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Carbamoylation of Aryl and Benzyl Chlorides by Direct C−H Functionalization of Formamide Derivatives via Ni/Photoredox-Catalyzed Cross-Coupling

Jihye Shin, Eunseo Sim, and Sun Dongbang*

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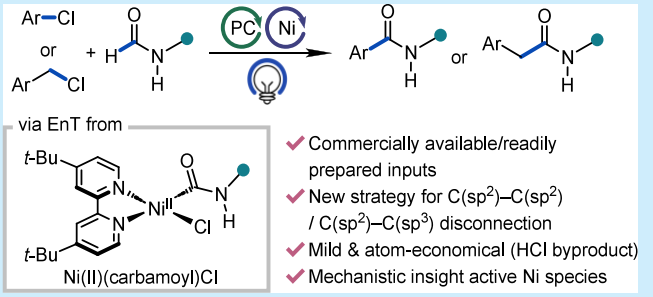
ABSTRACT: We report a Ni/photoredox dual catalytic protocol that activates the formyl C−H bond of simple formamides to enable C(sp^2)−C(sp^2)/C(sp^2)−C(sp^3) carbamoylation with aryl and benzyl chlorides. This transformation proceeds without the need for prefunctionalized carbamoyl radical precursors, external oxidants, or halogen atom transfer (XAT)/hydrogen atom transfer (HAT) reagents by harnessing *in situ*-generated Cl radicals for selective HAT followed by the cross-coupling event. This strategy provides a mild and atom-economical platform for accessing structurally diverse amides, including sterically hindered variants that are difficult to access through classical C−N bond-forming methodologies. Stoichiometric studies of independently synthesized Ni complexes reveal a distinct pathway involving a Ni(II)(carbamoyl)Cl complex as the active intermediate, diverging from the previously established C(sp^3)−H functionalization chemistry.



Amide bonds represent fundamental structural motifs across pharmaceuticals, agrochemicals, and functional materials, displaying a wide range of molecular conformations, bioactivities, and stabilities depending on their substitution patterns.[1,2] In particular, *N*-alkyl amides offer unique structural modularity, such as conformational rigidity and enhanced metabolic stability.[3−5] Despite their significance, most amide bond-forming reactions are not limited to C−N bond disconnections but also require the use of stoichiometric amounts of reagents to activate carboxylic acids (e.g., carbodiimide-mediated couplings) (Figure 1a, top).[6−10] Other methods utilizing transition metals for amide bond formation often require CO gas and high pressure (Figure 1a, bottom),[6] pointing toward the need for alternative platforms that can synthesize alkyl amides under mild conditions.

In recent years, installation of the carbamoyl group via one-electron radical pathways has emerged as an attractive alternative for amide construction (Figure 1b).[11−13] Early reports demonstrated hydrogen atom transfer (HAT) of formamides to undergo Minisci reactions with heteroarenes or Giese-type addition to alkenes using peroxy radical initiators, in which harsh reaction conditions at higher temperatures (>90 °C) are often required.[14,15] Alternatively, photoredox catalysis has also enabled efficient generation of nucleophilic carbamoyl radicals using their corresponding radical precursors, such as 1,4-dihydropyridines,[16−18] oxamic acids,[19−21] and carbamoyl chlorides.[22] These can be activated by photocatalysis to undergo additions to alkenes or heteroarenes under mild conditions. However, these approaches are generally limited to radical additions to electron-deficient π bonds and often require the prefunctionalization of radical precursors.

