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Article

Amidative β-Scission of Alcohols Enabled by Dual Catalysis of Photoredox Proton-Coupled Electron Transfer and Inner-Sphere Ni-Nitrenoid Transfer

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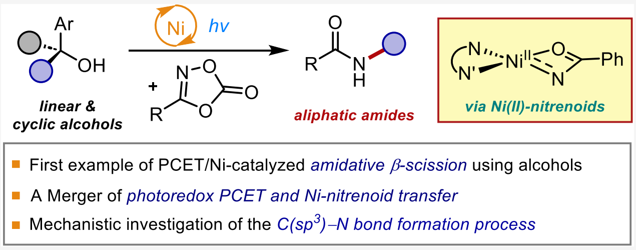

- First example of PCET/Ni-catalyzed *amidative β-scission* using alcohols
- A Merger of *photoredox PCET and Ni-nitrenoid transfer*
- Mechanistic investigation of the *C(sp^3)–N bond formation process*

ABSTRACT: The photoredox/Ni dual catalysis is an appealing strategy to enable unconventional C−heteroatom bond formation. While significant advances have been achieved using this system, intermolecular C(sp^3)−N bond formation has been relatively underdeveloped due to the difficulty in C(sp^3)−N reductive elimination. Herein, we present a new mechanistic approach that utilizes dioxazolones as the Ni(II)-nitrenoid precursor to capture carbon-centered radicals by merging proton-coupled electron transfer (PCET) with nickel catalysis, thus forming synthetically versatile *N*-alkyl amides using alcohols. Based on mechanistic investigations, the involvement of (κ^2-*N*,*O*)Ni(II)-nitrenoid species was proposed to capture photoredox PCET-induced alkyl radicals, thereby playing a pivotal role to enable the C(sp^3)−N bond formation.

INTRODUCTION

The photoredox/Ni dual catalysis has witnessed significant achievements in recent years, leading to noteworthy accomplishments to enable various unconventional transformations, particularly in facilitating the formation of C−heteroatom bonds.[1−6] As pioneered independently by MacMillan, Molander, Doyle, and their co-workers, these systems are distinguished by their ability to harness the reactivity of nickel catalysts, which play a dual role to initiate and also propagate radical reactions, ultimately generating nickel(III) intermediates.[2,7−20] These transient species exhibit a remarkable capability to undergo C−heteroatom bond formation via reductive elimination under mild reaction conditions. Aliphatic amides, including amino carbonyl compounds, are prevalent structural motifs in various bioactive molecules, pharmaceuticals, and natural products.[21−24] Despite the utmost relevance of alkyl amides, visible-light-induced intermolecular C(sp^3)−N bond formation is less commonly practiced[25−28] by using transition-metal catalysis. This is largely due to the facile β-hydride elimination of metal alkyl intermediates, thereby leading to the generation of a highly reactive metal-hydride species that can engage in various off-cycle pathways.[8,29]

Since the dual photoredox/Ni-catalysis has been widely explored, there are two main strategies for generating key alkyl-Ni(III)-N complexes to facilitate the formation of the C(sp^3)−N bond. The first approach involves an oxidative addition of Ni(I)-alkyl species to amine electrophiles to form the key alkyl-Ni(III)-N complex. This process exploits hydrogen atom transfer (HAT) to generate alkyl radicals from simple alkanes (Scheme 1a).[30] The second strategy utilizes alkyl radicals generated via single electron transfer (SET) from alkyltrifluoroborates.[31] These radicals subsequently undergo radical coupling with the Ni(II)-amido complex, thus resulting in the formation of a key alkyl-Ni(III)-N intermediate. To date, despite the notable advancements achieved in the field of dual photoredox/Ni-catalyzed C(sp^3)−amidation, a strategy of radical addition from a Ni(II)-nitrenoid has not been reported, to our best knowledge. While previous research has yielded elegant contributions to the C−N bond formation via nickel-nitrene intermediates using bulky ligand systems,[8,32−36] we wondered whether we could utilize 1,4,2-dioxazol-5-ones as precursors of Ni(II)-nitrenoid to capture photoredox-generated alkyl radicals, thus enabling intermolecular amidation with a simple ligand system (Scheme 1b).

