

Adaptive Photochemical Amination via Co(II) Catalysis

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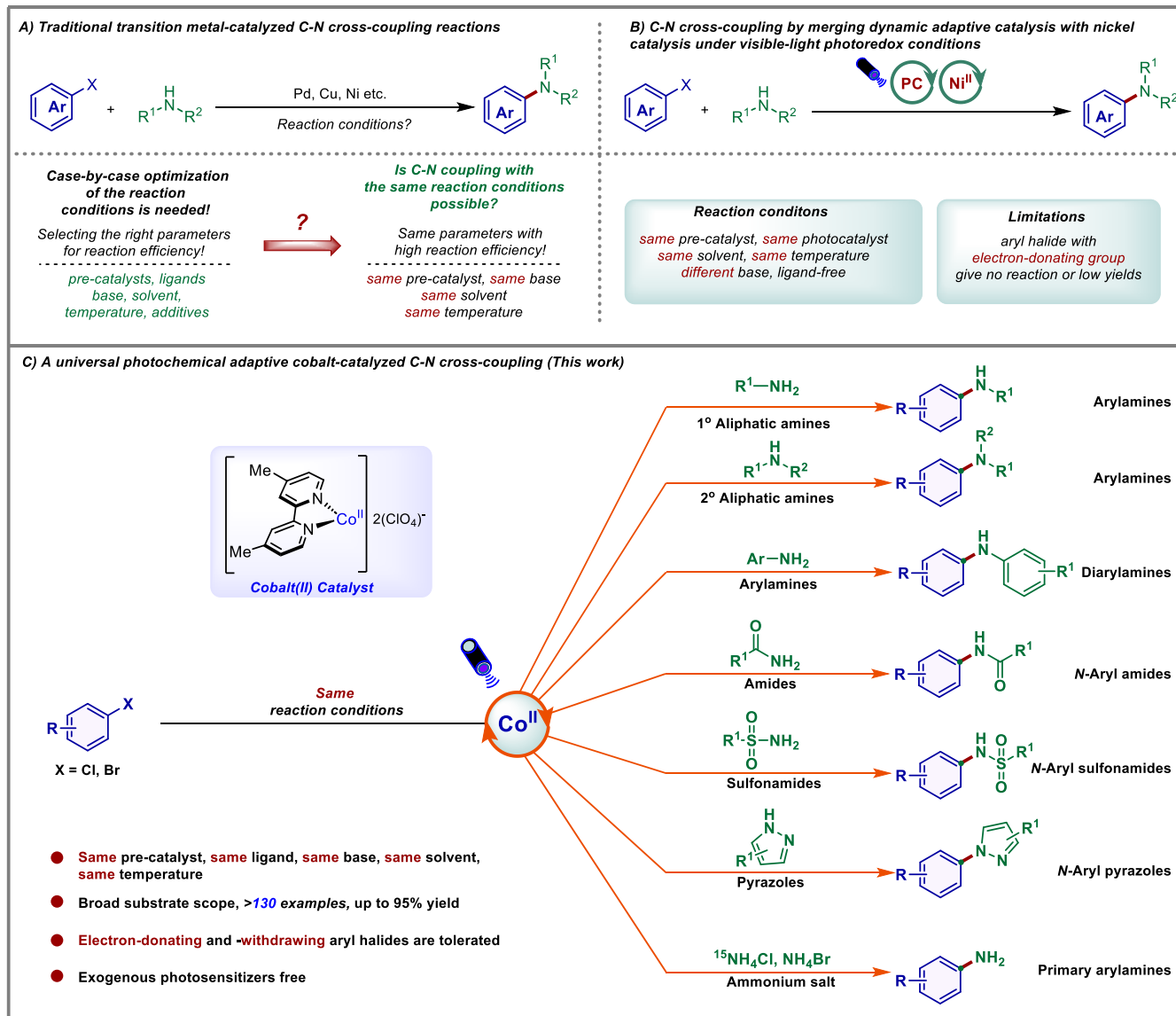
ABSTRACT: Transition-metal-catalyzed amination of aryl halides is one of the most employed methods for constructing *N*-arylation adducts. However, the broad success of these reactions is largely relying on the screening of pre-catalysts, elaborating ligands, and case-by-case optimization of the reaction conditions (solvent, base, additive, temperature *etc.*) and electronic or structural diversities of nucleophiles, for forging diverse C-N coupling products. Herein, we reported an adaptive photochemical C-N coupling of aryl halides with various nitrogen nucleophiles (aliphatic and aromatic amines, amides, sulfonamides, pyrazoles, and ammonium salts) by Co(II) catalysis under the same reaction conditions (same pre-catalyst, same ligand, same base, same solvent, same temperature) without the addition of any exogenous photocatalyst. This photochemical amination features a wide substrate scope (>130 examples, up to 95% yield) with excellent functional group tolerance. Mechanistic studies indicate that this C-N coupling reactions may proceed via a Co(I)/Co(III) catalytic cycle.

