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Article

Additive-Controlled Divergent Synthesis of Amides and Ketones via Ni/Photoredox-Catalyzed Deoxygenative Functionalization of Alcohols

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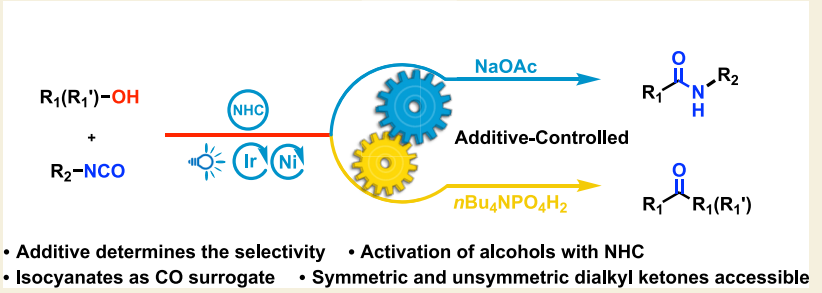

ABSTRACT: Amides and ketones are essential carbonyl compounds with widespread applications in pharmaceuticals, materials science, and synthetic chemistry. Herein, we present a Ni/photoredox dual-catalyzed strategy for the divergent synthesis of amides and ketones from isocyanates and alcohols. This transformation is facilitated by *N*-heterocyclic carbene (NHC)-mediated activation of alcohols and is selectively controlled by the choice of additive: NaOAc promotes amide formation, whereas nBu$_4$NPO$_4$H$_2$ directs the reaction toward ketone synthesis. This approach offers a versatile and practical route to access amides and ketones from readily available alcohol feedstocks.

KEYWORDS: *amide, ketone, Ni/photoredox dual catalysis, isocyanate, alcohol, additive-controlled selectivity*

INTRODUCTION

Amides[1−5] and ketones[6−10] are among the most prevalent carbonyl-containing motifs found ubiquitously in pharmaceuticals, natural products, and functional materials. The versatile reactivity of the carbonyl group further establishes these structures as pivotal intermediates in synthetic chemistry.[9,11−14] Consequently, the development of efficient methodologies for constructing amides and ketones remains a cornerstone of both academic research and industrial synthesis. In particular, synthetic routes that employ readily available feedstocks to access these carbonyl compounds hold great promise for advancing chemical innovation and practical applications.

Classical amide synthesis typically relies on C−N bond formation via condensation between carboxylic acid derivatives and amines.[15−19] However, this approach often requires stoichiometric activating reagents and can be ineffective for sterically hindered or weakly nucleophilic amines. Moreover, the direct conversion of alternative substrates such as halides or alcohols into amides remains challenging. In this context, isocyanates have emerged as strategically advantageous amide precursors due to their commercial availability and favorable reactivity profiles under both conventional and catalyzed reaction conditions[20−23] Although organometallic reagents can directly react with isocyanates to form amides, their moisture sensitivity and limited functional group tolerance significantly restrict their synthetic utility (Scheme 1a right).[24−28] To address these limitations, nickel-catalyzed alkyl radical−isocyanate coupling has recently broadened the scope of amide synthesis. Notable advances include Martin's Ni-catalyzed amidation of unactivated alkyl bromides,[29,30] Molander's photoredox/Ni dual-catalyzed amidation of alkylsilicates,[31] and Murakami/Nevado's benzyl C(sp^3)−H amidation.[32,33] Inspired by these developments, we sought to explore whether more abundant and commercially accessible alcohols could similarly engage with isocyanates under nickel catalysis.

In parallel, ketone synthesis has seen significant progress beyond classical alcohol oxidation, particularly through nickel-catalyzed cross-coupling of carboxylic acid derivatives with alkyl radicals (Scheme 1b, right).[34−40] However, these methods are limited by their dependence on prefunctionalized

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Scheme 1. Overview of Amide and Ketone Synthesis Strategies Utilizing CO Surrogate such as Isocyanates