Dioxazolones were previously developed as a powerful amino source in the C−H amidation via metal-nitrenoid intermediacy[37−41] or under photochemical conditions.[30,42−46] Also, our group recently validated the intermediacy of Rh(III)-acylnitrene within a bidentate ligand system using dioxazolone under photochemical conditions.[47] Drawing inspiration from recent works using β-scission of alkoxy radicals to activate C−C bonds and reconstruct organic motifs,[25,48−69] we conceived an idea of applying our proposed Ni(II)-nitrenoid system to

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Scheme 1. Regiospecific C(sp^3)−N Bond Formations Using Photoredox Catalysis via Ni-Nitrenoid

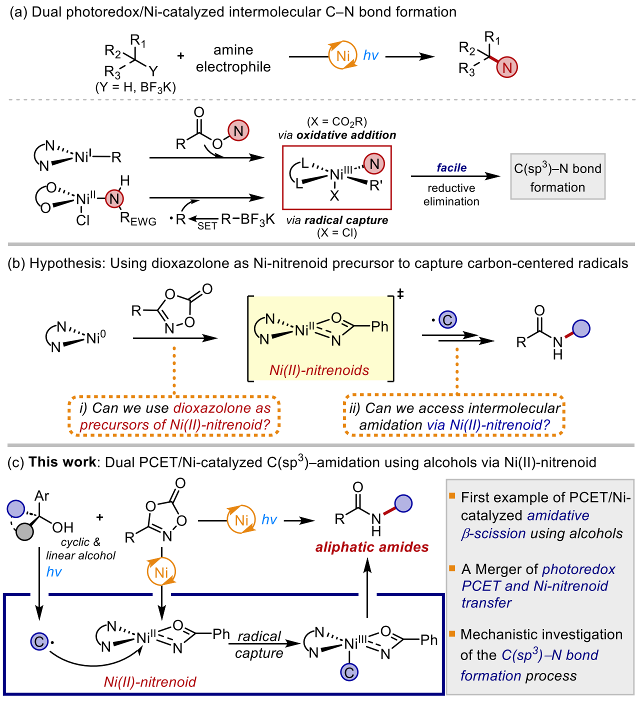
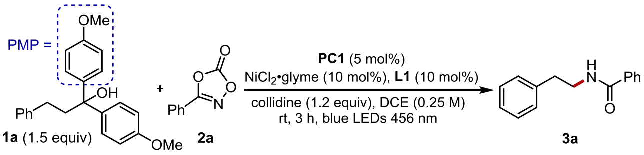
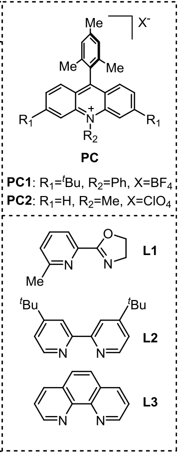


Table 1. Optimization of Reaction Parameters[a]



entry	deviation from the standard conditions	3a (%)
1	none	95 (89^b)
2	**PC2** instead of PC1	48
3	**L2** instead of **L1**	15
4	**L3** instead of **L1**	<5
5	DCE (0.1 M) instead of DCE (0.25 M)	27
6	w/o **PC1**	<5
7	w/o $NiCl_2$•glyme	<5
8	w/o **L1**	44
9	w/o collidine	<5
10	w/o blue LEDs irradiaction	<5



[a]Reaction conditions: 0.1 mmol scale in a 4 mL glass vial and yields were based on ^{1}H NMR analysis of the reaction mixture using an internal standard (dibromomethane). **PC1**, *di-*^{t}Bu-Mes-Acr$^+$ BF_4^-; **PC2**, Mes-Acr$^+$ ClO_4^-; glyme, ethylene glycol dimethyl ether; collidine, 2,4,6-collidine; DCE, 1,2-dichloroethane. [b]Isolated yield.

capture carbon-centered radicals driven by photoredox catalysis. Specifically, we hypothesized that the carbon-centered radical, once captured by the Ni(II)-nitrenoid, would lead to the formation of an electrophilic alkyl-Ni(III)-nitrenoid. This would make an opportunity to facilitate reductive elimination to form C(sp^3)−N bonds, thereby significantly expanding the reactivity compared to the traditional radical-coupling process.

