# Mild Amide *N*-Arylation Enabled by Nickel-Photoredox Catalysis

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**ABSTRACT:** This paper describes a mild strategy to promote amide arylations. Photoinduced oxidation of a Ni(II) aryl amido intermediate is proposed to facilitate the challenging C–N reductive elimination step at moderate temperatures. Notably, the mildly basic conditions employed facilitate access to a broad scope including protected amino acids, heterocycles, phenols, and sterically hindered substituents. Hence, this work presents an attractive strategy to enable late-stage functionalization of pre-existing amide moieties in commercial drugs and natural products.

## INTRODUCTION

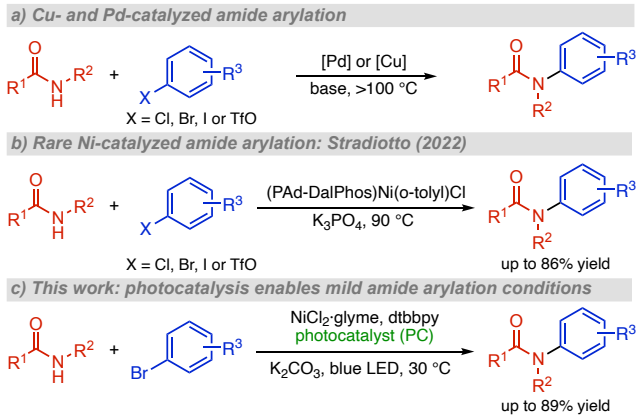
Amides are ubiquitous functional groups in nature, present in the peptide bonds of proteins and making frequent appearances in small molecules and polymers of industrial significance.[1] Indeed, amides are present in 16 of the top 20 best-selling small molecule drugs of 2020.[2] As such, the development of methods to access substituted amides from existing amides is of great importance for medicinal chemistry.

The amide functional group can be accessed through a broad range of synthetic methods. These include the coupling of amines and carboxylic acids (typically requiring the use of a coupling reagent),[1e] nucleophilic acyl substitutions,[3] rearrangements (e.g., Beckmann,[4] Favorskii[5]), and transamidations.[6] All of these approaches involve either a retrosynthetic disconnection at the N–carbonyl bond or a rearrangement of the core structure of the substrate, thereby limiting the synthetic routes available to accessing highly functionalized amides. Alternatively, the direct functionalization of a primary or secondary amide substrate offers a strategic disconnection at the N–H bond, which enables modular and divergent synthetic routes to highly functionalized amides.

In this context, alkylation of amide N–H bonds can be accessed by the use of either strong bases and alkyl halides[7] or transition metal catalysts.[8] In contrast, amide arylation cannot be achieved in the absence of organometallic reagents and only a limited number of catalytic methods have been reported. Most of these strategies rely on Cu[9] and Pd[10] catalysis (Scheme 1a), although a few isolated examples have been mediated by Ni bisphosphine complexes (Scheme 1b).[11] While progress has been made in this area, the reduced nucleophilicity of amides still presents a challenge for promoting reductive elimination that has only been overcome by employing high reaction temperatures.[9-12] Thus, complementary methods that enable facile reductive elimination at moderate temperatures would be highly desirable to broaden the scope of this transformation.

Alternatively, we envisioned that the amide reductive elimination step could be accelerated via *in situ* oxidation of a Ni(II) aryl amido complex. Promotion of reductive elimination of C–N bonds by oxidation of Ni(II) complexes has been described in the context of amine functionalization. Stoichiometric studies utilizing chemical oxidants[13] and catalytic variants of this strategy utilizing visible light and a photoredox catalyst have been reported.[14] This approach has been subsequently exploited to forge a variety of C–heteroatom bonds.[15] Although these strategies utilize highly nucleophilic species when compared to amides, with the exception of one isolated example,[15f] it was envisioned that this approach could be enabling for targeted amide functionalization.