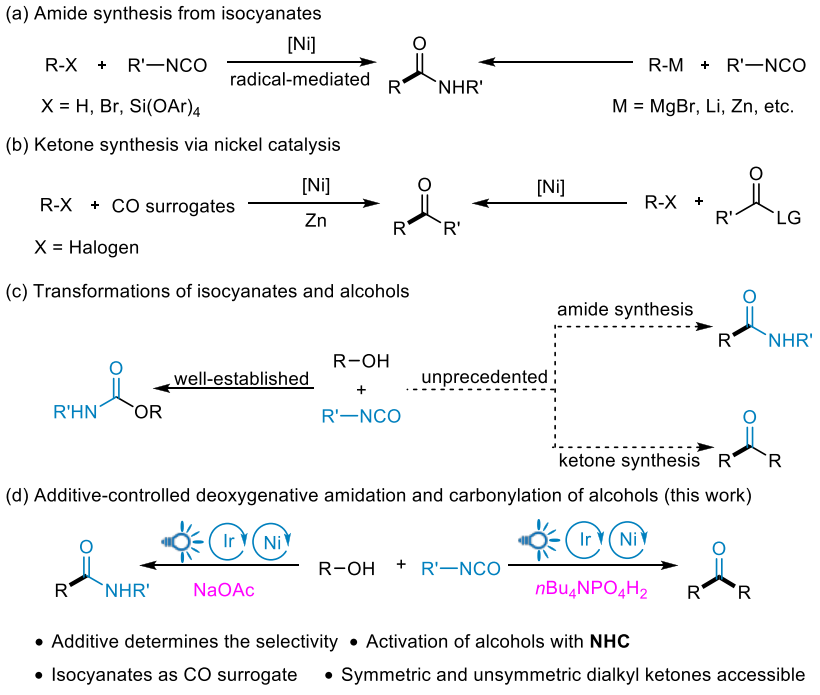
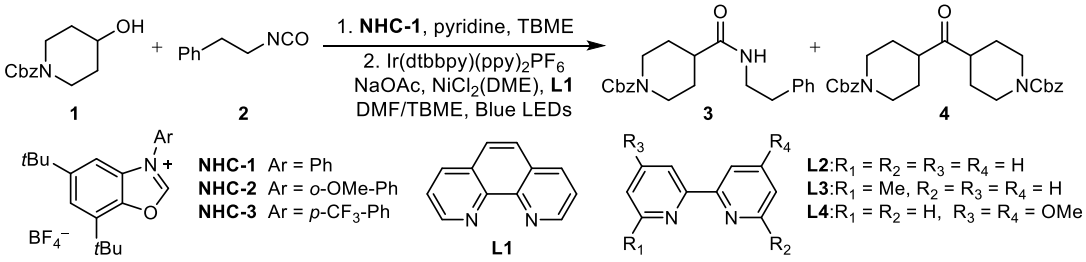


Table 1. Optimization of Reaction Conditions[a]



Entry	Deviation of standard conditions	Yield[b] 3	Yield[b] 4
1	none	82%[c]	trace
2	**L2** instead of **L1**	59%	trace
3	**L3** instead of **L1**	38%	0
4	**L4** instead of **L1**	58%	trace
5	**NHC-2** instead of **NHC-1**	56%	trace
6	**NHC-3** instead of **NHC-1**	33%	0
7	4CzIPN instead of $Ir(dtbbpy)(ppy)_2PF_6$	77%	trace
8	$Ru(bpy)_3PF_6$ instead of $Ir(dtbbpy)(ppy)_2PF_6$	0	0
9	No [Ni] or no light or no photocatalyst	0	0
10	KH_2PO_4 instead of NaOAc	11%	5%
11	$nBu_4NPO_4H_2$ instead of NaOAc	20%	52%
12	$nBu_4NPO_4H_2$ instead of NaOAc	16%[d]	65%
13	$nBu_4NPO_4H_2$ instead of NaOAc	6%[d]	74%[ce]

[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **NHC-1** (1.2 equiv), and pyridine (1.1 equiv) in TBME (0.1 M), then **2** (2.0 equiv), $NiCl_2(DME)$ (10 mol %), **L1** (10 mol %), NaOAc (2.0 equiv), and $Ir(dtbbpy)(ppy)_2PF_6$ (1 mol %) in DMF/TBME (6/6 mL), 10 W 450 nm bule LEDs, 10 h, 25−30 °C. [b]Yields determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield. [d]1 mmol scale using *n*Hex-NCO instead of **2**, affording amide products containing *n*-hexyl substituents. [e]DMF/TBME/*t*BuOH (10/10/4 mL).

carboxylate substrates and often show limited efficiency for symmetrical dialkyl ketones. The strategic use of CO surrogates offers a solution by enabling in situ formation of nickel-acyl intermediates via radical carbonylation (Scheme 1b, left). Seminal contributions include Hu's 2019 nickel-catalyzed reductive carbonylation of alkyl halides using ethyl chloroformate as a CO source,[41] and Gong's 2021 protocol employing diphenyl oxalate as a CO surrogate.[42] Moreover, the Shi and Zhao group has reported a carbonylation protocol for protected benzylamines employing isocyanates as the

