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Amide Synthesis by Nickel/Photoredox-Catalyzed Direct Carbamoylation of (Hetero)Aryl Bromides

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In memory of Giuseppe Bartoli

Abstract: *Herein, we report a one-electron strategy for catalytic amide synthesis that enables the direct carbamoylation of (hetero)aryl bromides. This radical cross-coupling approach, which is based on the combination of nickel and photoredox catalysis, proceeds at ambient temperature and uses readily available dihydropyridines as precursors of carbamoyl radicals. The method's mild reaction conditions make it tolerant of sensitive-functional-group-containing substrates and allow the installation of an amide scaffold within biologically relevant heterocycles. In addition, we installed amide functionalities bearing electron-poor and sterically hindered amine moieties, which would be difficult to prepare with classical dehydrative condensation methods.*

Introduction

Amides are widespread structural units in nature, since the amide bond is the core linkage of natural proteins and peptides.[1] This moiety is also present in polymers, agrochemicals, and pharmaceutical molecules.[2] For example, 70% of the top 50 selling small molecule drugs of 2018 contain an amide bond linkage.[3] Despite the prevalence and importance of amides, improved methods for their synthesis are still highly sought-after,[4] especially if they can offer high efficiency and reduced environmental impact.[5] This is because the most common methods for amide preparation—dehydrative condensation—typically use stoichiometric amounts of high molecular weight coupling reagents, which are often expensive, toxic, and/or potentially explosive.[6] While often tolerable on a small scale, this inefficiency has significant implications when it comes to the manufacture of bio-active molecules, such as drugs or agrochemicals, which may need to be synthesized on multi-ton scale.[7] This explains why the pharmaceutical industry has recently posed a great emphasis into methods for amide bond formation that avoid poor atom economy reagents.[8]

Catalytic methods for amide synthesis have the potential to minimize waste, improve the environmental burden, and lower costs of the process.[5] Some recent key advances include the use of group IV metal salts[9] or boron compounds[10] as catalysts and the development of Pd-catalyzed aminocarbonylation—the three-component coupling of an aryl halide with an amine and carbon monoxide.[11] However, the need for toxic gaseous CO and copious amounts of molecular sieves as drying agents complicates the use of these catalytic methods. In addition, most of the protocols require severe reaction conditions and elevated temperatures, which limit the tolerance for substrates with sensitive functional groups. Therefore, there is still a need for catalytic amide synthesis approaches that operate at room temperature, offer a broad substrate scope, and avoid the use of excess drying agents.[12]

Herein, we describe the ambient temperature catalytic conversion of aryl and heteroaryl bromides to their corresponding amides enabled by the combination of nickel and photoredox catalysis (Figure 1).[13] We used readily available, cheap and stable 4-carbamoyl-1,4-dihydropyridines **1** that, upon single-electron transfer (SET) oxidation, can generate carbamoyl radicals.[14] The ability of a nickel catalysts to undergo oxidative addition with aromatic bromides **2** while engaging in radical capture mechanisms secured the formation of the cross-coupled amide products **3**.[15]

The method requires mild reaction conditions and avoids the need for any dehydrating agents. It offers a wide scope allowing the straightforward preparation of secondary and tertiary amides and the direct installation of an amide scaffold within biologically relevant heterocycles. In addition, we installed amide functionalities bearing electron-poor amine moieties, which would be difficult to prepare with classical dehydrative condensation methods.

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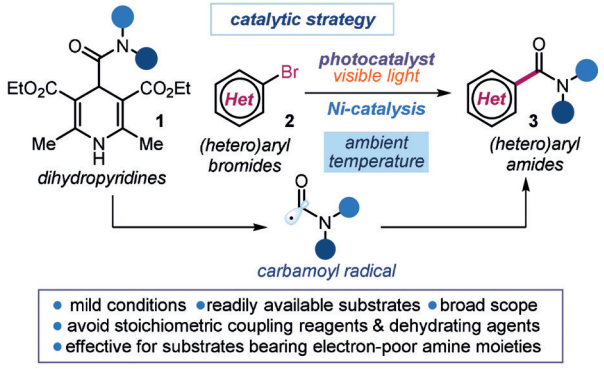
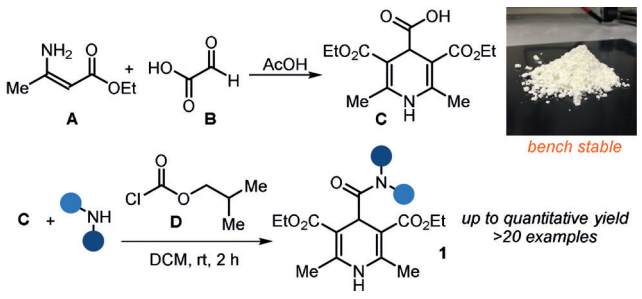