**Scheme 1. Transition metal-catalyzed amide arylation**



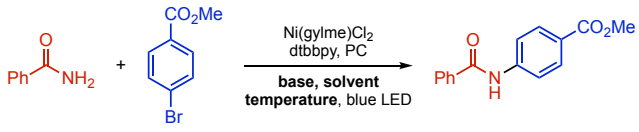

This work aims to leverage the functional group compatibility that photoredox-mediated oxidations typically facilitate. However, all currently known Ni-photoredox strategies present a main limitation: the requirement of a strong organic base (like 1,4-diazabicyclo[2.2.2]octane (DABCO) or tetramethylguanidine (TMG)) to act as an electron shuttle between the photocatalyst and the reaction intermediates.[14b] These conditions are incompatible with base-sensitive substrates, and can lead to undesired side reactivity spanning from the propensity of these bases to facilitate hydrogen atom transfer when oxidized.[16]

Herein a Ni-photoredox tandem is used to promote amide arylations under moderate temperatures and in the absence of a strong, redox-active base (Scheme 1c). The broad scope presented, which includes heterocycles, cyclic secondary amides, and epimerizable stereocenters, highlights the mildness of the strategy and its suitability for late-stage functionalization.

## RESULTS AND DISCUSSION

The reaction between benzamide (**1a**) and methyl 4-bromobenzoate (**2a**) was chosen as a model system to study this reactivity (Table 1). Solvent selection proved to be particularly crucial in order for cross-coupling to be observed, as trace or no conversion to product was observed in most of the solvents tested. The best yields were initially obtained in dimethylformamide (DMF), while other polar solvents like $PhCF_3$, MeCN and MeOH gave low yields (Table 1, entries 1-4). Despite the encouraging results obtained in DMF, it was soon identified that these reactions also lead to substantial formation of the debrominated phenol byproduct (~25% yield). The phenol side product observed is presumed to be formed due to the coupling of water with the aryl bromide.[15a, 17] Unfortunately, inclusion of molecular sieves or the use of rigorously dry glassware did not prevent its formation, but interestingly, the combination of $PhCF_3$ and DMF as co-solvents leads to higher yields (Table 1, entry 5). It is hypothesized that the poor solubility of benzamide **1a** was responsible for the lack of reactivity observed in $PhCF_3$ alone, but that the presence of $PhCF_3$ in the reaction is otherwise beneficial, as coordination of π-acidic, electron-poor arenes to Ni has been shown to increase the rate of reductive elimination.[18] Under the optimized conditions, the yield of this undesired phenol side product typically did not exceed 10%.

**Table 1. Optimization of the reaction conditions**




**1a** **2a** **3a**

| Entry | Solvent | Base | Temperature (°C) | Yield (%) [a] |
|---|---|---|---|---|
| 1 | MeOH | $K_2CO_3$ | rt (≈ 25) | 11 |
| 2 | MeCN | $K_2CO_3$ | rt | 39 |
| 3 | $PhCF_3$ | $K_2CO_3$ | rt | < 5 |
| 4 | DMF | $K_2CO_3$ | rt | 45 |
| 5 | 3:1 $PhCF_3$:DMF | $K_2CO_3$ | rt | 62 |
| 6 | 3:1 $PhCF_3$:DMF | $K_2CO_3$ | 10 | 26 |
| 7 | 3:1 $PhCF_3$:DMF | $K_2CO_3$ | 20 | 57 |
| 8 | 3:1 $PhCF_3$:DMF | $K_2CO_3$ | 30 | 79 |
| 9 | 3:1 $PhCF_3$:DMF | $Na_2CO_3$ | 30 | 30 |
| 10 | 3:1 $PhCF_3$:DMF | $KHCO_3$ | 30 | 52 |
| 11 | 3:1 $PhCF_3$:DMF | $K_3PO_4$ | 30 | 64 |
| 12 | 3:1 $PhCF_3$:DMF | TMG | 30 | 61 |

[a] Reaction conditions: $NiCl_2$•glyme (0.02 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridine (dtbbpy, 0.03 mmol), $Ir(dtbbpy)(ppy)_2PF_6$ (0.004 mmol), base (0.4 mmol), aryl bromide **2** (0.2 mmol), amide **1** (0.4 mmol), and 1 mL of solvent, 24 h.