Introduction

C-N coupling reactions catalyzed by transition-metals is one of the most employed tools for the preparation of *N*-containing compounds,¹ which have been recognized as prevalent building blocks in fine chemicals,² organic optoelectronic materials,³ and biologically active pharmaceutical agents.⁴ However, these methods are still largely depending on the proper design and implement of various specialized ligands (phosphines, carbenes or oxamides *etc.*), pre-catalyst and case by case of optimization of reaction conditions for general and reliable protocols (Scheme 1A).⁵ Furthermore, a recent examination of electronic notebooks by Merck showed that C-N coupling still is a hit-or-miss affair, and remain 35% failure rate within ~10000 examples.⁶ Therefore, the application of machine learning and artificial intelligence provides an efficient strategy for reaction conditions screening through high-throughput experimentation (HTE), which avoids the traditional manual case-by-case optimization of reaction conditions.⁷ Meanwhile, one another alternative solution is to develop a general reaction system to address aforementioned issues within one catalytic system under the same reaction conditions (same pre-catalyst, ligand, base, solvent, temperature *etc.*). In this regard, König and co-workers demonstrated a powerful strategy, which allowed construction C-N bond by merging adaptive dynamic homogeneous catalysis with nickel catalysis under visible-light photoredox condition (Scheme 1B).⁸ However, different bases are still required for diverse cross-coupling products, and aryl halides with

electron-donating groups were proved challenging substrates in this protocol. Due to the impressive importance of C-N cross-coupling in organic synthesis, the development of generality-orientated and adaptive C-N cross-coupling with the same reaction conditions (same pre-catalyst, ligand, solvent, base, temperature) would still be highly desirable.

Cobalt (Co), a nontoxic and earth-abundant metal, is one of the most useful metal catalysts in organic synthesis, which shows strong catalytic activity and thus being an ideal replacement for precious metal catalysts.⁹ Therefore, cobalt-catalyzed cross-coupling reactions for the construction of carbon-carbon bonds have been extensively developed⁹ during the last two decades, however, the use of cobalt for carbon-heteroatom¹⁰ coupling reactions are rarely studied. In continuation of our studies on light-induced transition-metal catalyzed cross-coupling reactions,^{11, 12a} herein, we report an efficient and adaptive^{12b} photochemical C-N coupling reaction system by Co catalysis. The reaction enables the C-N coupling of aryl halides with seven different *N*-containing nucleophiles under the same reaction conditions (same pre-catalyst, same ligand, same solvent, same base, same temperature) without any exogenous photosensitizers (Scheme 1C). This adaptive photochemical amination utilize a single cobalt catalyst to achieve the dual effects of light absorption and organometallic processes, exhibiting excellent functional group tolerance, including challenging electron-donating aryl halides and sterically hindered ortho-substituted aryl halides. This work may contribute to a renewed



Scheme 1. Cobalt-catalyzed C-N coupling reactions.

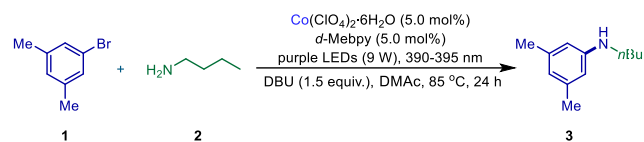
understanding of Co catalyst systems in cross-coupling reactions.

Results and Discussion

The coupling of 3,5-dimethylbromobenzene (**1**) with *n*-butylamine (**2**) were chosen as a model reaction for our initial exploration of the reaction conditions (Table 1). Firstly, we screened cobalt catalysts with 4,4'-dimethyl-2,2'-bipyridyl (*d*-Mebpy) as a ligand and found that CoBr₂, and Co(ClO₄)₂·6H₂O showed high activity under irradiation with purple light (390–395 nm) (entry 1). In sharp contrast, other Co(II) and Co(III) catalysts gave little to none of the target product **3** (Tables S1 and S2).¹³ The choice of base markedly affected the yield of the coupling reaction, with DBU was proved to be the best (Scheme S5). The solvent also affected the reaction yield, with dimethylacetamide

(DMAc) was the optimal choice (Table S6). Additional experiments indicated that the light wavelength between 390–395 nm gave the highest yield. Other wavelengths delivered trace amount or no product (entries 2–6, and Table S10). The reaction failed to proceed at room temperature or in the absence of light (even at 120 °C, entries 7–11). The ligand also had a remarkable effect, and no reaction occurred in the absence of *d*-Mebpy ligand (entry 10). Control experiments showed that no reaction was observed when the reaction was carried out in the absence of the ligand, base, the Co catalyst, or under an air atmosphere (entries 11–13).