Recently, cross-coupling strategies that exploit carbamoyl radicals as coupling partners in transition metals and photocatalysis have been developed (Figure 1c). In 2020, Melchiorre and co-workers developed a Ni/photoredox-catalyzed carbamoylation of aryl bromides with 4-carbamoyl-1,4-dihydropyridines (DHPs) by their oxidation to generate the carbamoyl radical along with pyridine.[23] Analogously, in 2023, Kuniyil/Yatham[24] and Sparr and co-workers[25] developed a decarboxylative carbamoylation of aryl bromides using oxamic acids. In 2022, Maiti and co-workers expanded the Ni/photoredox-catalyzed amidation of aryl chlorides, as well as bromides via a distinct strategy. In this protocol, silyl radical-mediated halogen atom transfer (XAT) of carbamoyl chlorides provides access to the carbamoyl radical for cross-coupling,[26,27] initiated either via energy transfer (EnT)- or single-electron transfer (SET)-mediated Ni−halide homolysis.

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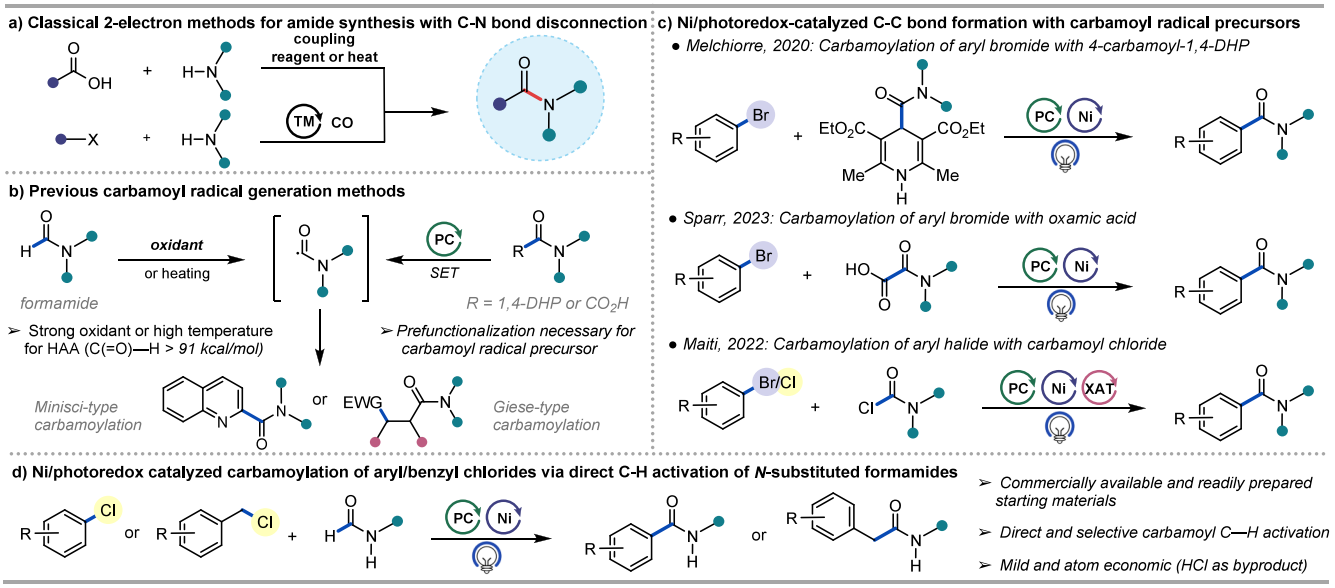


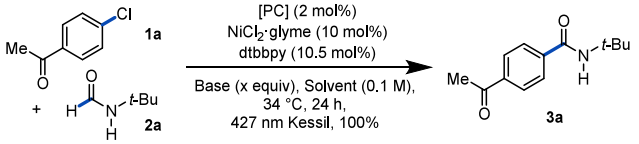
Figure 1. Recent developments in amide bond synthesis strategies.

While several methods for carbamoyl radical generation have been reported for C−C bond formation, they typically require multistep precursor synthesis and additional reagents such as HAT and XAT agents or radical initiators. A mild approach that directly generates carbamoyl radicals from readily accessible formamides would streamline access to these motifs. Moreover, most precedents employ aryl bromides (6.4×10^5), whereas reactions with the more abundant and economical aryl chlorides (1.4×10^6) remain less explored.[28] Notably, to the best of our knowledge, benzyl chlorides have not been previously used as electrophiles for C(sp^3) carbamoylation.