The reaction temperature also had a significant effect on yield, with lower yields obtained at temperatures lower than ambient temperature (Table 1, entries 5-8). The greatest yields were achieved when the reaction was maintained at 30 °C, and temperatures higher than this produced only equivalent or inferior yields. It is worth noting that temperature-controlled water baths are necessary to ensure reproducible yields, as different reaction vessels are heated to different degrees by the incident blue light, and the fans commonly used in photoredox setups are unable to reproducibly maintain a constant reaction temperature.

A final key hurdle in our optimization was identifying a mild base capable of mediating the chemistry. To our knowledge, there are no reactions based on the photochemical oxidation of Ni where reductive elimination occurs in the absence of a strong, redox non-innocent base (*vide supra*). Furthermore, a weaker base will not be able to deprotonate the amide, thereby slowing the ligand exchange steps to form Ni amidate intermediates. To our delight, $K_2CO_3$ was identified as a suitable base for overcoming these challenges, outperforming other mild inorganic bases (Table 1, entries 8-11). Unsurprisingly, strong organic bases that can facilitate electron transfer processes like TMG were also suitable for this transformation (Table 1, entry 12), although higher yields were obtained with $K_2CO_3$.

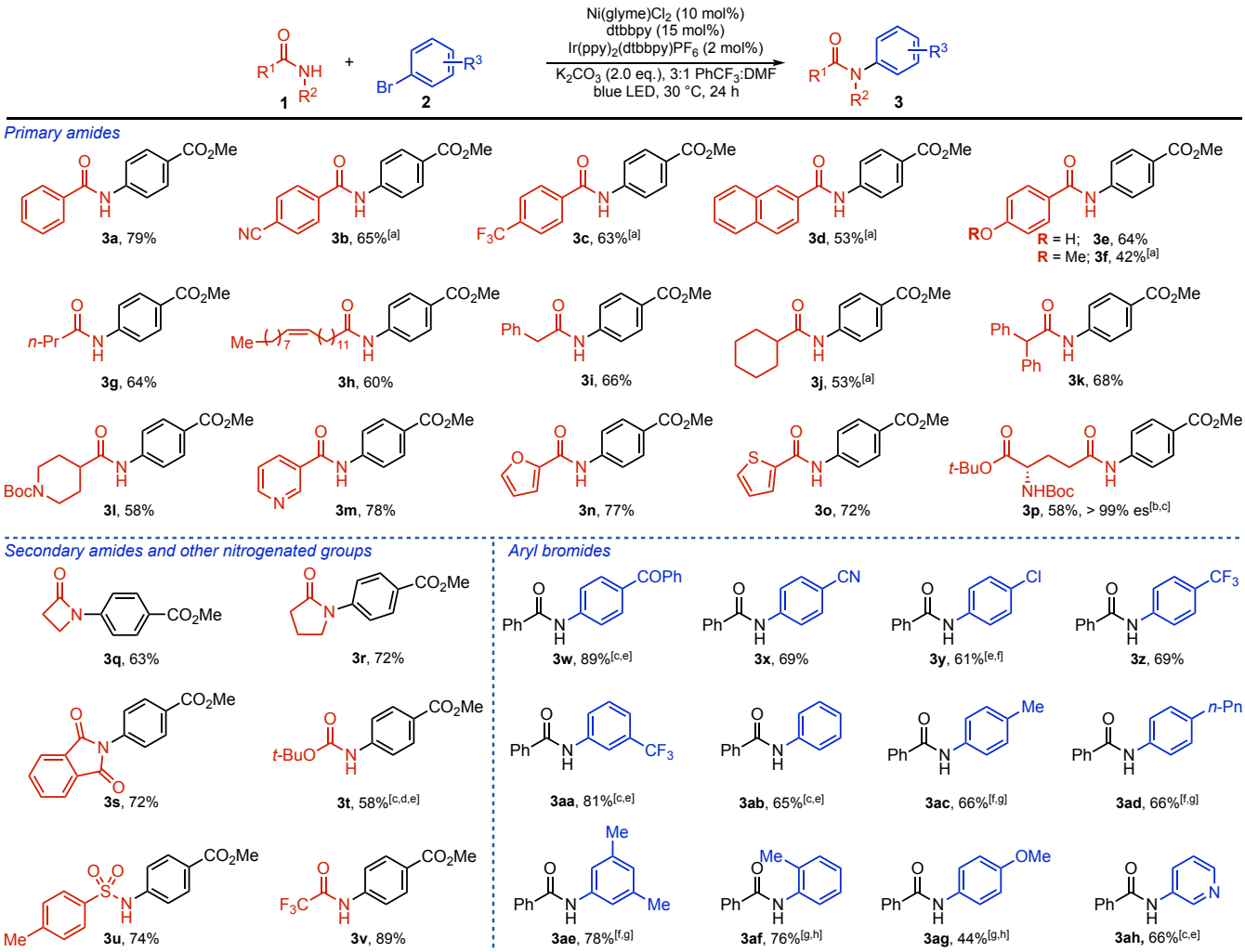
With the optimized reaction conditions in hand, the arylation of a diverse array of amides was tested (Figure 1). Since amide solubility varies greatly between substrates, the ratio of $PhCF_3$ to DMF affected the conversion of each substrate differently. Use of either solvent alone almost always led to a significant decrease in yield, except for *tert*-butylcarbamate (product **3t**). High yields were obtained for electron-poor benzamides (**3a** to **3c**), in contrast to the moderate yields observed for more electron-rich