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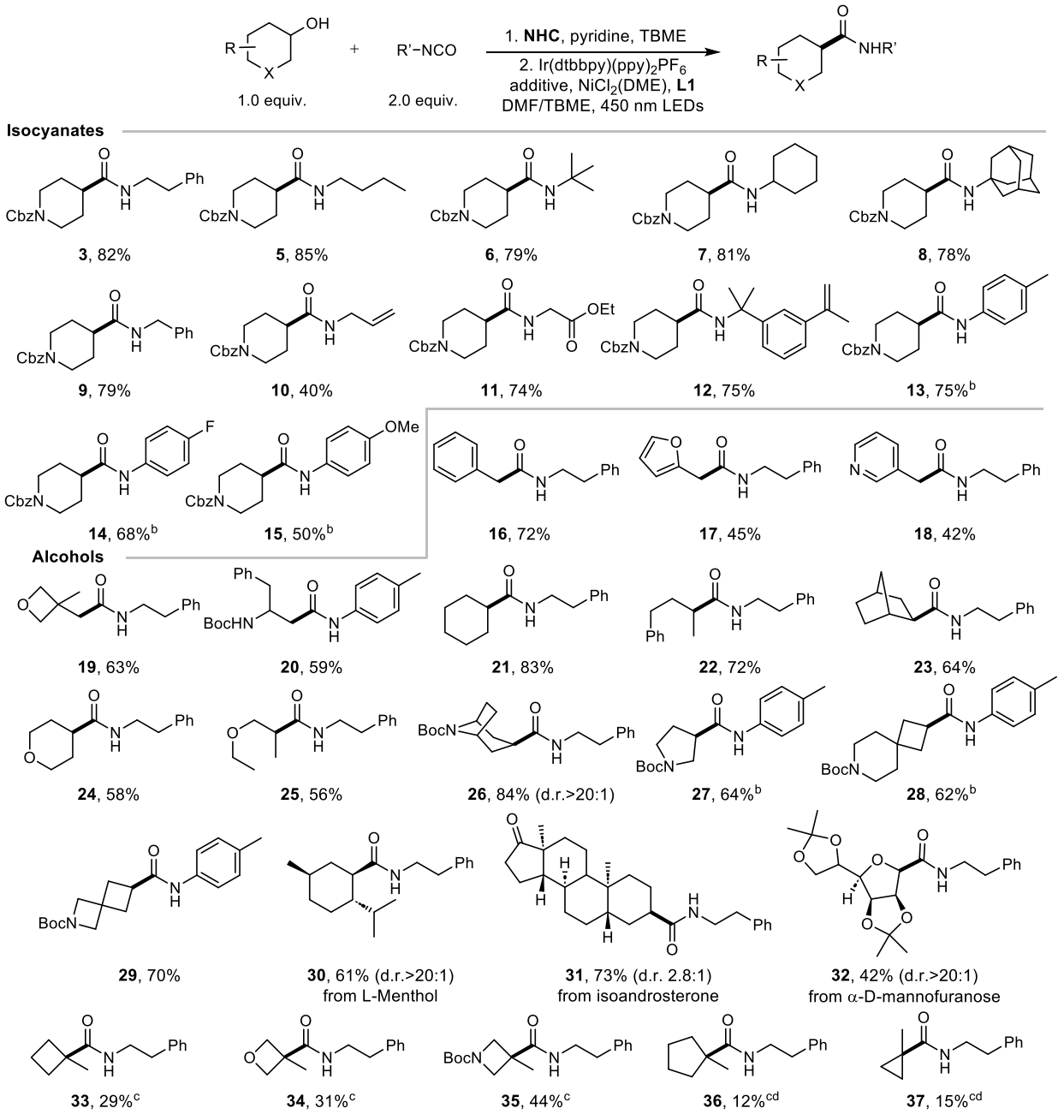
Table 2. Substrate Scope for Amide Synthesis from Alcohols and Isocyanates[abcd]



[a]Reaction conditions: Alcohol (0.5 mmol, 1.0 equiv), **NHC-1** (1.2 equiv), and pyridine (1.1 equiv) in TBME (0.1 M), then isocyanate (2.0 equiv), NaOAc (2.0 equiv), $Ir(dtbbpy)(ppy)_2PF_6$ (1 mol %), $NiCl_2(DME)$ (10 mol %) and Phen (10 mol %) in TBME/DMF (1:1, 0.042 M), 10 W 450 nm LEDs, 25–30 °C, 10 h. Yields reported are isolated yields. [b]$nBu_4NPO_4H_2$ (1.5 equiv) instead of NaOAc. [c]**NHC-3** instead of **NHC-1**. [d]Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. See Supporting Information for full experimental details.

carbonyl source.[43] Despite these advances, radical-mediated deoxygenative carbonylation of alcohols remains largely unexplored, primarily due to two challenges: (i) the high bond dissociation energy of $C(sp^3)$–O bonds in alcohols, and (ii) the scarcity of practical and safe carbonyl precursors. Conventional carbonylation reagents such as toxic CO gas or unstable metal carbonyl complexes pose significant operational hazards.[44−47] While the Newman group has reported nickel-catalyzed couplings of activated phenols with primary alcohols,[48] direct deoxycarbonylative coupling of aliphatic alcohols remains a persistent synthetic challenge.

Alcohols are privileged synthons in organic synthesis owing to their commercial availability, stability, and low toxicity.[49−51] Although inherently nucleophilic, their direct reaction with isocyanates typically yields carbamates rather than enabling radical pathways (Scheme 1c left).[52−54] Effective transformation of alcohols thus requires activation strategies that simultaneously (i) mask the nucleophilicity of the alcohol and (ii) weaken the $C(sp^3)$–O bond to facilitate homolytic cleavage and radical generation. Existing activation methods, such as oxalate/xanthate salts or esters,[55−60] phosphoranyl radicals,[61−63] and low-valent titanium complexes,[64−66] are

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JACS Au 2025, 5, 6179−6188

limited by factors including interference by strong nucleophiles, cumbersome purification, or incompatibility with transition metals. In 2021, the MacMillan group developed a universal *N*-heterocyclic carbene (NHC)-mediated alcohol activation protocol under visible light irradiation,[67] which offers three key advantages: (1) broad compatibility with primary, secondary, and tertiary aliphatic alcohols; (2) operational simplicity involving only stirring and filtration; and (3) excellent compatibility with transition metals such as Ni and Cu. These attributes make NHC activation an ideal platform for our nickel-catalyzed radical coupling strategy.