Figure 1. The presented radical cross-coupling approach to amide synthesis under photoredox-nickel dual catalysis.

Results and Discussion

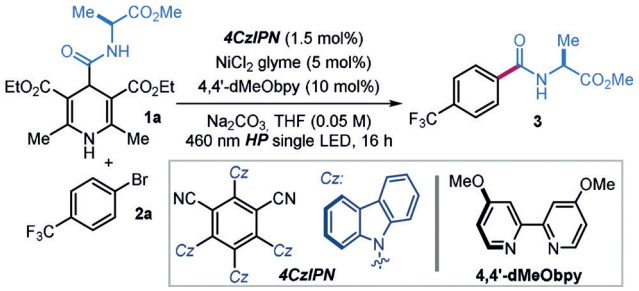
Developing this protocol required a suitable carbamoyl radical precursor. The choice of substrate **1** was motivated by the notion that 4-alkyl/acyl-1,4-dihydropyridines can generate alkyl[16] and acyl[17] radicals under oxidative conditions, respectively. We therefore surmised that dihydropyridines **1**, adorned with a carbamoyl moiety, would provide the target carbamoyl radical upon SET oxidation by a photoredox catalyst. We developed a straightforward synthesis of **1** from the dihydropyridine derivative **C** bearing a carboxyl moiety at the C4-position (Scheme 1). The bench-stable intermediate **C**[18] can be easily prepared in one step and on multigram scale from cheap and commercially available amino crotonate **A** and glyoxylic acid **B**. Subsequent condensation with amines in the presence of stoichiometric amounts of isobutylchloroformate **D** delivers the 4-carbamoyl-1,4-dihydropyridines **1** in excellent yields.

With the carbamoyl radical precursor in hand, we started our investigations (Table 1) by evaluating the cross-coupling reaction between the L-alanine-derived dihydropyridine **1a** (E_{ox} (**1a**$^{\bullet+}$/**1a**) = +1.39 V vs. Ag/Ag$^+$ in acetonitrile, CH_3CN) and 4-bromobenzotrifluoride **2a**.[19] The experiments were conducted at ambient temperature, using a single high-power (HP) blue LED emitting at 460 nm, a slight excess of **1** (1.5 equiv) and in the presence of $NiCl_2$ glyme (5 mol%), 4-4′-dimethoxy-2-2′-bipyridine (dMeObpy) as the ligand (10 mol%), and the organic photocatalyst **4CzIPN**.[20] When performing the reaction in tetrahydrofuran (THF) or 1,4-dioxane, the cross-coupling amide product **3** was obtained in quantitative yield (entries 1 and 2). The reaction also proceeds in "industrially preferred" solvents[21] (acetone and ethyl acetate (EtOAc), entries 3 and 4 respectively), therefore offering a good versatility to avoid potential substrate solubility issues. As a proof of the method's robustness, the reaction could be performed without degassing the solvent (entry 5)[22] and in the presence of water (entry 6), which only marginally affected the efficiency of the process. This reaction was also amenable to scale-up with no significant difference in reactivity using a simple experimental set-up (1.0 mmol, entry 7). The use of an immersion-well reactor (experimental details in Section D3 of the Supporting Information) allowed us to perform the process on a relevant preparative scale and without the need of re-optimization (entry 8, 15 mmol scale), delivering product **3** in 72% yield (>3 g). Control experiments confirmed that the reaction could not proceed in the absence of light, the photocatalyst, or nickel (entry 9). As a testament of the mild conditions of the system, we confirmed that, in all these experiments, no racemization of the enantiopure alanine scaffold occurred during the process.



