals. *J. Am. Chem. Soc.* **2016**, *138*, 12719-12722. (e) Welin, E. R.; Le, C.; Arias-Rotondo, D. M.; McCusker, J. K.; MacMillan, D. W. C. Photosensitized, Energy Transfer-Mediated Organometallic Catalysis Through Electronically Excited Nckel(II). *Science* **2017**, *355*, 380-385. (f) Oderinde, M. S.; Jones, N. H.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W. Highly Chemoselective Iridium Photoredox and Nickel Catalysis for the Cross-Coupling of Primary Aryl Amines with Aryl Halides. *Angew. Chem. Int. Ed*. **2016**, *55*, 13219-13233. (g) Escobar, R. A.; Johannes, J. A Unified and Practical Method for Carbon–Heteroatom Cross-Coupling using Nickel/Photo Dual Catalysis. *Chem. Eur. J.* **2020**, 26, 5168-5173. (h) Tian, L.; Till, N. A.; Kudisch, B.; MacMillan, D. W. C.; Scholes, G. D. Transient Absorption Spectroscopy Offers Mechanistic Insights for an Iridium/Nickel-Catalyzed C–O Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 4555-4559. (i) Ting, S. I.; Garakyaraghi, S.; Taliaferro, C. M.; Shields, B. J.; Scholes, G. D.; Castellano, F. N.; Doyle, A. G. ^{3}d-d Excited States of Ni(II) Complexes Relevant to Photoredox Catalysis: Spectroscopic Identification and Mechanistic Implications. *J. Am. Chem. Soc.* **2020**, *142*, 5800-5810. (j) Till, N. A.; Tian, L.; Dong, Z.; Scholes, G. D.; MacMillan, D. W. C. Mechanistic Analysis of Metallaphotoredox C–N Coupling: Photocatalysis Initiates and Perpetuates Ni(I)/Ni(III) Coupling Activity. *J. Am. Chem. Soc.* **2020**, *142*, 15830-15841. (k) Gisbertz, S.; Reischauer, S.; Pieber, B. Overcoming Limitations in Dual Photoredox/Nickel-Catalysed C–N Cross-Couplings due to Catalyst Deactivation. *Nat. Catal.* **2020**, *3*, 611-620.

(17) (a) Ishida, N.; Masuda, Y.; Ishikawa, N.; Murakami, M. Cooperation of a Nickel–Bipyridine Complex with Light for Benzylic C−H Arylation of Toluene Derivatives. *Asian J. Org. Chem.* **2017**, *6*, 669-372. (b) Shen, X.; Li, Y.; Wen, Z.; Cao, S.; Hou, X.; Gong, L. A Chiral Nickel DBFOX Complex as a Bifunctional Catalyst for Visible-Light-Promoted Asymmetric Photoredox Reactions. *Chem. Sci*. **2018**, *9*, 4562-4568.

(18) Shields, B. J.; Kudisch, B.; Scholes, G. D.; Doyle, A. G. Long-Lived Charge-Transfer States of Nickel(II) Aryl Halide Complexes Facilitate Bimolecular Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 3035-3039.

(19) (a) Lim, C.-H.; Kudisch, M.; Liu, B.; Miyake, G. M. C–N Cross-Coupling via Photoexcitation of Nickel–Amine Complexes. *J. Am. Chem. Soc.* **2018**, *140*, 7667-7673. (b) Kudisch, M.; Lim, C.-H.; Thordarson, P.; Miyake, G. M. Energy Transfer to Ni-Amine Complexes in Dual Catalytic, Light-Driven C–N Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 19479-19486.

(20) (a) Yang, L.; Lu, H.-H.; Lai, C.-H.; Li, G. Zhang, W.; Cao, R.; Liu, F.; Wang, C.; Xiao, J.; Xue, D. Light-Promoted Nickel Catalysis: Etherification of Aryl Electrophiles with Alcohols Catalyzed by a NiII-Aryl Complex. *Angew. Chem. Int. Ed.* **2020**, *59*, 12714-12719. (b) Li, G.; Yang, L.; Liu, J.-J.; Zhang, W.; Cao, R.; Wang, C.; Zhang, Z. Xiao, J.; Xue, D. Light-Promoted C–N Coupling of Aryl Halides with Nitroarenes. *Angew. Chem. Int. Ed.* **2021**, *60*, 5230-5234. (c) Song, G.; Yang, L.; Li, J.-S.; Tang, W.-J.; Zhang, W.; Cao, R.; Wang, C.; Xiao, J.; Xue, D. Chiral Arylated Amines via C−N Coupling of Chiral Amines with Aryl Bromides Promoted by Light. *Angew. Chem. Int. Ed.* **2021**, *60*, 21536-21542. (d) Yan; Y.; Sun; J.; Li G.; Yang, L.; Zhang; W.; Cao, R.; Wang, C.; Xiao, J.; Xue, D. Photochemically Enabled, Ni-Catalyzed Cyanation of Aryl Halides. *Org. Lett.* **2022**, *24*, 2271-2275. (e) Song, G.; Nong, D.-Z.; Li, J.-S.; Li, G.; Zhang, W.; Cao, R.; Wang, C.; Xiao, J.; Xue, D. General Method for the Amination of Aryl Halides with Primary and Secondary Alkyl Amines via Nickel Photocatalysis. *J. Org. Chem.* **2022**, *87*, 10285-10297. (f) Xiao, C.; Xiao, W. Light-Promoted Nickel Catalysis: Etherification of Aryl Electro-philes with Alcohols Catalyzed by Ni(II)/Aryl Complex. *Chin. J. Org. Chem.* **2020**, *40*, 3004-3006.