Given the widespread occurrence of ketones and amides in bioactive molecules and functional materials, a catalytic platform enabling their direct synthesis from alcohols would have transformative potential in drug discovery and materials science. Herein, we report a photoredox/Ni dual-catalyzed divergent synthesis of amides and ketones from isocyanates and alcohols (Scheme 1d). This protocol leverages NHC-mediated alcohol activation to generate alkyl radicals, with isocyanates serving a dual role as either amide precursors or CO surrogates. Crucially, the reaction outcome is governed by the choice of additive: NaOAc promotes deoxygenative amidation to afford amides, whereas nBu$_4$NPO$_4$H$_2$ directs the pathway toward deoxygenative carbonylation, yielding dialkyl ketones.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions

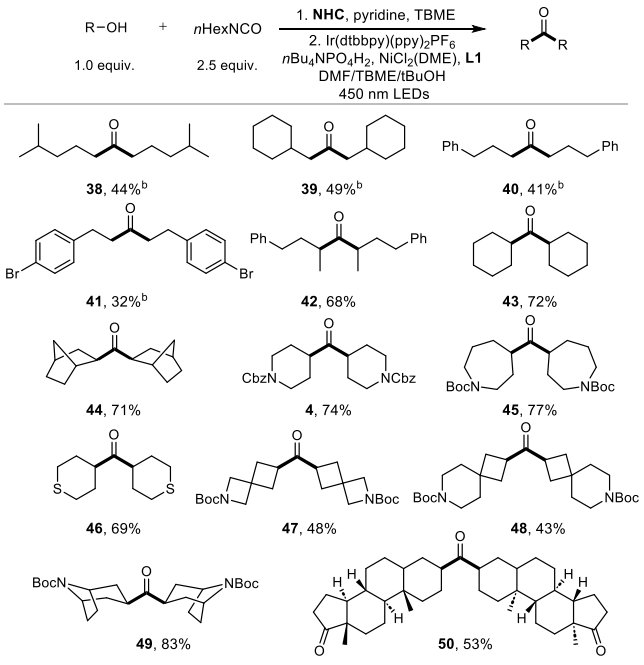
Following comprehensive condition screening (Table 1 and SI Tables S1−S15), the optimal conditions for the deoxygenative amidation were first established. The alcohol activation step involves stirring alcohol **1** (1.0 equiv) with **NHC-1** (1.2 equiv) and pyridine (1.1 equiv) in TBME to generate the corresponding **NHC**−alcohol adduct. This adduct was then reacted with a mixture containing isocyanate **2** (2.0 equiv), NaOAc (2.0 equiv), NiCl$_2$(DME) (10 mol %), phenanthroline (10 mol %), and Ir(dtbbpy)(ppy)$_2$PF$_6$ (1 mol %) in DMF under 450 nm irradiation for 10 h, affording amide **3** in 82% isolated yield (Entry 1). Ligand screening revealed that bipyridine derivatives **L2**−**L4** provided only moderate yields (Entries 2−4). **NHC** ligands bearing *ortho*-methoxy or *para*-trifluoromethyl substituents significantly diminished the yield (Entries 5 and 6). Replacing the photocatalyst with 4CzIPN resulted in a slight decrease in efficiency (Entry 7), whereas Ru(bpy)$_3$PF$_6$ was inactive under these conditions (Entry 8). Control experiments confirmed that Ni catalysis, light irradiation, and photocatalyst are all essential for the transformation (Entry 9). Interestingly, substituting NaOAc with KH$_2$PO$_4$ led to the formation of 5% ketone **4** (Entry 10). Employing nBu$_4$NPO$_4$H$_2$ as the additive significantly enhanced ketone formation (Entry 11). Further optimization using *n*-hexyl isocyanate improved the ketone yield (Entry 12), and increasing the phenanthroline loading to 20 mol % afforded ketone **4** in 74% yield (Entry 13).

Substrate Scope for Amide Synthesis

With the optimized conditions in hand, we next explored the substrate scope for the deoxygenative amidation of alcohols (Table 2). The reaction exhibited broad tolerance toward isocyanates bearing primary, secondary, and even sterically hindered tertiary alkyl substituents, delivering the corresponding amides (**3**−**8**) in uniformly high yields ranging from 72% to 89%, indicating minimal steric sensitivity. Benzyl isocyanates also proved to be excellent coupling partners, affording amide **9** in 85% yield, while allyl-substituted isocyanates provided moderate efficiency (**10**, 53%). Isocyanates containing styrenyl groups and electron-deficient ester functionalities coupled efficiently as well (**11**, **12**), highlighting the broad functional group compatibility of the method. Notably, aryl-substituted isocyanates exhibited high reactivity and were found to react directly with NaOAc, prompting the use of nBu$_4$NPO$_4$H$_2$ as the additive in these cases. Under these conditions, *para*-methyl and *para*-fluoro substituted aryl isocyanates afforded superior yields (**13**, **14**), whereas electron-donating para-methoxy substitution led to diminished reactivity, resulting in a moderate yield of 50% for amide **15**.