Scheme 1. Synthesis of the carbamoyl radical precursor **1**; AcOH: acetic acid; DCM: dichloromethane.

Table 1: Optimization studies and control experiments.[a]



Entry	Deviation from standard conditions	Yield **3a** [%][b]
1	none	99
2	1,4-dioxane instead of THF	99
3	acetone instead of THF	33
4	EtOAc instead of THF	99
5	non-degassed condition	90
6	H_2O (10 equiv)	87
7	34W Kessil 456 nm (1 mmol)	91[c]
8	immersion-well reactor (15 mmol)	72[c]
9	no 4CzIPN, nickel or light	0

[a] Reactions performed on a 0.1 mmol scale at ambient temperature for 16 h under illumination by a single high-power (HP) blue LED (λ_{max} = 460 nm, irradiance = 100 ± 3 mW cm^{-2}) and using 1.5 equiv of **1a** and Na_2CO_3. [b] Yield determined by ^{1}H NMR analysis of the crude mixture using trichloroethylene as the internal standard. [c] Yield of isolated **3a**. LED = light-emitting diode; Na_2CO_3 = sodium carbonate.

Using the optimized conditions described in Table 1, entry 1, we tested the generality of the nickel/photoredox-catalyzed carbamoylation process. We first evaluated the scope of the (hetero)aryl bromides (Figure 2). A wide range of aryl bromides, bearing both electron-rich and electron-poor substituents, underwent the carbamoylation with the L-alanine-derived dihydropyridine **1a** in moderate to excellent yields (adducts **4**–**13**). High yields were achieved with bromobenzene (**4**) and bromonaphthalene (**5**). An *ortho*-substituent was well-tolerated (**6**), while an *ortho*-*ortho*′-