Herein, we disclose a Ni/photoredox dual catalysis that enables the cross-coupling of carbamoyl radicals and aryl and benzyl chlorides. This reaction enables direct activation of the formyl C−H bond with an *in situ*-generated HAT source, eliminating the need for prefunctionalization or external oxidants (Figure 1d).[29] We envisioned that Cl radicals generated from the homolytic cleavage of the Ni−Cl complex could directly abstract the formyl C−H of formamides[30] to furnish carbamoyl radicals with the concomitant formation of HCl[30] as the sole byproduct.[31−34] This strategy enables atom-economic synthesis of aryl and benzyl amides, including various sterically demanding *N*-alkyl amides, under mild conditions with a nontraditional bond disconnection.

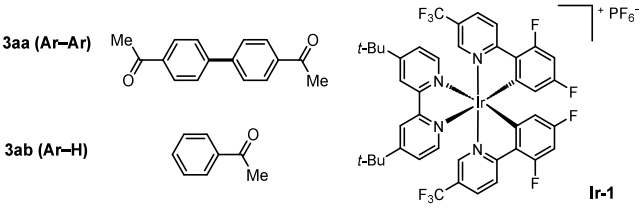
Our study began with the reaction using 4′-chloroacetophenone (**1a**) and *N*-*tert*-butylformamide (**2a**) as the model substrates. Using 2.0 mol % Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (**Ir-1**), 10 mol % $NiCl_2$·glyme, 10.5 mol % 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy), and K_3PO_4 (2.0 equiv) in MeCN (0.1 M) under visible light irradiation at 34 °C gave no product (Table 1, entry 1). Switching to benzene afforded **3a** in 29% yield, along with 1% Ar−Ar dimer **3aa** and 5% protodehalogenated **3ab** (entry 2). Both the base identity and its loadings were critical for improving the yield (entries 3−7). An organophotocatalyst such as 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene[35,36] and HAT photocatalyst such as tetrabutylammonium decatungstate (TBADT) were ineffective (entries 8 and 9, respectively). Addition of external chloride sources (TBACl and LiCl) decreased the yield (entries 10 and 11, respectively). Altering the amounts of **1a** and **2a** to 2.0 and 1.0 equiv, respectively, increased the yield to 81% (entry 12). A 1.0 mmol scale-up experiment using a round-bottom flask provided the product in 74% yield, demonstrating a consistent reaction performance (entry 13; for further details, see section III of the Supporting Information). Control experiments

Table 1. Optimization of the Reaction Conditions[a]



Entry	1a : 2a Equiv	Photocatalyst	Base / Equiv	Solvent	Additive	Yield (%)[b] 1a	3a	3aa	3ab
1	1.0 : 3.0	**Ir-1**	K_3PO_4 / 2.0	ACN	-	100	0	0	0
2	1.0 : 1.2	**Ir-1**	K_3PO_4 / 2.0	PhH	-	31	29	1	5
3	1.0 : 1.2	**Ir-1**	-	PhH	-	74	8	1	2
4	1.0 : 1.2	**Ir-1**	Cs_2CO_3 / 4.0	PhH	-	59	29	3	4
5	1.0 : 1.2	**Ir-1**	$NaHCO_3$ / 4.0	PhH	-	48	34	7	7
6	1.0 : 1.2	**Ir-1**	K_2CO_3 / 4.0	PhH	-	49	41	1	8
7	1.0 : 1.2	**Ir-1**	K_3PO_4 / 4.0	PhH	-	2	71	4	6
8	1.0 : 1.2	4-CzIPN	K_3PO_4 / 4.0	PhH	-	96	0	0	0
9	1.0 : 1.2	TBADT	K_3PO_4 / 4.0	PhH	-	89	1	1	0
10	1.0 : 1.2	**Ir-1**	K_3PO_4 / 4.0	PhH	TBACl	19	35	3	10
11[c]	1.0 : 1.2	**Ir-1**	K_3PO_4 / 2.0	PhH	LiCl	68	7	1	2
12[d]	2.0 : 1.0	**Ir-1**	K_3PO_4 / 4.0	PhH	-	86	81	2	12
13[e]	2.0 : 1.0	**Ir-1**	K_3PO_4 / 4.0	PhH	-	59	74	3	18