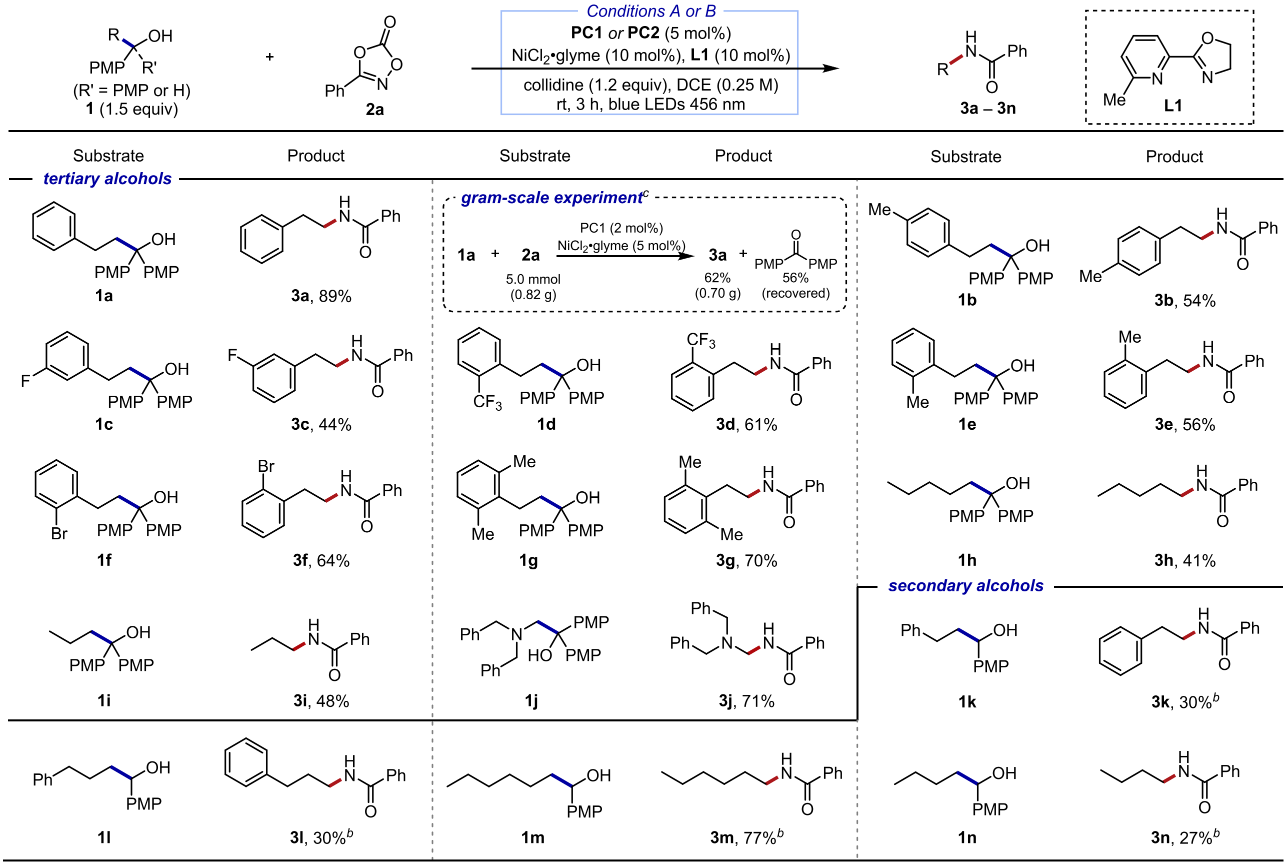
Continuing our efforts to utilize the *N*-centered reactive intermediates to develop novel nitrogen atom transfer reactions,[70−72] we envisioned utilizing photoredox proton-coupled electron transfer (PCET) to generate carbon-centered radicals within the inner-sphere nitrenoid transfer scaffold using nickel catalysts to outcompete the *β*-hydride elimination. Reported herein is the first example of using dioxazolones as a Ni(II)-nitrenoid precursor to synthesize aliphatic amides via dual photoredox PCET/Ni-catalysis (Scheme 1c). This strategy enables the C(sp^3)−amidation that is applicable to both cyclic or acyclic alcohols, providing an access to synthetically valuable aliphatic amides.[21−24] Integrated experimental and computational studies revealed that our hypothesized (κ^2-*N*,*O*)Ni(II)-nitrenoid effectively traps carbon-centered radicals, which in turn undergo inner-sphere nitrenoid transfer to form regiospecific C−N bonds.