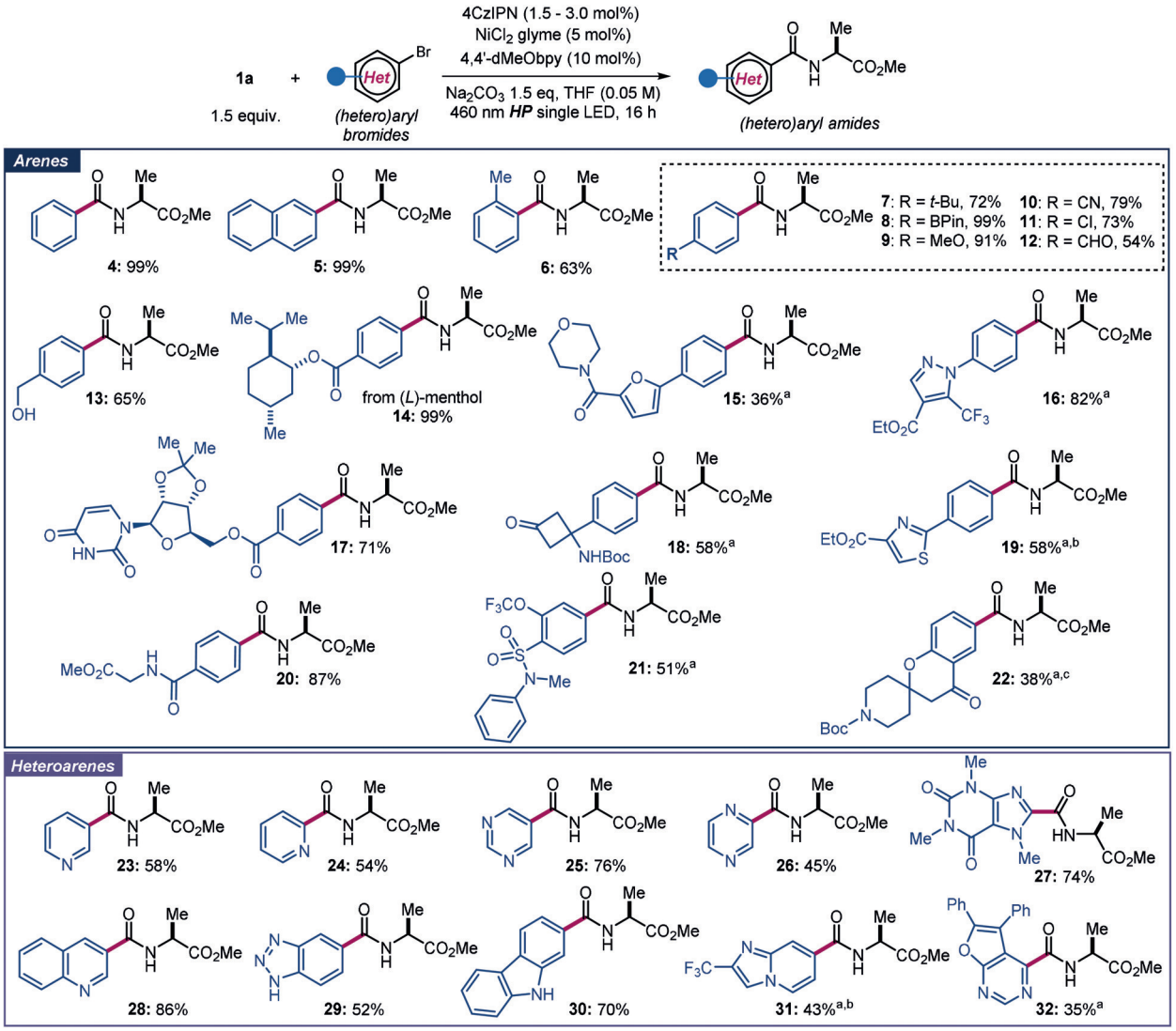


Figure 2. Scope of (hetero)aryl bromides. Reactions performed on 0.1 mmol scale at ambient temperature for 16 h under illumination by a single blue LED (λ_{max} = 460 nm) and using dihydropyridines (1.5 equiv), Na_2CO_3 (1.5 equiv) in THF (0.05 M). Yields of products refer to isolated material after purification (average of two runs per substrate).[a] Performed in 1,4-dioxane (0.05 M) using 3 mol% of the photocatalyst.[b] 0.2 mmol scale.[c] 0.2 mmol scale in 1,4-dioxane (0.025 M). Boc: *tert*-butyloxycarbonyl.

disubstituted aryl bromide remained unreactive, possibly because of steric hindrance (results not shown). The ability to tolerate aryl boronates (adduct **8**) and chlorides (**11**) demonstrated that the protocol is orthogonal to classical metal-catalyzed cross-coupling reactions and allows further functionalization. We then evaluated the compatibility with unprotected polar functional groups, which is an important criterion for assessing a method's applicability to complex molecule synthesis and drug discovery.[23] Aryl bromides bearing sensitive functional groups, including aldehydes (**12**), unprotected alcohols (**13**), ketones and Boc-protected amines (**18** and **22**), amides (**15** and **20**), and sulfonamide moieties (**21**) underwent the reaction smoothly. Our approach displayed a good level of tolerance towards heterocyclic substituents containing oxygen (**15**), nitrogen (**16**), and sulfur atoms (**19**). Functionalized aryl bromides bearing L-menthol (**14**), 2′,3′-*O*-isopropylideneuridine (**17**), and glycine (**20**) were tolerated, highlighting the method's potential for complex molecule synthesis. Given the prevalence of nitrogen-containing heterocycles in biologically active molecules,[24] we then evaluated the tendency of (hetero)aryl bromides to undergo the carbamoylation process. Pyridines (**23**–**24**), pyrimidine (**25**), pyrazine (**26**), quinoline (**28**), unprotected benzotriazole (**29**), imidazo[1,2-*a*]pyridine (**31**), and furo[2,3-*d*]pyrimidine (**32**) could all be functionalized. The protocol also provides a direct approach to carbamoylated caffeine (**27**) and carbazole (**30**), which would be difficult to access through traditional amidation methods because the carboxylic acid precursors are not readily available.