With the optimized conditions in hand, we explored the scope of this light-induced cobalt-catalyzed C-N coupling. As shown in scheme 2, various amines could be coupled with 3,5-dimethylbromobenzene, affording the desired products (**4–70**) in high yields. For primary amines with a

Table 1. Optimization of reaction conditions^a

Entry	Variation from standard conditions	Yield (%) ^b
1	None	96, 90 ^c
2	UV (360–365 nm)	34
3	385–390 nm	33
4	420–425 nm	25
5	Blue LEDs (460–465 nm)	NR
6	White LEDs (6500 K)	NR
7	Light, rt	NR
8	No light, rt	NR
9	No light, 120 °C	NR
10	No ligand	NR
11	No DBU	NR
12	No Co catalyst	NR
13	Under air	NR

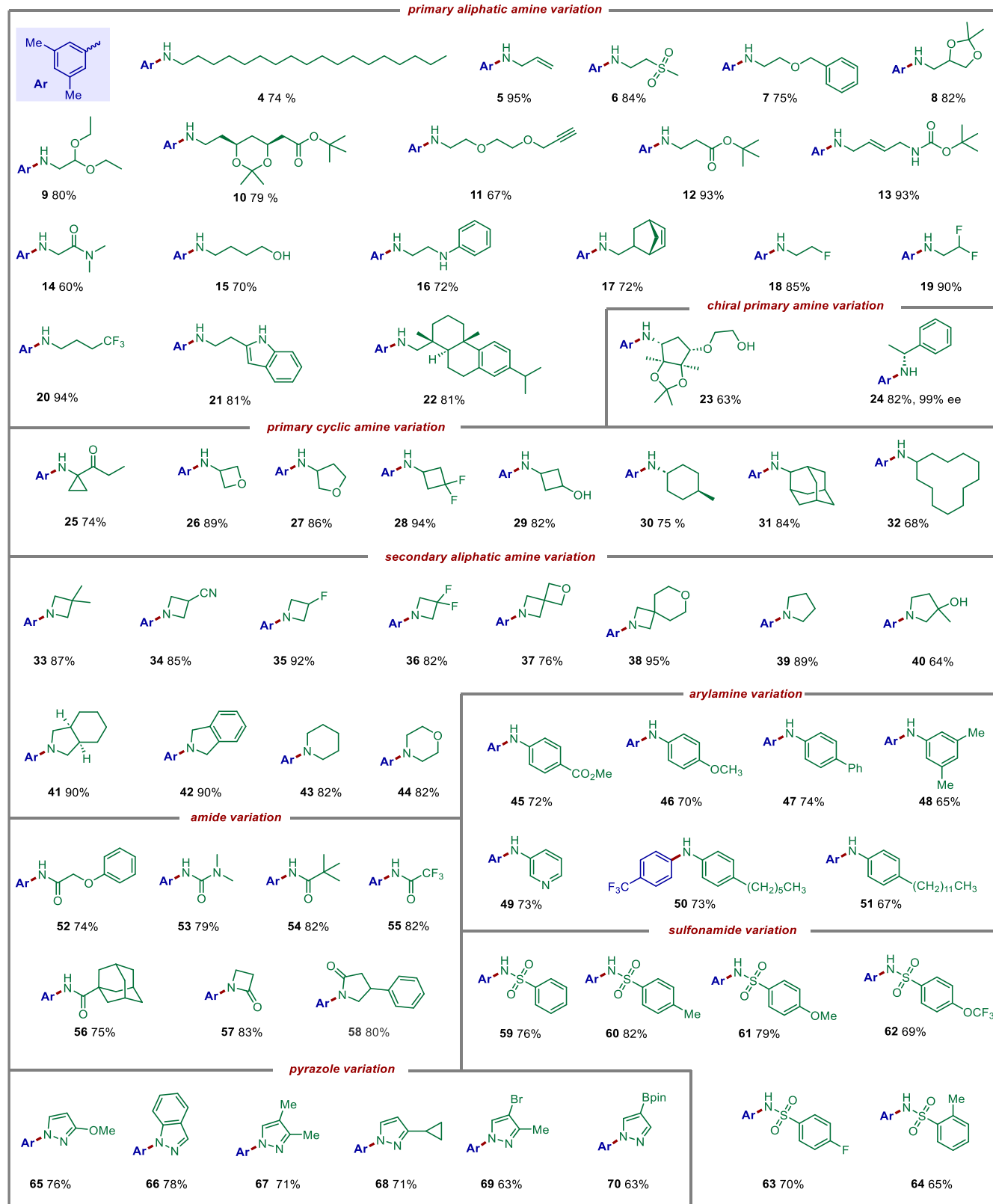
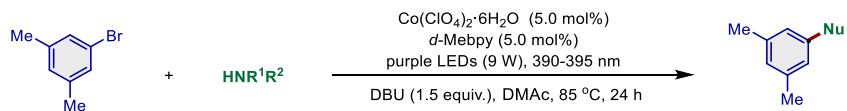
^a Reaction conditions: 3,5-dimethylbromobenzene (0.2 mmol), *n*-butylamine (2.0 equiv., 0.4 mmol), Co(ClO₄)₂·6H₂O (5.0 mol %), *d*-Mebpy (5.0 mol %), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 equiv., 0.3 mmol), dimethylacetamide (DMAc), 85 °C, 24 h, argon. ^b Yields were determined by ¹H NMR using 1,3-benzodioxole as an internal standard. NR = no reaction. ^c Isolated yield. See SI for the detailed screening of the reaction conditions.