benzamides (**3d**, **3e**). Electron-poor amides are better suited to this methodology, likely due to their relatively lower $pK_a$ values. The reaction is not limited to the use of aromatic amides, with alkyl-substituted primary amides leading to the formation of *N*-arylated products in moderate to good yields (**3g** to **3l** and **3p**). Of particular interest is the tolerance of the reaction to steric bulk around the amide moiety (**3j** to **3l**). Additionally, the reaction exhibits a good tolerance to a variety of functional groups, such as olefins (**3h**), hydroxy groups (**3e**), and protected amines (**3l** and **3p**). Unprotected amines were found to be incompatible with the reaction conditions. Gratifyingly, a variety of N-, O-, and S-heterocycles (**3l** to **3o**) were tolerated under the reaction conditions, furnishing the desired aryl amides in good yields.

To further investigate the tolerance of base-sensitive functional groups, which remain a challenge for other amide functionalization strategies, enantioenriched Boc-protected *tert*-butoxy glutamate bearing an epimerizable stereocenter was tested as a substrate. Excitingly, arylated amide **3p** was isolated in a moderate yield and no erosion of the enantiomeric excess was detected. This result highlights the mildness of our procedure and its potential application for derivatizing bioactive molecules.

Moving beyond primary amide substrates, cyclic secondary amides were also arylated in high yields (**3q**, **3r**). The tolerance of this protocol to amides bearing hydrogens in the α-position to the amide N atom is especially interesting. Similar reaction conditions to those described in this paper have been utilized to promote arylation of these C–H bonds.[19] We were surprised but pleased to only observe the *N*-arylation product with no C–H functionalization detected. Unfortunately, when more sterically demanding secondary acyclic amides were tested, poor yields (< 20%) were obtained.