[a]Reactions were performed on a 0.10 mmol scale.



[b]Yields were determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c]Upon 390 nm light irradiation with a 1:1 PhH/ACN solvent, as TBADT was insoluble in pure benzene. [d]With 4 mol % NiCl·glyme and 5.2 mol % dtbbpy. [e]Five percent of **2a** remained. The reaction was performed on a 1.0 mmol scale.

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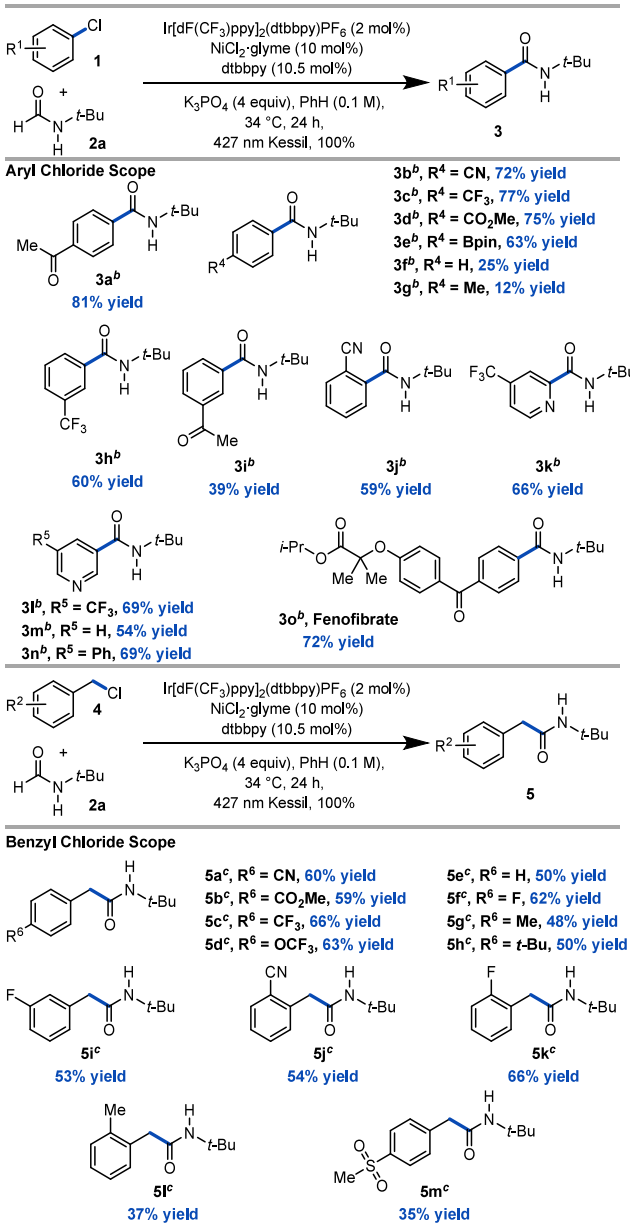
Org. Lett. XXXX, XXX, XXX−XXX

confirmed that all components are essential (entries 3 and 14–17).