We then examined the scope of alcohols for the deoxygenative amidation. Benzyl alcohol displayed excellent reactivity, affording amide **16** in 72% yield. Primary alcohols bearing heterocyclic motifs such as furan and pyridine delivered moderate yields (**17**, **18**). Substrates containing sensitive functional groups, including oxetane (**19**) and N-Boc amine (**20**), were also compatible, providing the corresponding products in fair yields. Secondary alcohols featuring cyclohexyl and 4-phenyl-2-butyl substituents furnished amides **21** and **22** in good yields. Notably, secondary alcohols with bridged ring systems coupled efficiently with isocyanates to afford products **23** (64% yield) and **26** (84% yield, mixture of rotamers)[68,69] with excellent diastereoselectivity (>20:1 dr). Alcohols containing ether (**24**, **25**) and cyclic carbamate (**26**, **27**) functionalities were also viable substrates. Spirocyclic quaternary centers as privileged motifs in drug discovery,[70] were efficiently amidated to give **28** and **29**. Furthermore, several

Table 3. Nickel-Catalyzed Carbonylative Homocoupling of Alcohols[ab]



[a]Reaction conditions: Alcohol (1.0 mmol, 1.0 equiv), **NHC-1** (1.2 equiv), and pyridine (1.1 equiv) in TBME (0.1 M), then *n*Hex-NCO (2.5 equiv), nBu$_4$NPO$_4$H$_2$ (1.5 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (1 mol %), NiCl$_2$(DME) (10 mol %) and Phen (20 mol %) in MTBE/DMF/*t*BuOH (5:5:2, 0.042 M), 10 W 450 nm LEDs, 25−30 °C, 10 h. [b]**NHC-2** instead of **NHC-1**.

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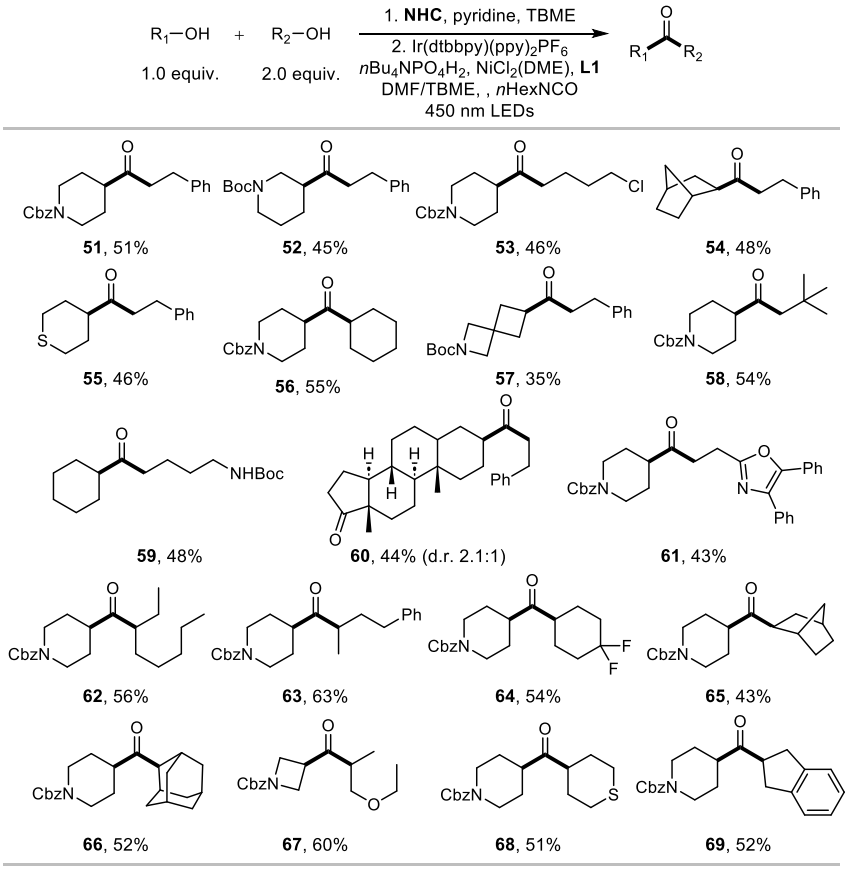
Table 4. Nickel-Catalyzed Carbonylative Cross-Coupling of Alcohols[a]



[a]Reaction conditions: R_1OH (0.3 mmol, 1.0 equiv), R_2OH (0.6 mmol, 2.0 equiv), **NHC-1** (3.6 equiv), and pyridine (3.3 equiv) in TBME (0.033 M), then *n*Hex-NCO (7.5 equiv), $nBu_4NPO_4H_2$ (4.5 equiv), $Ir(dtbbpy)(ppy)_2PF_6$ (5 mol %), $NiCl_2(DME)$ (20 mol %) and Phen (40 mol %) in MTBE/DMF/*t*BuOH (3:3:1, 0.015 M), 10 W 450 nm LEDs, 25−30 °C, 10 h.

natural products and their derivatives, including L-menthol (**30**), androsterone (**31**), and α-D-mannofuranose (**32**), underwent smooth transformation under the standard conditions. Remarkably, sterically hindered tertiary alcohols, which are typically challenging substrates for radical amidation,[30] exhibited divergent reactivity: tertiary cyclobutanol and its oxygen- and nitrogen-containing analogues (**33**−**35**) afforded moderate yields (29%−44%), outperforming the corresponding cyclopropanol (**37**) and cyclopentanol (**36**) analogues.