Finally, other nitrogenated functional groups with similarly moderate nucleophilicity to that of amides were also tolerated, including phthalimide (**3s**), Boc-protected amine (**3t**), sulfonamide (**3u**), and trifluoroacetamide (**3v**) moieties.

**Figure 1. Scope of amide and aryl bromide coupling partners in Ni-photoredox-catalyzed amide arylation**




Reaction conditions: $NiCl_2$•glyme (0.02 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridine (dtbbpy, 0.03 mmol), $Ir(dtbbpy)(ppy)_2PF_6$ (0.004 mmol), $K_2CO_3$ (0.4 mmol), aryl bromide **2** (0.2 mmol), amide **1** (0.4 mmol), and 1 mL of 3:1 $PhCF_3$:DMF, 30 °C, 24 h. All reported values are yields of the isolated products. [a] With 1:1 $PhCF_3$:DMF as solvent. [b] With 10:1 $PhCF_3$:DMF as solvent. [c] Stirred for 48 h. [d] With $PhCF_3$ as solvent. [e] At 40 °C. [f] Stirred for 4 days. [g] At 50 °C. [h] Stirred for 7 days.

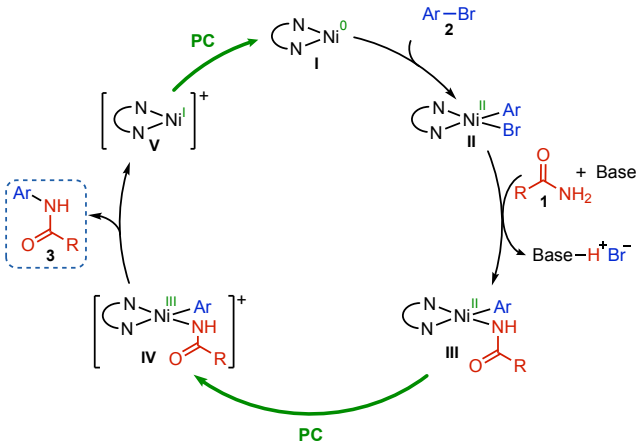
A variety of substituted aryl and heteroaryl bromides were also amenable to the reaction conditions. Electron-poor aryl bromides, including chlorinated aromatic groups, render the final amide products in high yields (**3a**, **3w** to **3aa**). Electron-rich aryl bromides were also tolerated, but were found to require slightly elevated temperatures and longer reaction times to form products (**3ab** to **3ag**). This behavior is consistent with other literature reports that demonstrate slower rates of oxidative addition for electron-rich aryl halides.[20] Employing sterically demanding aryl bromides also afforded the desired product in high yields, although longer reaction times were required (**3af**). In addition, the extension of the reaction to 3-bromopyridine shows that the presence of a heterocycle capable of binding to a metal center does not have a negative effect on the reaction yield (**3ah**). Lastly, when the starting aryl bromides (**2**) were substituted for aryl chlorides, only trace amounts of product were observed, presumably due to the reduced propensity of aryl chlorides to undergo oxidative addition.

From a mechanistic perspective, the proposed catalytic cycle, depicted in Figure 2, begins with oxidative addition of the aryl halide (**2**) to render Ni(II) complex **II**. Due to the reduced basicity of $K_2CO_3$, direct deprotonation of the amide is unlikely. Alternatively, amide coordination and deprotonation to provide intermediate **III** is proposed.[12d,21] Electron transfer from **III** to the excited photocatalyst would subsequently provide the high-energy Ni(III) intermediate **IV**, triggering an otherwise sluggish reductive elimination[13-14] and affording the aryl amide product (**3**). Finally, both catalysts are regenerated upon electron transfer from the reduced photocatalyst to Ni(I) intermediate **V**.