We then focused on the scope of the carbamoyl radical precursors (Figure 3). We first evaluated aminoacidic residues other than alanine that could be coupled with 4-bromobenzotrifluoride **2a**.[25] Glycine (**33**), phenylalanine (**34**), and valine

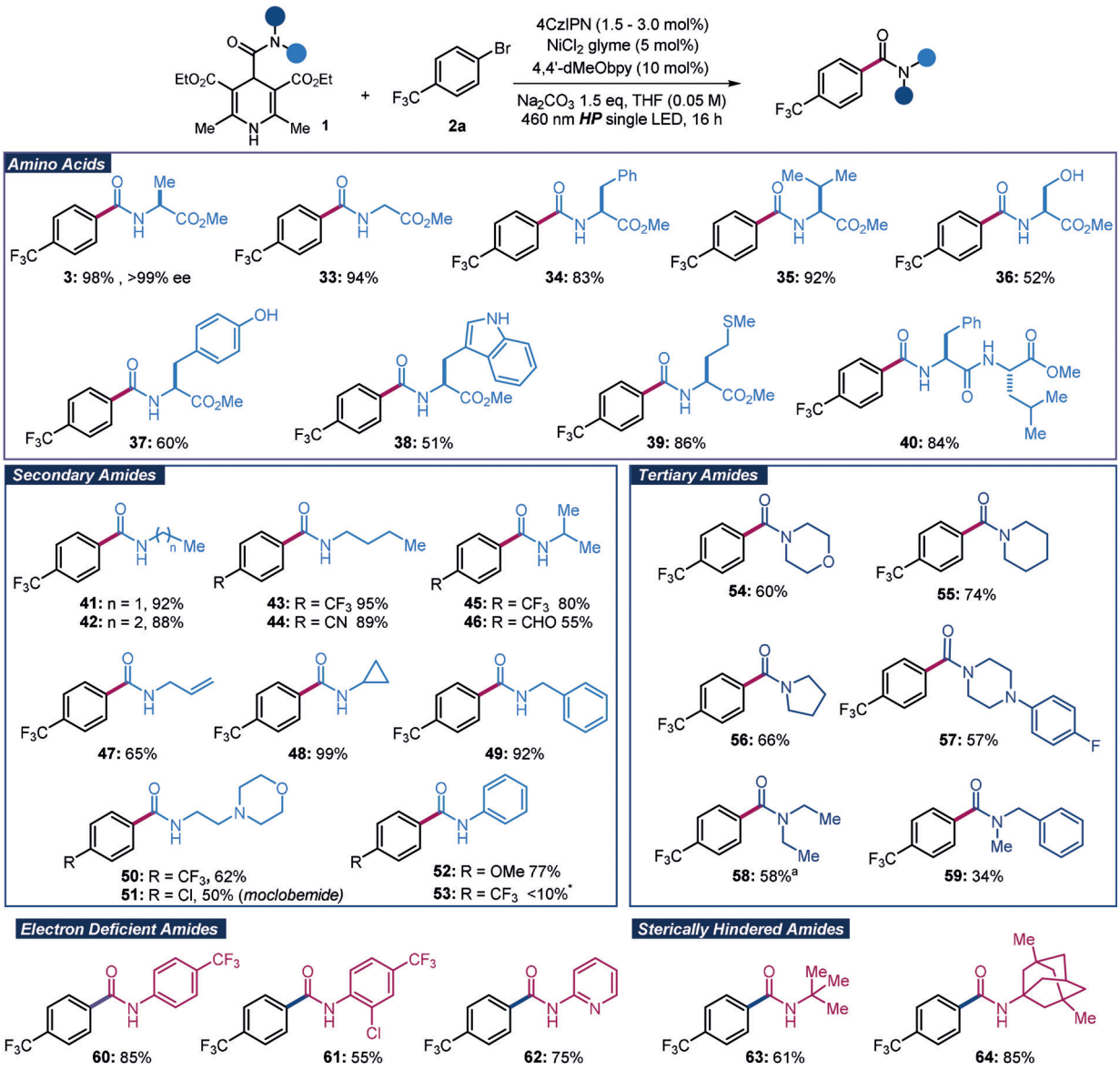


Figure 3. Scope of carbamoyl radical precursors. Reactions performed on 0.1 mmol scale at ambient temperature for 16 h under illumination by a single blue LED (λ_{max} = 460 nm) and using dihydropyridines (1.5 equiv), Na_2CO_3 (1.5 equiv) in THF (0.05 M). Yields of products refer to isolated material after purification (average of two runs per substrate).[a] Performed in 1,4-dioxane (0.05 M).