(21) (a) Ting, S. I.; Garakyaraghi, S.; Taliaferro, C. M.; Shields, B. J.; Scholes, G. D. Castellano, F. N.; Doyle, A. G. ^{3}d-d Excited States of Ni(II) Complexes Relevant to Photoredox Catalysis: Spectroscopic Identification and Mechanistic Implications. *J. Am. Chem. Soc.* **2020**, *142*, 5800-5810. (b) Abderrazak, Y.; Bhattacharyya, A.; Reiser, O. Visible-Light-Induced Homolysis of Earth-Abundant Metal-Substrate Complexes: A Complementary Activation Strategy in Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2021**, *60*, 21100-21115. (c) Zhu, C.; Yue, H.; Jia, J.; Rueping, M. Nickel-Catalyzed C-Heteroatom Cross-Coupling Reactions under Mild Conditions via Facilitated Reductive Elimination. *Angew. Chem. Int. Ed.* **2021**, *60*, 17810-17831. (d) Chernyshev, V. M.; Ananikov, V. P. Visible Light-Induced Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1543-1625. (e) Cagan, D. A.; B ́m, D.; Silva, B.; Kazmierczak, N. P.; McNicholas, B. J.; Hadt, R. G. Elucidating the Mechanism of Excited-State Bond Homolysis in Nickel–Bipyridine Photoredox Catalysts. *J. Am. Chem. Soc.* **2022**, *144*, 6516-6531. (f) Ting, S. I.; Williams, W. L.; Doyle, A. G. Oxidative Addition of Aryl Halides to a Ni(I)-Bipyridine Complex. *J. Am. Chem. Soc.* **2022**, *144*, 5575-5582. (g) Cagan, D. A.; B ́m, D.; Silva, B. N.; Kazmierczak, P.; McNicholas, B. J.; Hadt, R. G. Elucidating the Mechanism of Excited-State Bond Homolysis in Nickel–Bipyridine Photoredox Catalysts. *J. Am. Chem. Soc.* **2022**, *144*, 6516-6531. (h) Sun, R.; Qin, Y.; Nocera D. G. General Paradigm in Photoredox Nickel-Catalyzed Cross-Coupling Allows for Light-Free Access to Reactivity. *Angew. Chem. Int. Ed.* **2020**, *59*, 9527-9533.

(22) Vijeta, A.; Casadevall, C.; Reisner; E.; An Integrated Carbon Nitride-Nickel Photocatalyst for the Amination of Aryl Halides Using Sodium Azide. *Angew. Chem. Int. Ed.* **2022**, *61*, e202203176.

(23) See: Sodium Azide: Systemic Agent. https://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750027.html. Aate of Access for April 22, 2022.

(24) For Details, Please See SI.

(25) Oderinde, M. S.; Jin, S.; Das, J.; Jorge, C.; Yip, S.; Ramirez, A.; Wu, D.-R.; Li, Y.; Kempson, J.; Meanwell, N. A.; Mathur, A.; Murali Dhar, T. G. Photo-Initiated Nickel Catalysis (PiNiC): Unmasking Dimethylnickel with Light. *ACS Catal.* **2022**, *12*, 12511-12520.

(26) (a) Sperry, J. B.; Wiglesworth, K. E. P.; Edmonds, I.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Chekler, E. L. P.; Langille, J.; Coe, J. W. Kiloscale Buchwald–Hartwig Amination: Optimized Coupling of Base-Sensitive 6-Bromoisoquinoline-1-Carbonitrile with (S)-3-Amino-2-Methylpropan-1-ol. *Org. Process Res. Dev.* **2014**, *18*, 1752-1758. (b) Chen, Z.; Jiang, Y.; Zhang, L.; Guo, Y.; Ma, D. Oxalic Diamides and tert-Butoxide: Two Types of Ligands Enabling Practical Access to Alkyl Aryl Ethers via Cu-Catalyzed Coupling Reaction. *J. Am. Chem. Soc.* **2019**, *141*, 3541-3549.

(27) (a) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem*. **2016**, *59*, 4443-4458. (b) Torborg, C.; Beller, M. M.; Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries. *Adv. Synth. Catal*. **2009**, *351*, 3027-3043. (c) Devendar, P., Qu, R.-Y.; Kang, W.-M.; He, B.; Yang, G.-F. Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food Chem.* **2018**, *66*, 8914-8934.