Carbonylative Homocoupling of Alcohols

Using $nBu_4NPO_4H_2$ as the additive,[71] we explored the substrate scope for the nickel-catalyzed deoxycarbonylative homocoupling of alcohols (Table 3). Primary alcohols bearing linear and cyclic alkyl substituents afforded the corresponding ketones in moderate yields (**38**, **39**). A substrate containing a *para*-bromophenylethyl group (**41**) exhibited reduced efficiency (34% yield) compared to the phenylpropyl analogue (**40**, 41% yield). In contrast, secondary alcohols demonstrated enhanced reactivity: both linear aliphatic and cycloalkyl substrates furnished ketones (**42**−**44**) in synthetically useful yields. The method also exhibited good heteroatom tolerance, as evidenced by efficient coupling of nitrogen- and sulfur-containing secondary alcohols (**4**, **45**, **46**, 69%−77% yield). Importantly, special cyclic systems including spirocyclic (**47**, **48**), bicyclic bridged (**49**), and fused ring substrates (**50**) underwent efficient transformation. Although tertiary and benzylic alcohols do not provide the desired products under our conditions, this protocol remains particularly valuable. Classical approaches to symmetrical dialkyl ketones often face inherent limitations, such as substrate accessibility and the need for preactivation of starting materials. Notably, the selectivity for ketone formation over amidation is solely determined by the reaction conditions using alkyl isocyanates and $nBu_4NPO_4H_2$ (See Table S10). We have tested the alcohol precursors for ketone formation under amidation conditions, and the corresponding amides can be successfully obtained.

Carbonylative Cross-Coupling of Alcohols

Beyond homocoupling, this platform enables the synthesis of unsymmetric dialkyl ketones via cross-coupling of different alcohols (Table 4). It should be noted that stoichiometric imbalance can lead to the formation of symmetrical ketone byproducts (see Tables S14 and S15). Secondary alcohols containing cyclic carbamates (**51**−**53**), cyclic alkyl group (**54**), sulfur atom (**55**), and spirocyclic motif (**57**) were employed as the excess coupling partners with primary alcohols. Except for the relatively low yield of product **57**, cross-couplings involving other primary alcohols (**53**, **58**, **59**) proceeded with moderate yields. Notably, bioactive molecules such as androsterone (**60**) and oxaprozin (**61**) also served as viable substrates, affording the desired ketones in 44% and 43% yields, respectively. Cross-coupling between distinct secondary alcohols delivered moderate to good yields (43%−63%), demonstrating broad functional group compatibility. Compatible substituents

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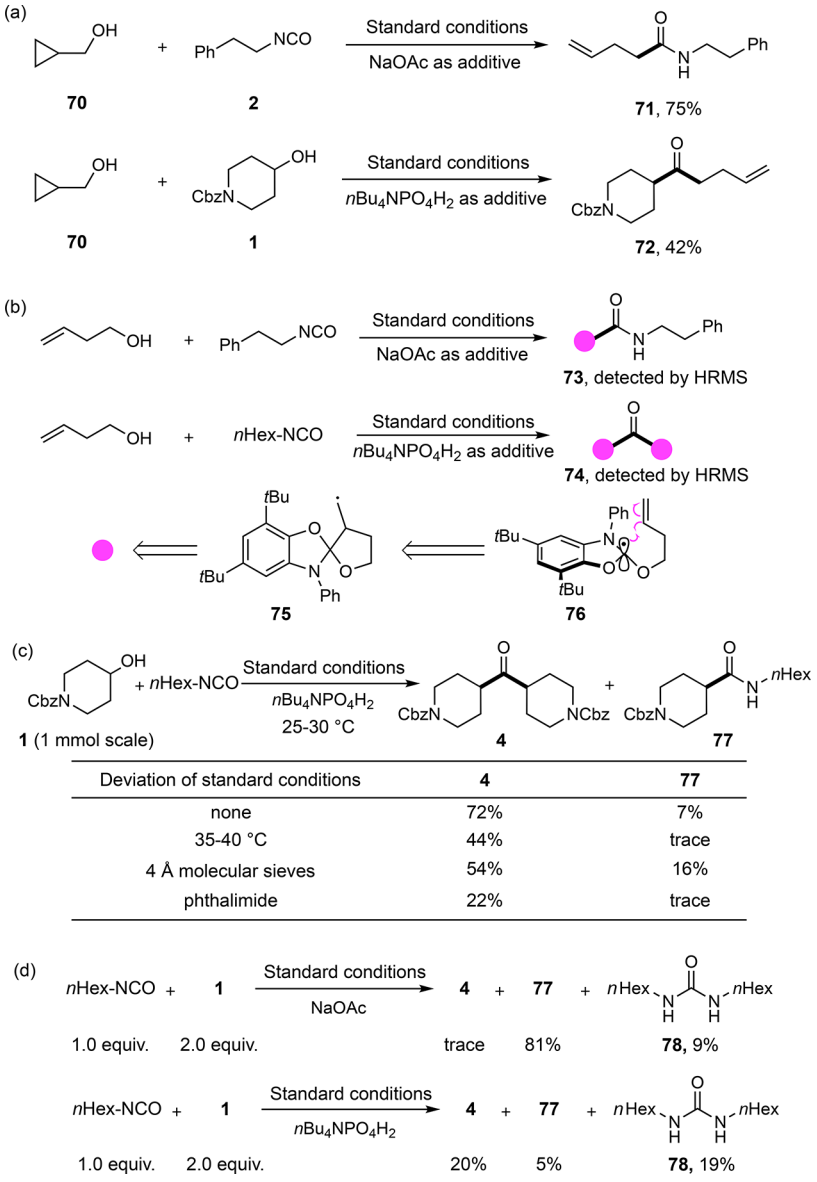
JACS Au 2025, 5, 6179−6188