We propose that the reductive elimination step to forge functionalized amides occurs from a Ni(III) intermediate based, in part, on the behavior observed for the related Ni-mediated reductive elimination to form amines.[14] The major obstacle to Ni-catalyzed C–N cross-coupling is that, in contrast to Pd, reductive elimination to forge these bonds from Ni(II) is endothermic.[15c, 22] Hillhouse first observed the facile reductive elimination from Ni(III) when exposing Ni bipyridine alkyl amido complexes to stoichiometric oxidants, which resulted in reductive elimination to afford the C–N cross-coupled amine products in high yields.[13] This was further supported by

DFT calculations suggesting that reductive elimination from a Ni(III) aryl amido complex has a drastically lower kinetic barrier (4.8 kcal mol$^{-1}$) compared to the analogous Ni(II) complex (31.1 kcal mol$^{-1}$).[15c, 22] While amides are much less nucleophilic than amines, this related mechanistic precedent is important to consider.

**Figure 2. Proposed catalytic cycle of Ni-photoredox cross-coupling of amides with aryl halides**




To challenge the alternative possibility of direct reductive elimination from a putative ground-state Ni(II) aryl amide complex, thorough control experiments were performed. No reactivity was observed in the absence of either Ni, light, or photocatalyst, suggesting that a photochemical step is involved in the catalytic cycle. Furthermore, if an energy transfer pathway is responsible for the acceleration of the reductive elimination step, an excited state of the Ni(II) complex **III** should also be directly accessible via excitation with light in the absence of the photocatalyst. However, no product formation was detected when the reaction was carried out in the absence of a photocatalyst under irradiation with a 390 nm light. In line with these control experiments and the stoichiometric studies for amine functionalization,[13] it is proposed that a photoinduced electron transfer is likely facilitating the reductive elimination step (**III** → **IV** → **V**, Figure 2). Nevertheless, the possibility of an energy-transfer from the excited photocatalyst to the Ni(II) aryl amide complex to promote reductive elimination cannot be discarded at this time.[23]

## CONCLUSION

In summary, we have developed a methodology for amide arylation which is effective at ambient temperatures and avoids the use of redox-active or strong bases. A wide scope is enabled by such mild reaction conditions, which allows for the tolerance of a variety of base-sensitive functional groups like phenols and epimerizable stereocenters. This study shows that the low nucleophilicity of the amide functional group can be overcome by utilizing a Ni-photoredox tandem system to accelerate the elusive C–N reductive elimination step. Further mechanistic investigations are currently ongoing in our laboratory, as it is expected that this methodology will inspire future mild heteroatom functionalization studies.

## ASSOCIATED CONTENT

### Supporting Information

The data underlying this study are available in the published article and its online supplementary material. The supporting information includes the following: general considerations, synthesis and characterization of (*S*)-Boc-Gln-O*t*Bu (**1p**), amide arylation general procedures, primary amide scope, secondary amide and other nitrogenated groups scope, and aryl bromide scope, references, $^{1}$H, $^{13}$C, and $^{19}$F NMR spectra. It is available free of charge on…

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### Author Contributions

The manuscript was written through contributions of all authors.

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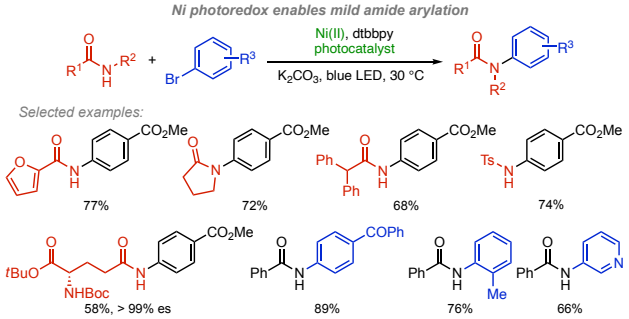
Ni photoredox enables mild amide arylation
Ni(II), dtbbpy
photocatalyst
K2CO3, blue LED, 30 °C
Selected examples:
77%
72%
68%
74%
58%, > 99% es
89%
76%
66%