wide range of functional groups, such as linear alkyl (**4**), alkenyl (**5**), sulfoxide (**6**), ether (**7**), ketal or acetal (**8–10**), alkynyl (**11**), ester (**12**), carbamate (**13**), amide (**14**), hydroxyl (**15**), aniline (**16**), 5-norbornene-2-methyl (**17**), fluoroalkyl (**18–20**), and indole (**21**), were suitable coupling partners, and the leelamine also gave the *N*-arylation product in 81% yield (**22**). Notably, C–O coupling products were not observed under the standard conditions when the substrate containing exposed NH₂ and OH functional groups (**15**, **23**). Moreover, when a secondary or heteroaromatic amine was introduced in the molecule, the primary amine preferentially underwent the coupling reaction to give a mono-aminated product (**16**, **21**). Chiral amines were also tolerated well, affording the coupling products (**23**, **24**) in high yields without erosion of stereoselectivities. Primary amines containing various rings also gave the desired products (**25–32**) in good yields. Notably, a highly sterically hindered nucleophiles, bearing a cyclopropyl ring afforded target product **25** in good yield without ring-opening product observed. Noteworthy, cyclic secondary amines could be coupled efficiently to furnish the corresponding arylamines (**33–44**) in 64–95% yields. Substituted (hetero)aromatic amines were also suitable substrates, delivering the diarylamine products (**45–51**) in 65–74% yields. Pleasingly,

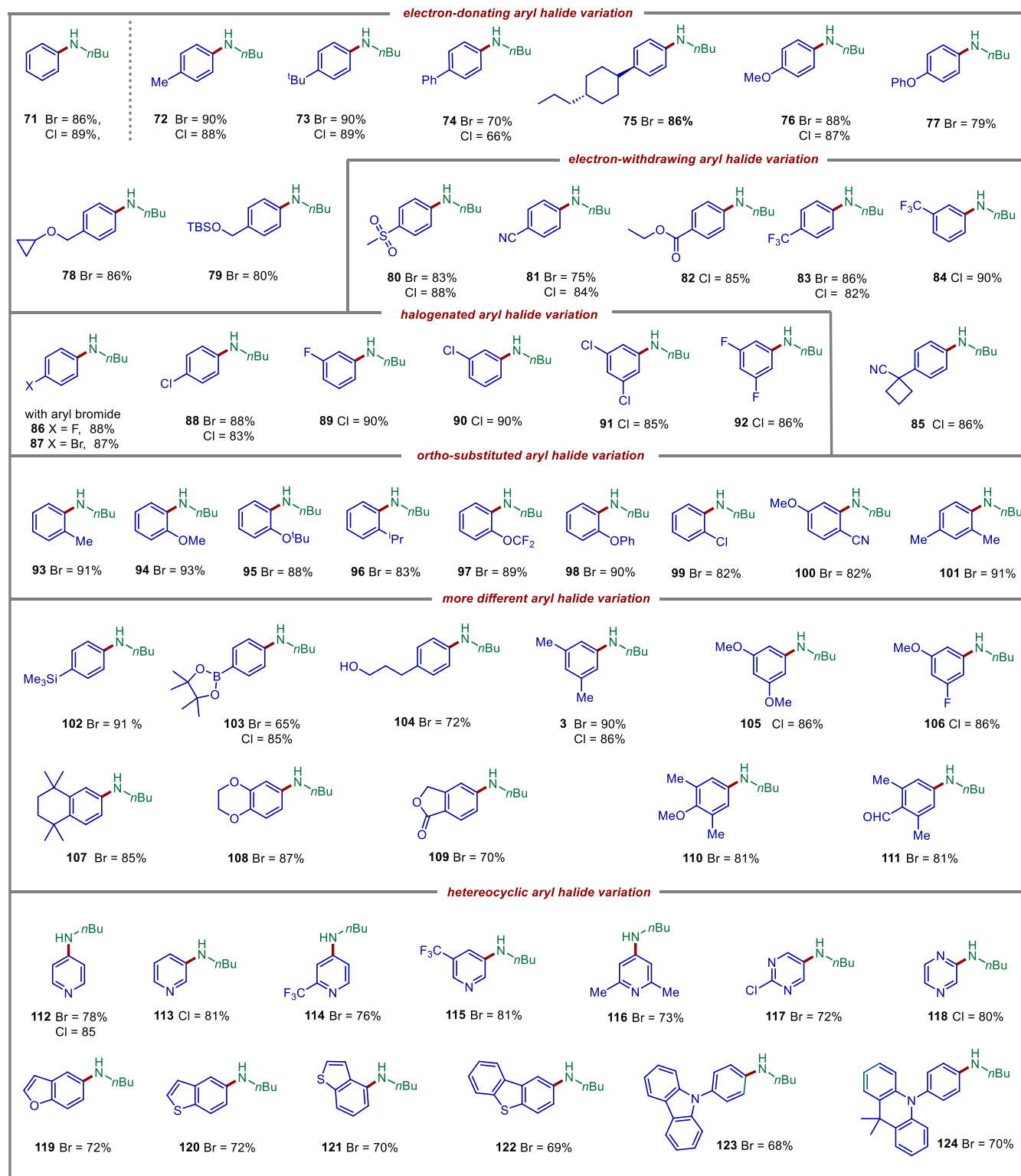
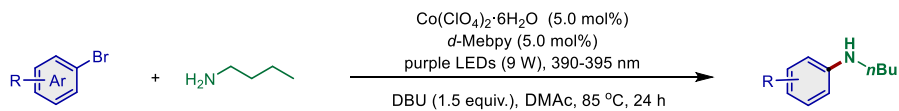
amides were also amenable to proceed the C–N coupling, thus giving *N*-arylation adducts (**52–58**) with diverse functional groups in high yields. Aromatic sulfonamides with electron-donating or -withdrawing substituents furnished the corresponding products (**59–64**) in 65–62% yields. Moreover, pyrazole derivatives bearing different functional group provided the C–N cross-coupling adducts **65–70** in 63–78% yields.