Scheme 2. Mechanistic Studies and Experimental Evidence



Deviation of standard conditions	4	77
none	72%	7%
35-40 °C	44%	trace
4 Å molecular sieves	54%	16%
phthalimide	22%	trace

included linear and branched alkyl groups (**56**, **62**, **63**), fluoroalkyl (**64**), norbornane (**65**), adamantane (**66**), ether (**67**), thioether (**68**), and 2-indenyl (**69**).

Mechanistic Studies

Despite the divergent outcomes governed by additive selection, we propose that alkyl radicals serve as key intermediates in both the amidation and ketone formation pathways. Radical clock experiments using cyclopropylmethanol (**70**) demonstrated ring-opening in both cases, affording amide **71** and ketone **72** featuring terminal olefins (Scheme 2a). When a homogeneous alcohol substrate was employed, the expected coupling products were not observed (Scheme 2b). Instead, HRMS analysis detected cyclized products **73** and **74**, consistent with the formation of radical intermediate **75**. This evidence supports a mechanism wherein the alcohol–**NHC** adduct undergoes a photoredox-induced single-electron oxidation and proton loss to generate a carbon-centered radical **76**. Rather than undergoing β-scission, the carbon radical in **76** attacks the terminal alkene intramolecularly via a 5-exo-trig radical cyclization to form **75**.

In line with established carbonylation mechanisms for alkyl halides,[41,42] a Ni^0 (CO) species is proposed as a key intermediate in the ketone formation pathway. Although we attempted to trap the CO intermediate, these efforts were unsuccessful. To further substantiate this hypothesis, we performed several alternative mechanistic experiments exploiting the lability of Ni^0 (CO) complexes. First, reducing the reaction scale led to diminished ketone yields (see Table S11), likely due to increased CO loss to the gas phase in smaller reactors of identical volume. Additionally, elevated reaction temperatures, the addition of 4 Å molecular sieves, or the introduction of phthalimide each resulted in decreased yields of ketone **4** (Scheme 2c). Higher temperatures promote CO dissociation from Ni^0 (CO) species, thereby lowering the effective CO concentration in solution. It is known that 4 Å molecular sieves act as CO scavengers,[72] while phthalimide serves as a ligand that coordinates to the Ni catalyst, facilitating CO dissociation and preventing its recoordination. This coordination inhibits the migratory insertion of alkyl radicals

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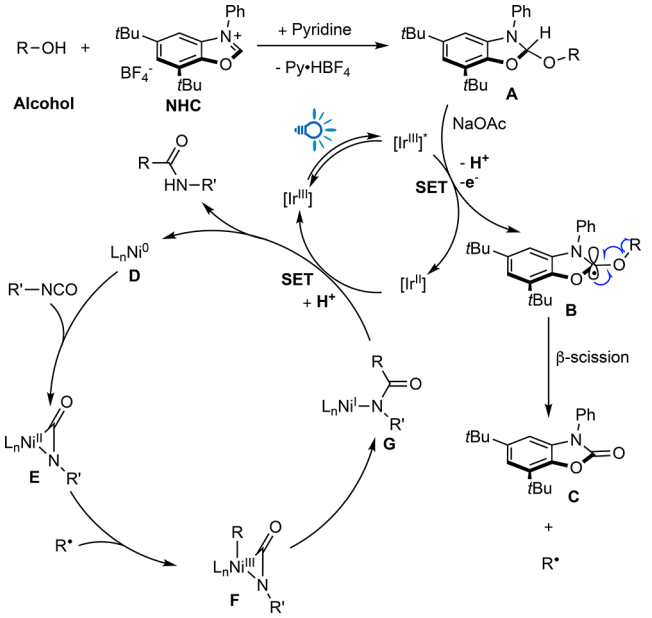
Scheme 3. Plausible Mechanism for Nickel/photoredox-Catalyzed Deoxygenative Amidation of Alcohols



into Ni–CO intermediates, thereby suppressing formation of the acyl–Ni species essential for ketone synthesis.[73]