(**35**) could be installed in the amide products in excellent yields. There was good tolerance of the presence of free alcohols within serine (**36**) and tyrosine (**37**) and of an unprotected nitrogen in tryptophan (**38**). The reaction also proceeded efficiently when using the methionine-derived dihydropyridine, affording amide **39** bearing the *S*-methyl thioether group. Peptides are generally considered poor drug candidates because of their low oral bioavailability.[26] However, modifications, including N-terminal-capping, can improve their bioavailability and stability.[26b] Our method enabled the coupling of a dipeptide with **2a** to provide the *N*-aroyl capped dipeptide **40** in high yield.

Further evaluation of the dihydropyridines amenable to this strategy revealed that a variety of *N*-alkyl carbamoyl groups could be tolerated, delivering secondary amides, including the drug molecule moclobemide **51**, in moderate to high yields. An aniline-containing carbamoyl group could also be installed, although an electron-rich aryl bromide was needed to secure high reactivity (adducts **52** and **53**). Tertiary amides bearing morpholines (**54**), piperidines (**55**), pyrrolidines (**56**), and piperazines (**57**) were successfully obtained in good yields, while acyclic tertiary amides were achieved in moderate yields (**58**–**59**). These results suggest that our protocol can complement amide formation strategies based on isocyanates, as they are limited to the synthesis of primary and secondary amides.[11f,27]

Finally, we evaluated the possibility of installing amide functionalities bearing either sterically hindered or electron-poor amine moieties, which would be difficult to prepare by classical dehydrative condensation methods. Amides bearing

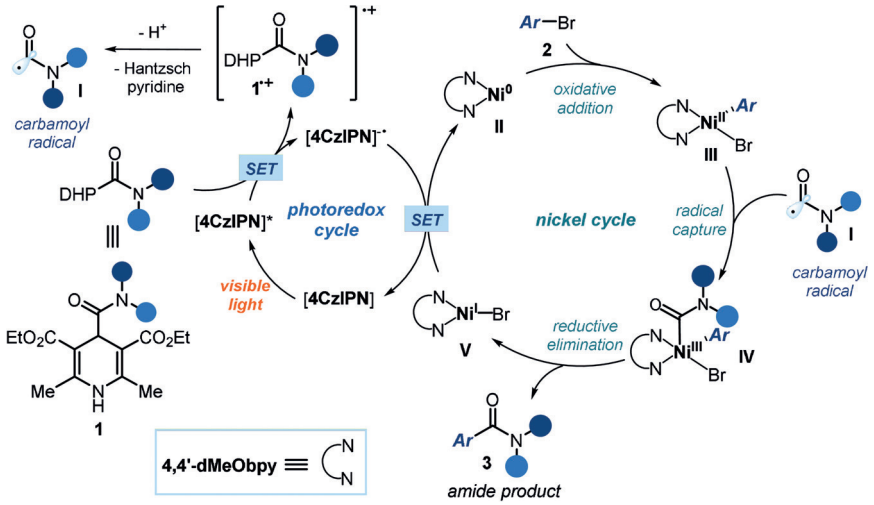


Figure 4. Proposed mechanism.

electron-poor anilines (**60** and **61**), pyridines (**62**), and hindered fragments (**63**–**64**) could all be effectively prepared using this nickel/photoredox dual catalysis approach.