With the optimized reaction conditions, we examined the scope of our Ni/photoredox-catalyzed carbamoylation with various carbon electrophiles (Table 2). Aryl chlorides bearing

Table 2. Carbon Electrophile Scope[a]



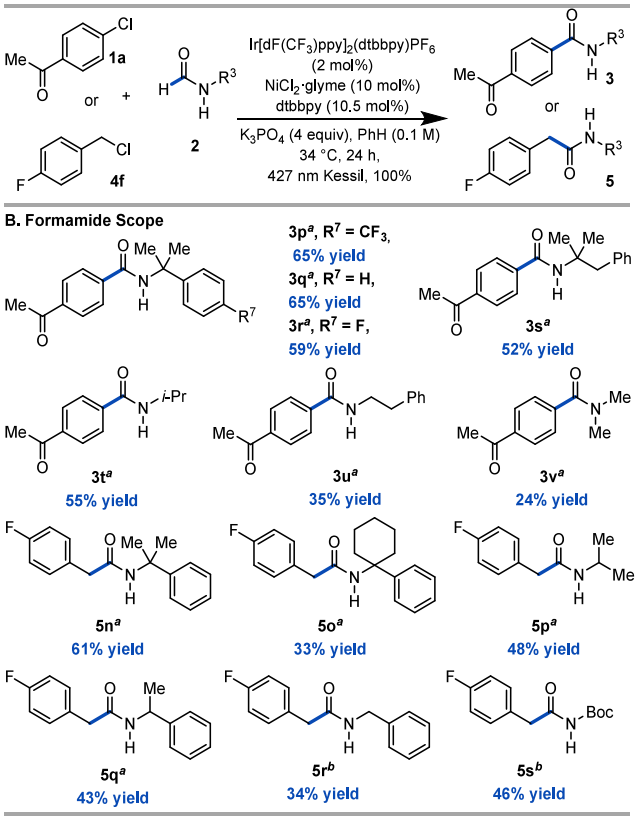
[a]Isolated yield from 0.20 mmol. [b]The reaction was performed with **1** or **4** (2.0 equiv) and **2** (1.0 equiv). [c]The reaction was performed with **1** or **4** (1.0 equiv) and **2** (1.2 equiv).

electron-deficient groups such as *p*-CN (**3b**), -CF_3 (**3c**), -CO_2Me (**3d**), and -Bpin (**3e**) coupled efficiently with **2a** in excellent yields. Electron-neutral substrates (**3f** and **3g**) provided modest yields, and *meta*- and *ortho*-substituted aryl chlorides were tolerated (**3h**–**3j**). Chloropyridine derivatives, common motifs in bioactive compounds, delivered the products in 54–69% yields (**3k**–**3n**).[37] Notably, late-stage carbamoylation of fenofibrate, a treatment for abnormal blood lipid levels,[38] was successful, affording an excellent yield (**3o**), showing the potential of this protocol for direct functionalization of pharmaceutical motifs.

We successfully extended this strategy to benzyl chlorides as C(sp^3) electrophiles, a substrate class that has been underexplored in Ni/photoredox-mediated photoelimination chemistry. Benzyl chlorides proved to be competent, unveiling a new bond disconnection for phenylacetamide synthesis and bypassing the need for phenylacetyl chlorides, which are often less stable and inconvenient to handle.[39] This method demonstrated excellent functional group tolerance, affording high yields for electron-deficient (*p*-CN, -CO_2Me, -CF_3, and -OCF_3 (**5a**–**5d**, respectively)), electron-neutral (*p*-H and F (**5e** and **5f**, respectively)), and electron-rich substituents (*p*-Me and *t*-Bu (**5g**–**5h**)), the latter showing improved reactivity relative to the corresponding aryl chlorides. *meta*- and *ortho*-substituted substrates afforded products in good yields (**5i**–**5l**). Sulfone-containing substrates (**5m**) exhibited smooth reactivity, highlighting the potential for pharmaceutical synthesis.[40]

We next explored the scope of formamides (Table 3). Notably, *N*-tertiary alkyl substituents, typically challenging to

Table 3. Formamide Scope



[a]The reaction was performed with **1** or **4** (1.0 equiv) and **2** (1.2 equiv). [b]The reaction was performed with **1** or **4** (2.0 equiv) and **2** (1.0 equiv).