Notably, both the deoxygenative amidation and carbonylative coupling pathways of alcohols generate urea byproduct **78** (Scheme 2d). This byproduct likely arises from the nucleophilic attack of alkyl amines on isocyanates. A control experiment in which nBu$_4$NPO$_4$H$_2$ was stirred with isocyanate alone furnished only trace amounts of **78**, indicating that moisture from nBu$_4$NPO$_4$H$_2$ does not contribute to the formation of **78**. Mechanistic investigations by the Molander[31] and Nevado[33] groups have demonstrated that isocyanates undergo oxidative addition to LnNi^0 species, forming a Ni(II)-isocyanate intermediate **E** (Scheme 4). The observation that the use of nBu$_4$NPO$_4$H$_2$ as the additive leads to increased formation of urea **78** suggests that the relatively acidic conditions facilitate C–N bond cleavage of intermediate **E**, thereby promoting alkyl amine generation and concomitant CO release.

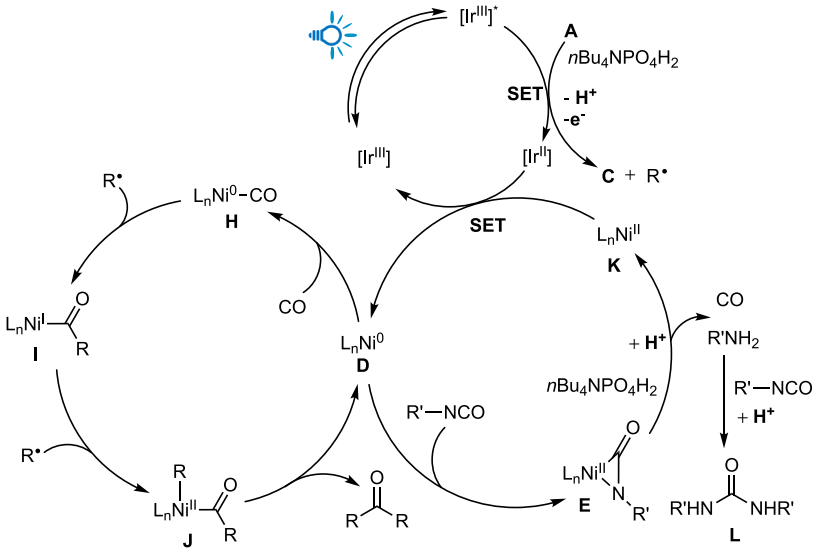
Although a more detailed mechanistic investigation is warranted in future studies, based on the above experimental results and literature precedents, we propose a plausible reaction mechanism (Schemes 3 and 4). The amidation process of alcohols begins with pyridine-facilitated formation of the alcohol–NHC adduct **A**. This adduct undergoes single-electron oxidation by the photoexcited [Ir^{3+}]* species, generating intermediate **B**, which then undergoes β-scission to produce an alkyl radical and byproduct **C**. Concurrently, the Ni^0 species undergoes oxidative addition with the isocyanate to form the Ni(II)–isocyanate intermediate **E**. In the deoxygenative amidation pathway (Scheme 3), NaOAc primarily acts as a base to promote the single-electron transfer (SET) process from **A** to **B**, which is also compatible with intermediate **E**. The amide-Ni complex **G** is then formed via the attack of alkyl radicals on intermediate **E** to generate Ni(III) species **F**, followed by reductive elimination. Subsequent single-electron reduction by [Ir^{2+}] and protonation releases the amide product.

In the deoxygenative carbonation pathway (Scheme 4), we believe nBu$_4$NPO$_4$H$_2$ serves a dual role. It first serves as a base, assisting the [Ir^{3+}]* species in oxidizing intermediate **A**, as we demonstrated previously. Additionally, unlike NaOAc, nBu$_4$NPO$_4$H$_2$ may not be compatible with intermediate **E**, instead, it likely promote the decomposition of intermediate **E** as a proton source, releasing CO, alkylamines, and the Ni(II) species **K**. The liberated alkyl amine then nucleophilically attacks isocyanate to form urea **L**. Ni(II) species **K** is reduced by [Ir^{2+}] to regenerate Ni(0) species **D**, which coordinates CO to form the Ni^0 (CO) complex **H**. Two sequential migratory insertions of alkyl radicals into **H** generate intermediates **I** and **J**, with the latter undergoing reductive elimination to furnish the ketone product.

CONCLUSIONS

In summary, we have demonstrated that alcohols and isocyanates can undergo additive-controlled, nickel/photoredox dual-catalyzed deoxygenative amidation or carbonylative coupling, providing a divergent strategy to access amides and

Scheme 4. Plausible Mechanism for Nickel/Photoredox-Catalyzed Deoxygenative Coupling of Alcohols



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dialkyl ketones. This approach offers a valuable alternative to traditional methods reliant on carboxylic acid derivatives. By utilizing widely abundant alcohol feedstocks, our protocol significantly expands the synthetic toolbox for constructing these important carbonyl-containing motifs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.5c01148.

Additional experimental details, methods, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Pin Xu** conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing - original draft; **Cong Ma** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, visualization, writing - review & editing.

Notes

The authors declare no competing financial interest.

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