RESULTS AND DISCUSSION

Reaction Development. Recognizing the potential amidation reactivity with cycloalkanols,[25,48,61,64] we first examined the proposed amidation by using 1,1-bis(4-methoxyphenyl)-3-phenylpropan-1-ol (**1a**, 1.5 equiv) as a model substrate (Table 1). Pleasingly, after extensive screenings of various reaction parameters, we successfully obtained the desired amidated *β*-scission product, *N*-phenethylbenzamide (**3a**), in 89% yield under newly optimized conditions, with the extrusion of a ketone byproduct (entry 1). Contrary to the standard conditions, the combination of $NiCl_2$·glyme with **PC2** instead of **PC1** afforded a lower yield (entry 2). The use of other types of *N*,*N*-bidentate ligands (**L2** or **L3**) was less effective (entries 3 and 4). When the reaction was carried out at a lower concentration, a decreased product yield was obtained (entry 5). Control experiments indicated that there was no conversion in the absence of a photocatalyst, nickel catalyst, 2,4,6-collidine, or visible-light irradiation (entries 6, 7, 9, and 10, respectively). In contrast, a moderate yield (44%) of the desired product was observed without the ligand **L1** (entry 8).

Reaction Scope. With the optimized dual photoredox PCET/Ni-catalysis conditions in hand, we subsequently investigated the generality of the current redox-neutral amidative *β*-scission of alcohols by exploring first a range of linear substrates (Scheme 2). Reaction of tertiary alcohols bearing *β*-phenyl moiety (**1a**−**1g**) provided the corresponding amides (**3a**−**3g**) in moderate to good yields. It should be noted that it represents the first catalytic C−C bond cleavage accompanying with amidation of tertiary linear alcohols. Substrates having only alkyl moieties (**1h**−**1i**) were also viable to furnish the aliphatic amides (**3h**−**3i**). A tertiary linear alcohol bearing a dibenzylamino group (**1j**) was competent toward the current amidation reaction conditions. In addition to tertiary alcohols, secondary counterparts (**1k**−**1n**) also proved to be reactive for this amidative *β*-scission, with the emission of 4-anisaldehyde. With the proven reactivity, the practicality of this C(sp^3)−amidation was also tested by a gram-scale reaction of linear alcohol **1a**, resulting in the formation of the desired product **3a** in 62% yield using only 2 mol % **PC1**, 5 mol % $NiCl_2$·glyme, and 5 mol % **L1** under blue LED irradiation (1.5 h) with recovery of bis(4-methoxyphenyl)methanone (56%), which could be directly reused to prepare the starting material **1a**.

Scheme 2. Synthesis of Aliphatic Amides Using Linear Secondary or Tertiary Alcohols[a]