A possible mechanism for the nickel/photoredox-catalyzed carbamoylation process is proposed in Figure 4. Photoexcitation of the organic photocatalyst **4CzIPN** ($E_{1/2}$ (**4CzIPN***/**4CzIPN**$^{\bullet-}$) = +1.43 V vs. SCE in CH_3CN)[20] forms an oxidant strong enough to take an electron from the dihydropyridine radical precursor **1** (E_{red} (**1a**$^{\bullet+}$/**1a**) = +1.39 V vs. Ag/Ag^+ in CH_3CN). This SET event triggers the formation of the carbamoyl radical **I**. Simultaneously, the Ni^0 complex **II** undergoes oxidative addition with aromatic bromide **2** to afford the Ni^{II} complex **III**. This intermediate intercepts the nucleophilic carbamoyl radical **I** to form the Ni^{III} intermediate **IV**, which, after reductive elimination, forges the desired $C(sp^2)$–$C(sp^2)$ bond in the cross-coupled amide product **3**. Finally, the ensuing Ni^I intermediate (E_{red} [Ni^I/Ni^0] = −1.13 V vs. $Ag^+/AgNO_3$ in DMF)[28] undergoes SET reduction by the reduced form of the photoredox catalyst ($E_{1/2}$ (**4CzIPN**/**4CzIPN**$^{\bullet-}$) = −1.24 V vs. SCE in CH_3CN), completing the catalytic cycle while regenerating both active catalysts.

Conclusion

In summary, we have reported a catalytic method for amide synthesis that occurs at ambient temperature. The chemistry exploits the ability of readily available 4-carbamoyl-1,4-dihydropyridines **1** to generate carbamoyl radicals upon SET oxidation by a visible-light-activated photoredox catalyst. This carbamoyl radical generation was used to develop a nickel cross coupling process to synthesize (hetero)aryl amides from readily available aryl bromides. This method tolerates unprotected polar functional groups and heterocycles, and it could be applied to the carbamoylation of complex molecules. We also demonstrated that the process is directly scalable without re-optimization. These findings, along with the experimental simplicity and the low cost and the stability of the substrates, suggest that this catalytic approach to amide synthesis can effectively complement conventional carbonylation chemistry and be useful in life science endeavours.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amides · cross-coupling · nickel catalysis · photoredox catalysis · radical chemistry

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[1] A. Greenberg, C. M. Breneman, J. F. Liebman, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, Wiley-VCH, Weinheim, **2003**.
[2] a) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479; b) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.
[3] For a freely accessible database, see: https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster; N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348–1349.
[4] a) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; b) R. Marcia de Figueiredo, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.* **2016**, *116*, 12029–12122; c) B. Shen, D. M. Makley, J. N. Johnston, *Nature* **2010**, *465*, 1027–1032.