(28) (a) Watanabe, E.; Watanabe, S.; Ito, S.; Hayashi, M.; Watanabe, T.; Yuasa, Y.; Nakazawa, H. Development of an Enzyme-Linked Immunosorbent Assay for the Fungicide Imazalil in Citrus Fruits. *J. Agric. Food Chem.* **2000**, *48*, 5124−5130. (b) Haria, M.; Fitton, A.; Peters D. H.; A Reappraisal of its Pharmacological Properties and Therapeutic Use in Allergic Disorders. *Drugs*, **1994**, *48*, 617-637. (c) Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S.; A Reappraisal of its Pharmacological Properties and Therapeutic Use in Allergic Disorders. *Drugs*, **1978**, 16, 177-201. (d) Godefroi, E. F.; Heeres, J.; Cutsem, J. V.; Janssen, P. A. J.; Preparation and antimycotic properties of derivatives of 1-phenethylimidazole. *J. Med. Chem.* **1969**, *12*, 784-791. (e) Yang, L. P.; Keating, G. M. Fenofibric Acid in Combination Therapy in the Treatment of Mixed Dyslipidemia. Am. J. Cardiovasc. *Drugs.* **2009**, 9, 401-409.

(29) (a) Artemov, D.; Bhujwalla, Z. M.; Maxwell, R. J.; Griffiths, J. R.; Judson, I. R.; Leach, M. O.; Glickson, J. D. Pharmacokinetics of the ^{13}C labeled anticancer agent temozolomide detected in vivo by selective cross-polarization transfer. *Magn. Reson. Med.* **1995**, *34*, 338-342. (b) Browne, T. R.; Szabo, G. K.; Ajami, A.; Browne, D. G.; Performance of Human Mass Balance Studies with Stable Isotope-Labeled Drug and Continuous Flow-Isotope Ratio Mass Spectrometry: A Progress Report. *J. Clin. Pharmacol*. **1998**, *38*, 309–314. (c) Browne, T. R.; Stable Isotope Techniques in Early Drug Development: An Economic Evaluation. *J. Clin. Pharmacol*. **1998**, *38*, 213-220. (d) Hesk, D.; McNamara, P.; Synthesis of Isotopically labelled Compounds at Schering-Plough, an Historical Perspective. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 875–887. (e) Khojasteh, S. C.; Yue, Q.; Ma, S.; Castanedo, G.; Chen, J. Z.; Lyssikatos, J.; Mulder, T.; Takahashi, R.; Ly, J.; Messick, K.; Jia, W.; Liu, L.; Hop, C. E.; Wong, H. Investigations into the Mechanisms of Pyridine Ring Cleavage in Vismodegib. *Drug Metab. Dispos.* **2014**, *42*, 343-351. (f) Park, H.; Wang, Q. State-of-the-art Accounts of Hyperpolarized ^{15}N-labeled Molecular Imaging Probes for Magnetic Resonance Spectroscopy and Imaging. *Chem. Sci.* **2022**, *13*, 7378-7391.

(30) (a) Deev, S. L.; Khalymbadzha, I. A.; Shestakova, T. S.; Charushin, V. N.; Chupakhin, O. N. ^{15}N labeling and Analysis of ^{13}C–^{15}N and ^{1}H–^{15}N Couplings in Studies of the Structures and Chemical Transformations of Nitrogen Heterocycles. *RSC Adv.* **2019**, *9*, 26856-26879. (b) He, J.; Zhang, X.; He, Q.; Guo, H.; Fan, R. Synthesis of ^{15}N-labeled Heterocycles Via the Cleavage of C–N bonds of Anilines and Glycine-^{15}N. *Chem. Commun.* **2021**, *57*, 5442-5445.

(31) Bleasdale, C.; Ellis, M. K.; Farmer, P. B.; Golding, B. T.; Handley, K. F.; Jones, P.; McFarlane, W. Synthesis and Spectroscopic Characterisation of 3-Chloroperbenzoic Acid-^{17}O, ^{18}O, Nitrosobenzene-^{17}O, ^{18}O and Nitrosobenzene-^{15}N. *J. Labelled Compd. Radiopharm.* **1993**, 33, 739-746.

(32) Prosser, T. J.; Eliel, E. L. Confirmation of the Intramolecular Nature of the Hofmann "Haloamide" Reaction by Double Labeling. *J. Am. Chem. Soc.* **1957**, *79*, 2544-2546.

(33) (a) Gonz ́alez, E.; Rodrigue-Witchel, A.; Reber, C. Absorption Spectroscopy of Octahedral Nickel(II) Complexes: A Case Study of

Interactions Between Multiple Electronic Excited States. *Coordin. Chem. Rev.* **2007**, *251*, 351-363. (b) Sørensen, R. Z.; Hummelshøj, J. S.; Klerke, A.; Reves, J. B.; Vegge, T.; Nørskov, J. K.; Christensen, C. H. Indirect, Reversible High-Density Hydrogen Storage in Compact Metal Ammine Salts. *J. Am. Chem. Soc.* **2008**, *130*, 8660-8668.

(34) Sun, R.; Qin, Y.; Ruccolo, S.; Schnedermann, C.; Costentin, C.; Nocera, D. G. Elucidation of a Redox-Mediated Reaction Cycle for Nickel-Catalyzed Cross Coupling. *J. Am. Chem. Soc.* **2019**, *141*, 89-93.