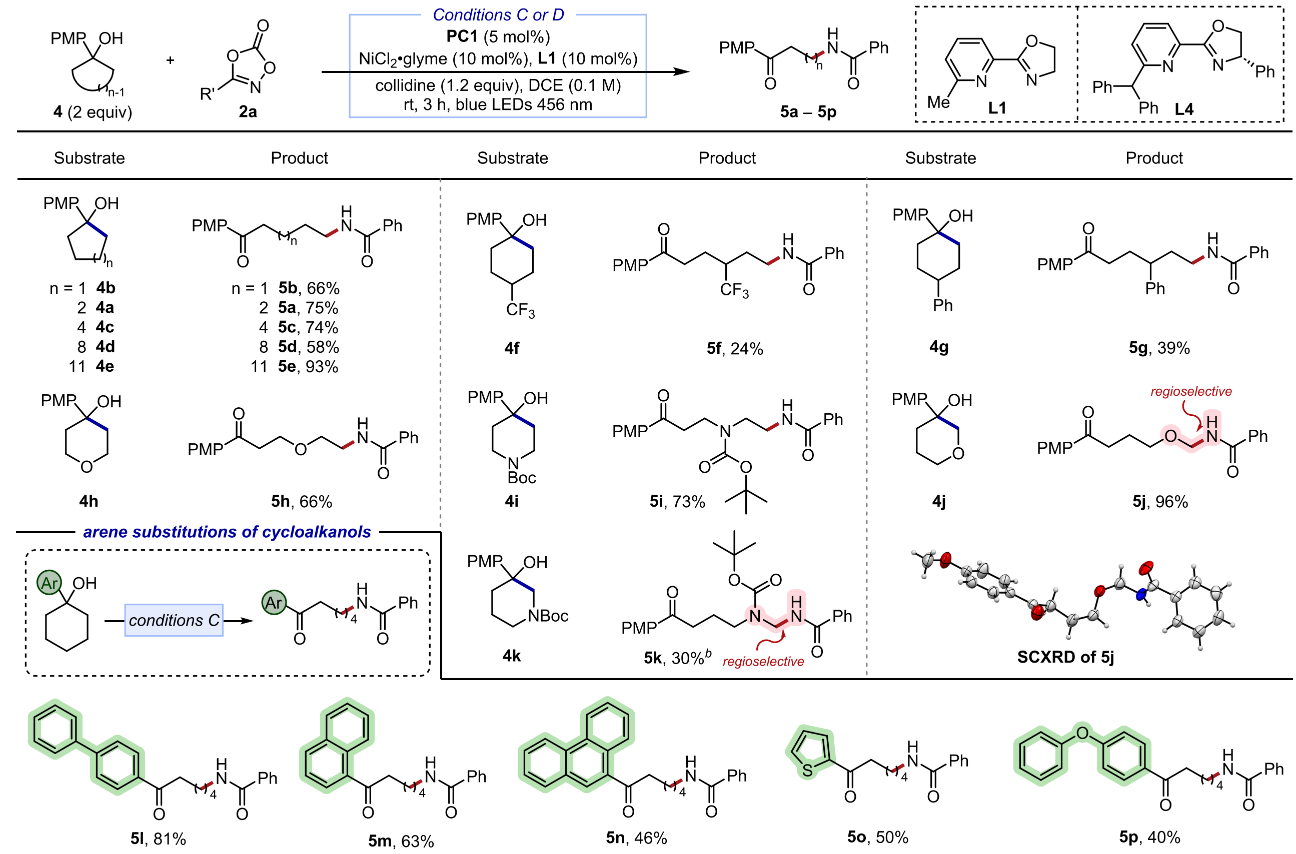
[a] Conditions A: **1** (0.15 mmol), **2a** (0.1 mmol), **PC1** (5 mol %), $NiCl_2$·glyme (10 mol %), **L1** (10 mol %), and 2,4,6-collidine (1.2 equiv) in 1,2-dichloroethane (0.4 mL) at room temperature for 3 h under 456 nm blue light irradiation. [b] Conditions B: **PC2** (5 mol %) instead of **PC1**. [c] Gram-scale reaction with **PC1** (2 mol %), $NiCl_2$·glyme (5 mol %), and **L1** (5 mol %) under 456 nm for 1.5 h under 456 nm blue light irradiation.

In addition to the $C(sp^3)$−amidation of linear alcohols, we were curious about the feasibility of using easily accessible cycloalkanols as carbon-centered radical sources in our designed Ni(II)-nitrenoid system to furnish newly installed amides equipped with a remote ketone moiety via the presupposed amidative ring-opening (Scheme 3). Tertiary cycloalkanols with various ring sizes were all viable in this C−C bond cleavage-initiated remote amidation (**5a**−**5e**). Reaction efficiency was not significantly influenced by the ring size as evidenced by the facile amidation of 5-, 6-, 8-, 12-, and 15-membered substrates under otherwise identical conditions. However, the reaction of substituted cyclohexanol derivatives was rather sluggish (**5f** and **5g**). Substrates containing heteroatoms such as oxygen or nitrogen inside the ring were facile for these ring-opening amidation reactions (**5h**−**5k**). Notably, with *unsymmetrical* substrates having a heteroatom in the ring (**4j** and **4k**), the bond scission was observed to take place exclusively at the *α*-position to the oxygen or nitrogen atom (**5j** and **5k**). This regioselectivity is attributed to the difference in the relative stability of the postulated radical intermediate,[73] generated upon the *β*-scission of the C−C bond. The structure of the obtained product **5j** was confirmed by X-ray crystallographic analysis. In the case of **4k**, 60% of benzamide was formed as a major side product, which lowered the formation of the desired product **5k**. We subsequently examined the flexibility of the aryl moiety in cyclohexanol substrates to find that biphenyl, naphthyl, phenanthrenyl, thienyl, and 4-phenoxyphenyl groups were all compatible to furnish the desired amide products in moderate to good yields (**5l**−**5p**).