access via classical carboxylate activation or transamidation processes due to the poor nucleophilicity of sterically hindered amines,[41] coupled efficiently to afford products such as **3p**–**3s** and **5n**. *N*-secondary alkyl (**3t** and **5p**) and *N*-primary alkyl-substituted formamide (**3u**) similarly underwent efficient coupling with aryl chlorides. When dimethylformamide

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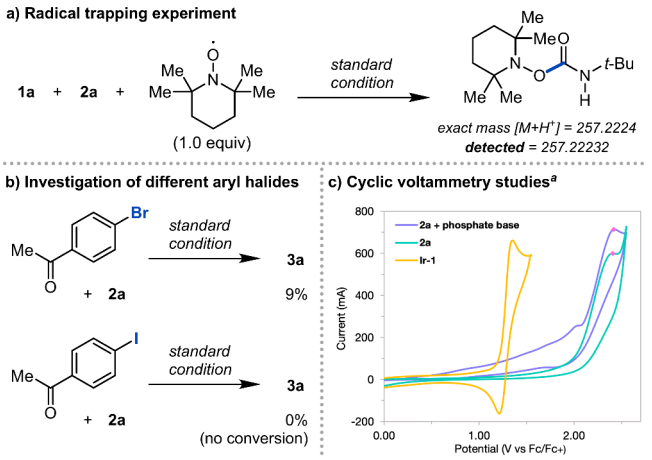
Org. Lett. XXXX, XXX, XXX–XXX

(DMF) was employed as a tertiary formamide, the desired product was obtained in a relatively lower yield. Benzyl chlorides exhibited greater tolerance to various *N*-alkyl substituents, including sterically hindered formamide (**5o**), and furnished products from *N*-secondary and *N*-primary alkyl-substituted formamides (**5q** and **5r**, respectively). Furthermore, a Boc-protected formamide proved to be feasible, allowing further postfunctionalization upon deprotection (**5s**).

To gain insight into the mechanism, we examined carbamoyl radical formation using a radical trapping experiment. Addition of TEMPO completely suppressed the reactivity and yielded the corresponding TEMPO−carbamoyl adduct (Scheme 1a).

Scheme 1. Mechanistic Studies for the Investigation of Intermediates for Generating the Carbamoyl Radical



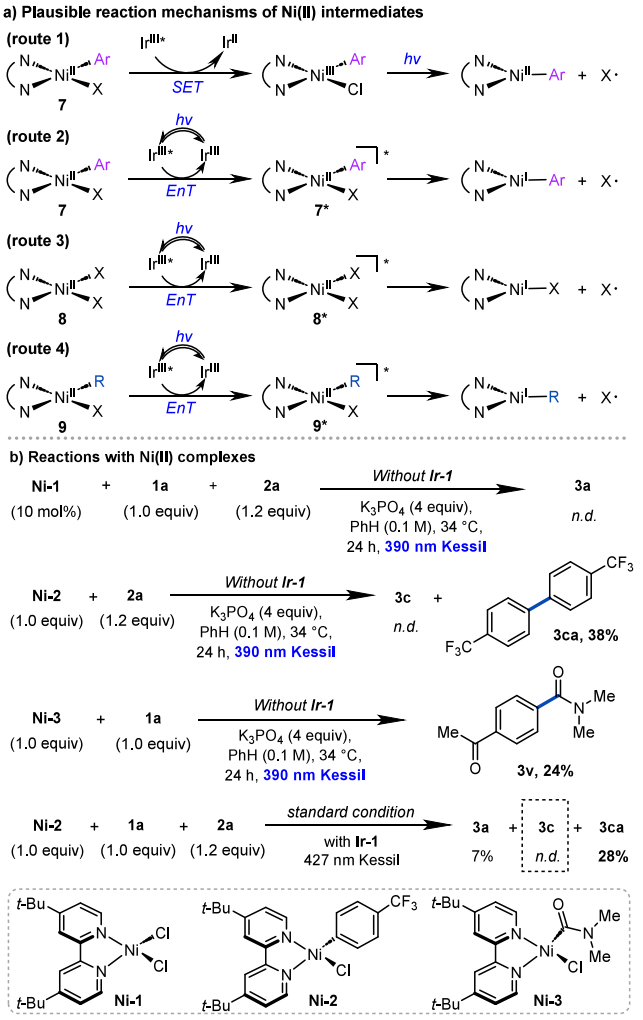
[a]Cyclic voltammogram from 0.00 to 2.50 V (positive scan), at a scan rate of 0.10 V s^{-1}.