[5] M. T. Sabatini, L. T. Boulton, H. F. Sneddon, T. D. Sheppard, *Nat. Catal.* **2019**, *2*, 10 – 17.
[6] E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606 – 631.
[7] J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, *20*, 140 – 177.
[8] D. J. C. Constable, et al., *Green Chem.* **2007**, *9*, 411 – 420.
[9] For selected examples, see: a) R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* **2013**, 7453 – 7465; b) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196 – 4197; c) R. K. Mylavarapu, G. C. M. Kondaiah, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya, R. Bandichhor, *Org. Process Res. Dev.* **2007**, *11*, 1065 – 1068; d) K. Ishihara, Y. Lu, *Chem. Sci.* **2016**, *7*, 1276 – 1280; e) M. T. Sabatini, L. T. Boulton, T. D. Sheppard, *Sci. Adv.* **2017**, *3*, e1701028.
[10] For selected examples, see: a) H. Lundberg, F. Tinnis, H. Adolfsson, *Chem. Eur. J.* **2012**, *18*, 3822 – 3826; b) H. Lundberg, H. Adolfsson, *ACS Catal.* **2015**, *5*, 3271 – 3277.
[11] a) A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327 – 3331; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114 – 4133; *Angew. Chem.* **2009**, *121*, 4176 – 4196; c) S. Roy, G. W. Gribble, *Tetrahedron* **2012**, *68*, 9867 – 9923; d) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 8460 – 8463; *Angew. Chem.* **2007**, *119*, 8612 – 8615; For a method requiring mild conditions, see: e) S. D. Friis, T. Skrydstrup, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4296 – 4299; For a review on the use of stable CO-surrogates, see: f) E. Serrano, R. Martin, *Eur. J. Org. Chem.* **2018**, 3051 – 3064.
[12] S. M. Mennen, et al., *Org. Process Res. Dev.* **2019**, *23*, 1213 – 1242.
[13] J. A. Milligan, J. P. Phelan, S. O. Badir, G. A. Molander, *Angew. Chem. Int. Ed.* **2019**, *58*, 6152 – 6163; *Angew. Chem.* **2019**, *131*, 6212 – 6224.
[14] For the use of carbamoyl radicals, generated under photoredox conditions, in the carbamoylation of heterocycles via a Minisci pathway, see: a) M. Jouffroy, J. Kong, *Chem. Eur. J.* **2019**, *25*, 2217 – 2221; b) A. H. Jatoi, G. G. Pawar, F. Robert, Y. Landais, *Chem. Commun.* **2019**, *55*, 466 – 469.
[15] For a recent example of Pd-catalyzed cross coupling for amide synthesis based on the use of a photoredox catalyst to generate carbamoyl radicals, see: W.-M. Cheng, R. Shang, H.-Z. Yu, Y. Fu, *Chem. Eur. J.* **2015**, *21*, 13191 – 13195. This method, besides using more expensive catalysts, offers a narrower substrate scope.
[16] For a review, see: a) P.-Z. Wang, J.-R. Chen, W.-J. Xiao, *Org. Biomol. Chem.* **2019**, *17*, 6936 – 6951; For selected examples: b) K. Nakajima, S. Nojima, K. Sakata, Y. Nishibayashi, *ChemCatChem* **2016**, *8*, 1028 – 1032; c) Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui, G. A. Molander, *J. Am. Chem. Soc.* **2017**, *139*, 12251 – 12258; d) L. Buzzetti, A. Prieto, S. R. Roy, P. Melchiorre, *Angew. Chem. Int. Ed.* **2017**, *56*, 15039 – 15043; *Angew. Chem.* **2017**, *129*, 15235 – 15239.
[17] a) G. Goti, B. Bieszczad, A. Vega-Peñaloza, P. Melchiorre, *Angew. Chem. Int. Ed.* **2019**, *58*, 1213 – 1217; *Angew. Chem.* **2019**, *131*, 1226 – 1230; b) B. Bieszczad, L. A. Perego, P. Melchiorre, *Angew. Chem. Int. Ed.* **2019**, *58*, 16878 – 16883; *Angew. Chem.* **2019**, *131*, 17034 – 17039.
[18] G. Y. Dubur, Y. R. Uldrikis, *Chem. Heterocycl. Compd.* **1972**, *5*, 762 – 763.
[19] We have optimized the reaction conditions (solvents and ligands) using a high-throughput experimentation (HTE) approach. See Section D1 in the Supporting Information for details.
[20] a) J. Luo, J. Zhang, *ACS Catal.* **2016**, *6*, 873 – 877; b) E. Speckmeier, T. G. Fischer, K. Zeitler, *J. Am. Chem. Soc.* **2018**, *140*, 15353 – 15365.
[21] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.* **2016**, *18*, 288 – 229.
[22] For a study discussing the compatibility of molecular oxygen in photoredox/Ni dual catalyzed cross-coupling reactions, see: M. S. Oderinde, A. Varela-Alvarez, B. Aquila, D. W. Robbins, J. W. Johannes, *J. Org. Chem.* **2015**, *80*, 7642 – 7651.
[23] a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383 – 394; b) W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952 – 2963.
[24] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257 – 10274.
[25] A radical precursor bearing a free acidic moiety, prepared upon methyl ester hydrolysis of compound **1a**, remained unreacted under the optimal nickel/photoredox-catalyzed carbamoylation conditions. See Section D4 of the Supporting Information for details.
[26] a) P. Vlieghe, V. Lisowski, J. Martinez, M. Khrestchatisky, *Drug Discovery Today* **2010**, *15*, 40 – 56; b) H.-J. Zhou, et al., *J. Med. Chem.* **2009**, *52*, 3028 – 3038.
[27] For selected examples: a) G. Schäfer, C. Matthey, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 9173 – 9175; *Angew. Chem.* **2012**, *124*, 9307 – 9310; b) A. Correa, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 7253 – 7256; c) S. Zheng, D. N. Primer, G. A. Molander, *ACS Catal.* **2017**, *7*, 7957 – 7961.
[28] M. Börjesson, T. Moragas, R. Martin, *J. Am. Chem. Soc.* **2016**, *138*, 7504 – 7507.

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