In addition, the feasibility of other amidating sources was also briefly tested (Scheme 4). It should be mentioned that alcohol substrates and dioxazolones are all easily accessible from the corresponding ketones (aldehydes) and carboxylic acids, respectively. Dioxazolone derivatives bearing not only aryl substituents but also alkyl variants such as methyl or cyclohexyl all participated in the current amidative ring-opening reaction with cyclopentanol substrate **4b** to afford the corresponding products (**5q**−**5s**). In addition, we briefly explored the synthetic utility of newly developed $C(sp^3)$−amidation. The current procedure was proved to be applicable for dioxazolone derived from oxaprozin (**5t**), an FDA-approved nonsteroidal anti-inflammatory drug. Also, dioxazolones prepared from lithocholic acid and isonipecotic acid were viable to furnish the remote amino-ketones bearing a biorelevant motif. Moreover, carbonyl or sulfonyl azides[74] served as effective amidating precursors for this ring-opening process (**5w**−**5y**), which suggests that not only dioxazolone but also other acyl nitrene precursors can afford the postulated Ni(II)-nitrenoid intermediates.

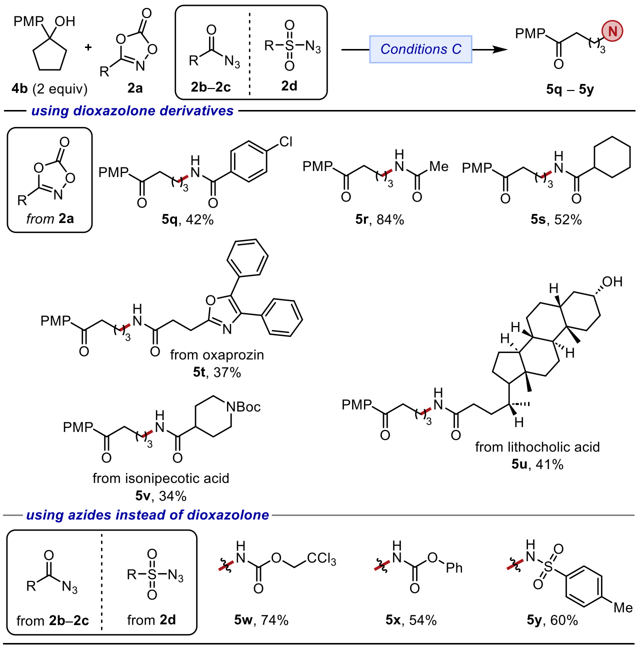
Mechanistic Investigation on Intermolecular $C(sp^3)$−Amidation. To elucidate the mechanism of the current amidation reaction, we tried to address three fundamental questions: (a) do Ni(0) or Ni(I) species act as an active

Scheme 3. Synthesis of Remote Amino-Ketones Using Tertiary Cycloalkanols[a]



[a]Conditions C: **4** (0.2 mmol), **2a** (0.1 mmol), **PC1** (5 mol %), $NiCl_2$·glyme (10 mol %), **L1** (10 mol %), and 2,4,6-collidine (1.2 equiv) in 1,2-dichloroethane (1.0 mL) at room temperature for 3 h under 456 nm blue light irradiation. [b]Conditions D: **L4** (10 mol %) instead of **L1** (10 mol %).

Scheme 4. Investigation of Amidation Sources



catalyst; (b) does the photoredox PCET process generate a carbon-centered radical; and (c) can the hypothesized Ni(II)-acylnitrenoid generated *in situ* from dioxazolone undergo the C(sp^3)–N bond formation? In light of these queries, we initially proposed three plausible catalytic pathways based on the precedent literature (Figure 1a-1).[7,12,19,61,75–77] To first see whether Ni(0) species is involved within the catalytic cycle, we performed control experiments using different Ni sources (Figure 1a-2).[77] When $Ni(cod)_2$ was used along with **L1**, notable conversion of **1a** toward the desired amidation product **3a** was observed. However, in the absence of the ancillary ligand **L1**, the system became unreactive, suggesting that ligated (**L1**)Ni(0) would likely be involved in the catalytic manifold of either path 1 or 2.[78]