Next, the halide effect in aryl electrophiles was examined. Aryl chlorides furnished the amide product in high yields, whereas aryl bromides and iodides gave only 9% yield and trace amounts, respectively (Scheme 1b). These results underscore the crucial role of Cl radicals as efficient HAT reagents for selective abstraction of the formyl C−H bond, consistent with the thermodynamic favorability of HCl formation.[30]

While HAT with Cl radicals is thermodynamically feasible, we also considered the possibility of the radical initiator being the N-centered radical of formamide, given that a proton-coupled electron transfer (PCET) of the N−H bond may be feasible under our reaction condition with a phosphate base and an oxidizing photocatalyst (see section V-B of the Supporting Information).[42] However, cyclic voltammetry revealed oxidation potentials of formamide, both with (E_{ox}N−H = 2.43 V vs Fc/Fc^+) and without (E_{ox}N−H = 2.41 V vs Fc/Fc^+) the phosphate base, far above that of the excited Ir photocatalyst[36] (Scheme 1c). Moreover, Stern−Volmer studies showed no quenching between Ir(III)* and formamide, ruling out a PCET pathway (see Figures S17 and S18).

We next sought to gain insight into the active Ni species that directly enable Cl radical formation. Previously, SET (Scheme 2a, route 1)[31,43−47] or EnT (route 2)[34,48,49] from Ni(II)ArX **7** followed by homolysis of the Ni−X bond has been proposed for C(sp^3)−H arylation. On the other hand, recent studies show the possibility of EnT-mediated Ni−X homolysis from excited state Ni(II)X_2 **8** (route 3), streamlined with comproportionation steps.[50,51] Another possibility is an EnT-

Scheme 2. Mechanistic Studies with Independently Synthesized Ni Complexes



mediated halogen radical homolysis from a Ni(II)−(alkyl)X complex, generated via a rapid radical recombination onto a Ni(I)−X species of the alkyl C−H coupling partner (route 4).[52] As our method targets C(sp^2)−H functionalization, where mechanistically relevant Ni species remain underexplored, we sought to elucidate the C(sp^2)−C cross-coupling mechanism.

To identify catalytically relevant Ni species, we synthesized three Ni(II) complexes, (dtbbpy)Ni(II)Cl_2 (**Ni-1**), (dtbbpy)-Ni(II)(*p*-CF_3Ph)Cl (**Ni-2**), and (dtbbpy)Ni(II)(DMF)Cl (**Ni-3**), to examine their photophysical and stoichiometric behavior (Scheme 2a).[53] All three complexes quenched the excited state Ir(III)* in the Stern−Volmer experiments, suggesting that SET or EnT is feasible from Ir(III)* to each Ni(II) species (Figures S21−S27). Furthermore, the complexes were subjected to reaction conditions (see section V-E of the Supporting Information), giving **3a** in 55−80% yield. Given only minor differences thus far, we next examined whether the Ni complexes could be directly excited at 390 nm without a photocatalyst to distinguish between SET and EnT (Scheme 2b). While **Ni-1** was inactive, **Ni-2** afforded the Ar−Ar dimer, whereas **Ni-3**, analogous to complex **9** in route 4, gave the desired product in 24% yield (Scheme 2b).[54] Combined with the Stern−Volmer data, we propose that **Ni-**