Next, the scope of the aryl halides was examined. As shown in scheme 3, aryl halides with various functional groups reacted efficiently with *n*-butylamine (**2**), delivering the desired arylamines (**71–124**) in high yields. It should be noted that aryl chlorides could produce the coupling products under the standard conditions with comparable yield (Table S7), and the yield could be further improved by adding tetra-*n*-butylammonium iodide as an additive (Tables S11–S12).¹³ Specifically, aryl halides with electron-neutral (**71**), electron-donating (**72–79**), or electron-withdrawing (**80–85**) *para*-substituents could deliver the corresponding products in good yields. It should also be noted that traditional problematic aryl halides bearing a cyano or an ester group under strong basic conditions, are suitable substrates for our coupling system, demonstrating the advantage of using an organic amine as a base.¹⁴ Moreover, halogenated aryl halides underwent the C–N coupling smoothly, providing the target products (**86–92**) in high yields regardless of the presence of extra halide (F, Cl or Br). Sterically hindered *ortho*-substituted aryl halides could also give desired products **93–101** in excellent yields. Other *para*-substituted functional groups such as TMS-, Bpin-, hydroxyalkyl- and multi-substituted aryl halides were successfully transformed into the target products in high yields (**102–111**). For aryl halides containing heteroaromatic moieties such as pyridines (**112–116**), pyrimidine (**117**), pyrazine (**118**), benzofuran (**119**), benzothiophenes (**120** and **121**), dibenzothiophene (**122**), carbazole (**123**, **124**), *N*-arylation adducts were readily obtained.

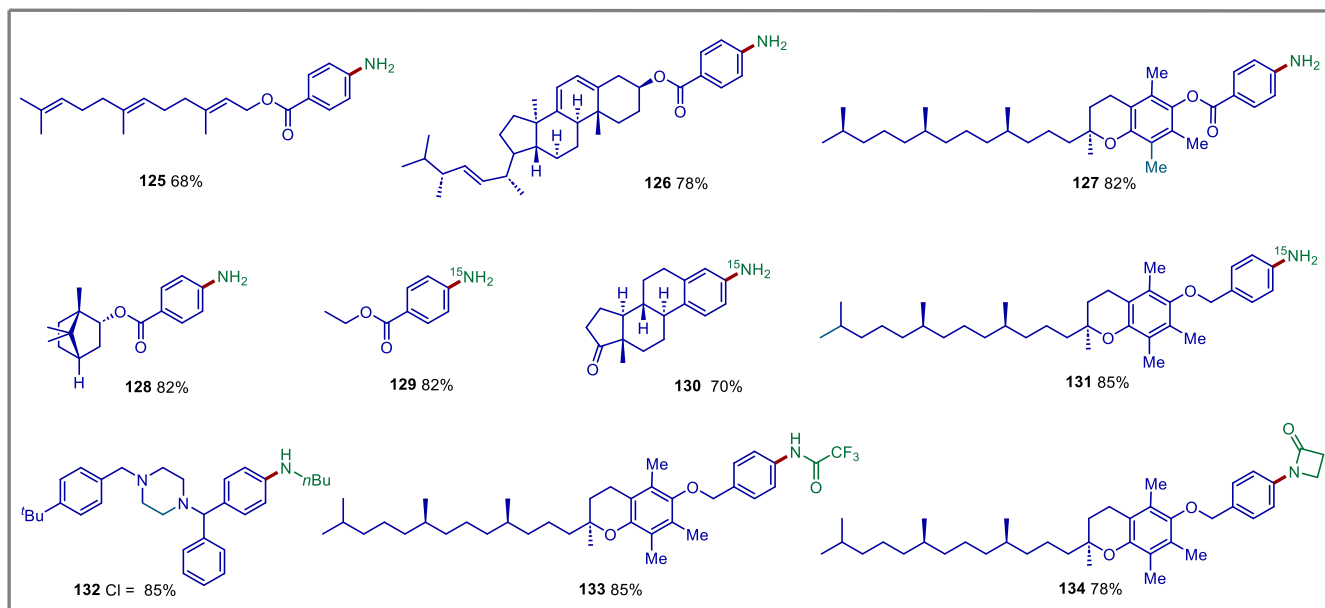
Finally, the current methodology could be employed to the late-stage functionalization of complex molecules (Scheme 4). Ammonium salts, including ¹⁵N-labeled ammonium salts, could also be used as nitrogen sources to afford complex primary aromatic amines (**125–131**) in good yields. *N*-Arylation of histabutazine affords product **132** in 85% yield. Drug molecules tocopherol could also couple with amides, affording the products **133** and **134** in 85% and 78% yields, respectively. The above-described results indicate that this light-induced Co(II)-catalyzed C–N coupling reaction was suitable for a wide range of nitrogen nucleophiles. Unlike traditional transition-metal catalysis that require the design of structurally complex ligands to expand the diversity of amine scope, while this strategy allowed us to employ a cheap and commercially available 4,4'-bipyridyl as ligand to realize the C–N cross-coupling, implying the potential utility for druglike molecule synthesis.



Scheme 2. Substrate scope of amines on cobalt-catalyzed C–N coupling reaction. ^a Reaction conditions: 3,5-dimethylbromobenzene (0.2 mmol), nitrogen nucleophile (2.0 equiv., 0.4 mmol), Co(ClO₄)₂·6H₂O (5.0 mol %), *d*-Mebpy (5.0 mol %), DBU (1.5 equiv., 0.3 mmol), DMAc, 85 °C, 24 h, argon. Isolated yields are reported. For details, see Supporting Information.



Scheme 3. Substrate scope of aryl halides on cobalt-catalyzed C–N coupling reaction. ^a Reaction conditions: aryl halides (0.2 mmol), *n*-butylamine (2.0 equiv., 0.4 mmol), Co(ClO₄)₂·6H₂O (5.0 mol %), *d*-Meppy (5.0 mol %), DBU (1.5 equiv., 0.3 mmol), DMAc, 85 °C, 24 h, argon. Isolated yields are reported. For details, see Supporting Information.

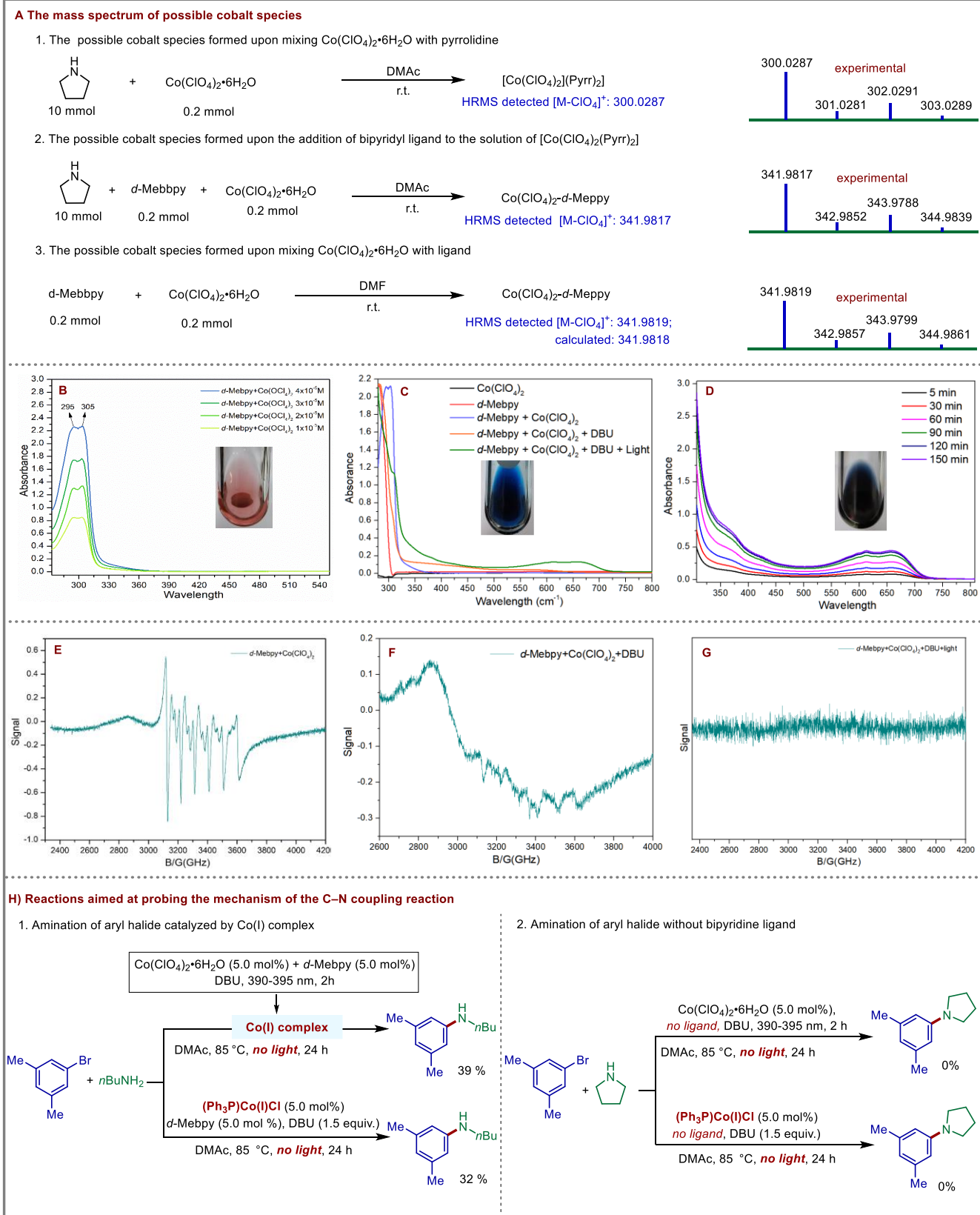


Scheme 4. Late-stage functionalization of complex molecules.

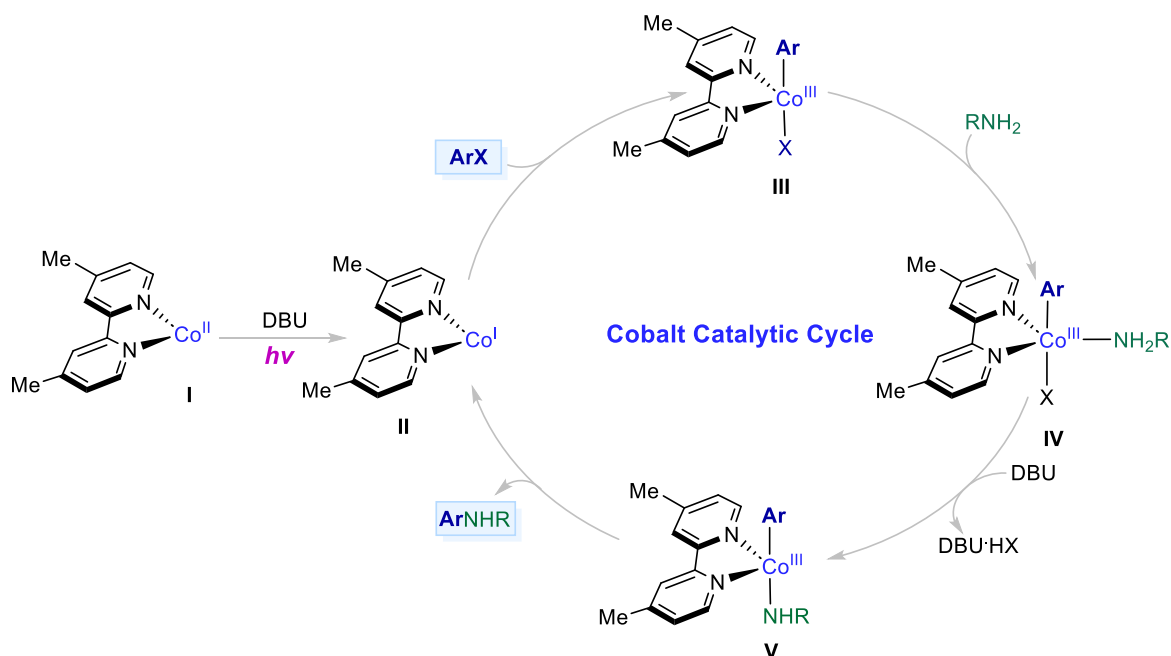
The preliminary mechanistic studies were carried aiming at elucidating the reaction mechanism (Scheme 5). Firstly, to further probe the role of the bipyridine ligand, we investigated the mass spectra of possible cobalt species formed between $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, pyrrolidine and *d*-Mebpy. When $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was mixed with an excess amount of pyrrolidine for 30 min in DMAc, the HRMS revealed a m/z peak at 300.0287, which is consistent with the mass spectra of $[\text{Co}(\text{ClO}_4)(\text{Pyrr})_2]^+$, indicating the formation of $[\text{Co}(\text{ClO}_4)_2(\text{Pyrr})_2]$ (Scheme 5A-1). However, a mass peak at m/z 341.9817 instead of 300.0287 was founded when $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was mixed with both pyrrolidine and *d*-Mebpy (Scheme 5A-2) or single *d*-Mebpy (Scheme 5A-3), which correlates to $[\text{Co}(d\text{-Mebpy})(\text{ClO}_4)]^+$ and implies the formation of $[\text{Co}(d\text{-Mebpy})(\text{ClO}_4)_2]$. These results indicate that the bipyridine ligand coordinates with $\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ during the catalysis, and explain why C-N coupling cannot occur in the absence of it. Furthermore, the cobalt complex was also subjected to UV-vis spectroscopy and found to exhibit absorption peaks near 295 and 305 nm in the long-wavelength UV region (Scheme 5B). Upon addition of DBU to a solution of the cobalt complex, the color of the solution changed from pale red to deep blue, and the absorption peaks of UV-vis spectroscopy were shifted from 295 and 305 nm to 284 nm (Scheme 5C and Fig. S5). Additionally, when the DBU containing solution was irradiated, a weak absorption was observed at 605 nm under light irradiation (Scheme 5B), along with a pronounced absorption in the 600–660 nm range that increased in intensity over time (Scheme 5D). This result suggests that single electron transfer from the metal to the ligand gives rise to the characteristic absorption of a $[d\text{-Mebpy-Co(I)ClO}_4]$ species upon irradiation, which is in agreement with literature data.¹⁴

Besides, electron paramagnetic resonance (EPR) spectra was conducted to confirm the presence of a Co(I) species, and found that the $[\text{Co(II)}-d\text{-Mebpy}-(\text{ClO}_4)_2]$ complex displayed distinct signals (Scheme 5E). However, those signals rapidly disappeared when the complex was mixed with DBU and irradiated with light (Scheme 5F and 5G), revealing the formation of a Co(I) species. The UV-vis and electron paramagnetic resonance spectra support our hypothesis that the organic base acts as an electron donor to reduce Co(II) to Co(I) upon irradiation with light. We next probed the oxidative addition of the Co(I) species with the aryl halide and the subsequent C-N coupling reaction (Scheme 5H). In the absence of the substrates, the $[\text{Co(II)}-d\text{-Mebpy}-(\text{ClO}_4)_2]$ complex was irradiated with purple light for 2 h in the presence of DBU to generate the Co(I) complex. Afterwards, substrates were introduced and allowed to react for 24 h in the dark, affording arylamine in 39 % NMR yield (Scheme 5H-1). Furthermore, the corresponding arylamine was obtained in 32% yield when a commercially available Co(I) complex was used as a catalyst under thermal conditions (Scheme 5H-1). Notably, no desired product was observed in the absence of bipyridine ligand (Scheme 5H-2).

On the basis of these results and recent related studies,¹⁵ we proposed the reaction mechanism in Scheme 6. Co(I) species **II** was generated by irradiation of $[\text{Co(II)}-d\text{-Mebpy}-(\text{ClO}_4)_2]$ complex **I** at 390–395 nm in the presence of DBU, followed by oxidative addition of aryl halides to afford Co(III)-Ar intermediate **III**. This intermediate readily underwent the reductive elimination upon substitution of the halide by the amine (presumably facilitated by DBU), affording the *N*-arylation product and regenerating the Co(I) species for the next catalytic cycle.



Scheme 5. (A) The mass spectrum of possible Co species; (B) UV-vis absorption spectra of $[\text{Co}(\text{II})$ -*d*-Meppy- $(\text{ClO}_4)_2]$ in DMAc at various concentrations; (C) *d*-Meppy and $\text{Co}(\text{II})(\text{ClO}_4)_2$ + *d*-Meppy- $\text{Co}(\text{II})(\text{ClO}_4)_2$ + DBU in DMAc (4×10^{-4} M, 1 mm path length, quartz cuvette), (D) $[\text{Co}(\text{II})$ -*d*-Meppy- $(\text{ClO}_4)_2]$ + DBU under light irradiation in DMAc (3×10^{-4} M, 1 mm path length, quartz cuvette) from 0 to 150 min; (E–G) Electron paramagnetic resonance spectra; (H) Reactions aimed at probing the mechanism of the C–N coupling reaction. Yields were determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard. For more details, see Supporting Information.



Scheme 6. Possible mechanism of the light-induced cobalt-catalyzed amination.

Conclusion

In summary, we have developed an adaptive light-induced cobalt-catalyzed C–N cross-coupling reactions between various *N*-nucleophiles and aryl halides under the same reaction conditions (same pre-catalyst, same ligand, same base, same solvent and same temperature), thus delivering diverse *N*-arylation products in generally high yields with excellent functional group tolerance (>130 examples, up to 95% yield), showing excellent potentials in pharmaceutical chemistry. It is worthy to note that the current single-cobalt catalytic system could address the scope limitations in terms of electron-donating aryl halides and sterically hindered *ortho*-substituted aryl halides, which was proved challenging substrates in traditional transition-metal catalyzed C–N coupling reaction. Preliminary mechanistic studies suggest that the current C–N cross-coupling reactions proceed *via* a Co(I)/Co(III) catalytic cycle.

ASSOCIATED CONTENT

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

Experimental procedures, analytical data and copies of NMR spectra for synthesized compounds (PDF).

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Notes

The authors declare no competing financial interest.

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Experimental procedures, analytical data and copies of NMR spectra for synthesized compounds (PDF).

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