Our proposed photoredox PCET cycle is depicted in Figure 1b-1. Upon visible-light irradiation, an aryl moiety in substrates undergoes oxidation by the excited state of **PC** to form a transient arene radical cation (**1a**$^{\bullet+}$). An intramolecular PCET process may follow to provide an alkoxy radical intermediate (**1a**$^{\bullet}$), which is subsequently transformed into a reactive carbon-centered radical **1a′** via the critical *β*-scission. The Stern–Volmer analysis revealed that the excited state of **PC** was efficiently quenched by alcohol **4a** in CH_2Cl_2, irrelevant to the existence of collidine. To validate the proposed PCET, a series of mechanistic experiments were conducted (Figure 1b-2; see the Supporting Information for details). A hydroxy-protected ether (**1o**) did not undergo amidative *β*-scission under standard conditions A. When a reaction of **4a** was performed in the presence of TEMPO (2,2,6,6-tetramethyl-1-

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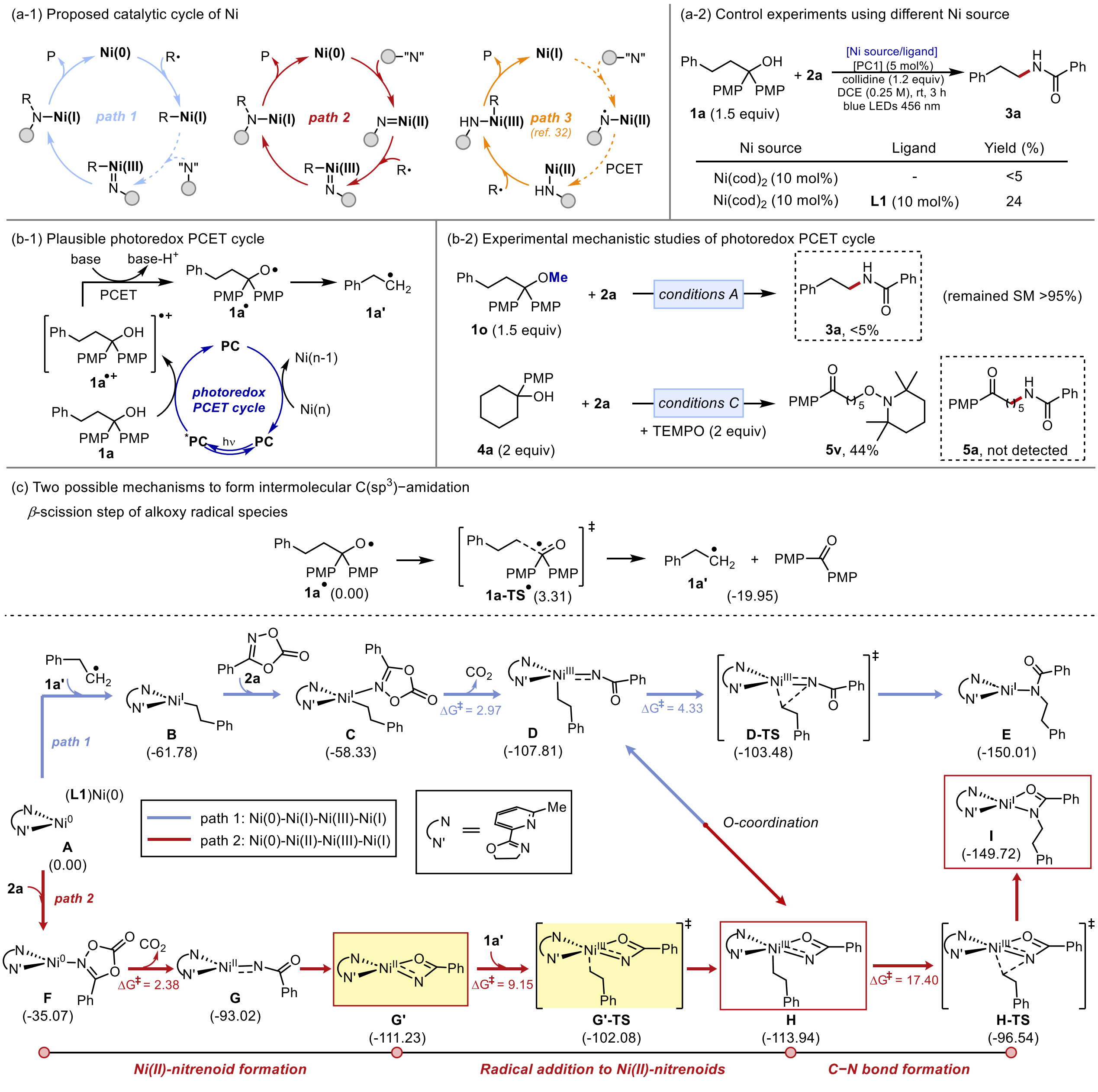

Figure 1. Mechanistic studies of dual photoredox PCET/Ni-catalyzed amidative β-scission of alcohols using dioxazolone as a Ni(II)-nitrenoid precursor. DFT calculation with Gaussian 09 SMD(dichloroethane)-M06/def2tzvpp/def2tzvpp(Ni)//PBE/def2svp/def2tzvp(Ni).

piperidinyloxy), TEMPO-trapped ketone **5z** was obtained in 44%, while amidated β-scission product (**5a**) was not observed.

To shed light on the key questions regarding the dual photoredox/Ni-catalysis, density functional theory (DFT) calculations were carried out using model substrate **1a** and dioxazolone **2a** (Figure 1c; see the Supporting Information for details).[9,77,79] In our DFT study, the alkoxy radical intermediate ($\mathbf{1a}^{\bullet}$) was shown to smoothly undergo the β-scission with a 3.31 kcal/mol energy barrier, readily generating alkyl radical **1a′** with the release of the ketone byproduct. Starting from (**L1**)Ni(0) **A**, two plausible pathways 1 and 2 were considered. For the former path, a radical addition of **1a′** to (**L1**)Ni(0) **A** gives an alkyl-Ni(I) intermediate **B**, being thermodynamically favored. In the pathway 2, however, nitrenoid formation from **A** gives (κ^2-*N,O*)-bound Ni(II) species *G′* upon extrusion of CO_2 via the (κ^1-*N*)-binding mode (**G**) with an overall ΔG value of −18.21 kcal/mol.[34,80] It is noteworthy that the current amidative β-scission system appears to be distinctive from our previous NiH-catalyzed amidation system, where (κ^1-*N*)Ni(III)-nitrenoid was proposed.[39,40,81] Interestingly, when the relative energy was compared between alkyl-Ni(I) intermediate **B** and (κ^2-*N,O*)Ni(II)-nitrene *G′*, the notable thermodynamic stability of the latter species may support the initial nitrenoid formation via path 2. Additionally, since this decarboxylative process of dioxazolone by **A** is believed to be kinetically feasible, the (κ^2-*N,O*)Ni(II)-nitrenoid *G′* would be considered as the catalytically competent species involved in the dioxazolone activation step. Subsequently, following path 2, the addition of **1a′** to the Ni-nitrenoid *G′* was calculated to have a reasonable activation barrier (*G′*-**TS**, $\Delta G^{\ddagger} = 9.15$ kcal/mol), thereby leading to alkyl-Ni(III)-nitrenoid **H**. It should be noted that although an interconversion between nitrenoid intermediate **D** (path 1) and **H** (path 2) would be conceived, **H** was calculated to be thermodynamically more viable than **D** by 6.13 kcal/mol, presumably due to an additional carbonyl coordination (see the Supporting Information for details). While an outer-sphere radical addition was revealed to be energetically more demanding (see the Supporting Information for details), this inner-sphere C−N bond formation through **H-TS** is assumed to be plausible.

■ CONCLUSIONS

In summary, we have successfully developed a convenient method for the amidative β-scission of both linear and cyclic alcohols by a cooperative photoredox PCET and nitrenoid transfer, thus readily furnishing *N*-alkyl amide products over a broad range of substrates and amidating sources. The reaction was elucidated to initiate by the decarbonylative generation of alkyl radicals via photoredox catalysis, which are subsequently captured by the Ni(II)-nitrenoid and ultimately undergo an inner-sphere nitrenoid transfer. It is anticipated that the current dual photoredox PCET/Ni-catalysis protocol using dioxazolone as the nitrenoid precursor may serve as a powerful tool for the design of new reactions having potential applicability in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c11813.

> Experimental procedures; characterization data; spectra for all new compounds; crystallographic data; Cartesian coordinates of all computed structures; crystallographic data for **5j** (PDF)

Accession Codes

CCDC 2301599 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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