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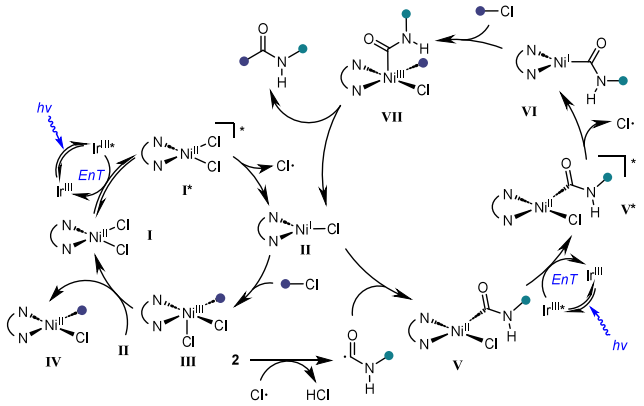
Org. Lett. XXXX, XXX, XXX−XXX

3 is likely the catalytically relevant species, where carbamoyl radicals are intercepted by a Ni(I)−Cl complex to produce Ni(II)−carbamoyl chloride (**Ni-3**). This complex, upon excitation, could undergo Ni−halide homolysis to afford the Ni(I)−carbamoyl intermediate. To further corroborate that the **Ni-2** species is not likely the catalytically relavant species under our standard conditions, we subjected a stoichiometric amount of **Ni-2** to crossover experiments under photocatalytic 427 nm irradiation. In this experiment, the only product containing a *p*-CF_3-aryl fragment, originating from the aryl ligand bound to **Ni-2**, was biaryl dimer **3ca**. No carbamoylated product **3c** was detected, indicating that **Ni-2** most likely participates in an off-cycle pathway leading to Ar−Ar formation.

Scheme 3. Proposed Mechanism



Based on these results and prior reports,[50] we propose a mechanism for the Ni/photoredox-catalyzed carbamoylation (Scheme 3). The cycle begins with the excitation of Ni precatalyst **I** via EnT from Ir(III)* to form **I***, which undergoes homolysis to generate the Cl radical and Ni(I)−Cl species **II**. Complex **II** can either react with Ar−Cl followed by comproportionation to afford **IV** and regenerate **I** (left cycle)[50] or capture the carbamoyl radical formed via HAT of formamide with the Cl radical to furnish **V** (right cycle). Ni(II)(carbamoyl)Cl complex **V** was shown catalytically to generate the Cl radical and **VI**. Complex **VI** then undergoes oxidative addition to form **VII**, followed by reductive elimination to afford product **3** and regenerate **II**. We propose that Ni(II)ArCl complex **IV** does not engage in product formation via carbamoyl radical capture as reported previously[23,25,26] but instead serves as the resting state linked to off-cycle dimer formation (see Figure S12).

In conclusion, we have developed a Ni/photoredox protocol that directly couples formamides to aryl and benzyl chlorides to forge amide bonds. The reactivity enables unprecedented $C(sp^2)-C(sp^2)/C(sp^2)-C(sp^3)$ carbamoylation under mild, oxidant-free conditions. Mechanistic studies of discrete Ni complexes reveal new Ni-mediated $C(sp^2)-C$ pathways involving halogen radical HAT, providing insight into the observed selectivity and future design of radical amide synthesis.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c04820.

Experimental details, characterization data, and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Sun Dongbang − *Department of Chemistry and Center for Nano Materials, Sogang University, Seoul 04107, Republic of Korea*; orcid.org/0000-0001-6599-3603; Email: dongbang@sogang.ac.kr

Authors

Jihye Shin − *Department of Chemistry, Sogang University, Seoul 04107, Republic of Korea*

Eunseo Sim − *Department of Chemistry, Sogang University, Seoul 04107, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.5c04820

Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX