

Photoexcited Direct Amination/Amidation of Inert Csp³–H Bonds via Tungsten–Nickel Catalytic Relay

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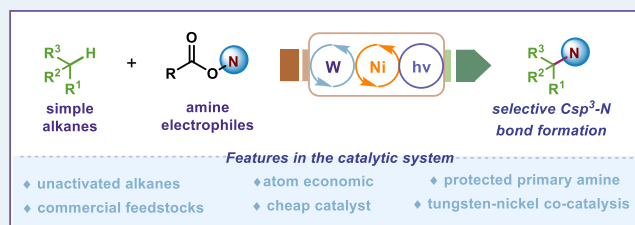
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ABSTRACT: Light alkanes are the most abundant resources in nature. It is of great significance to develop convenient methods to realize the conversion of alkanes to high value-added products. However, the examples of aliphatic amines derived from unactivated alkanes remain rare. This work describes a rapid construction of C(sp³)–N bonds from light alkanes with amine/amide electrophile reagents via high-valent tungsten and nickel catalysis in high efficiency. The photoexcited metal relay provides a powerful tool for the activation of inert sp³-hybridized C–H bonds and stabilization of C–Ni(III)–N intermediates.

KEYWORDS: light alkane, amination, amidation, tungsten, nickel catalysis



Over the last decade, converting alkanes to high-value chemicals has been an active research focus in the synthetic community.^{1–4} Among of them, the construction of the C–N bond is one of the major tasks.^{5,6} Aliphatic amines widely exist in natural products, therapeutic drugs, agrochemicals, and materials science.^{7–12} In particular, several methods have been developed to install a nitrogen atom in the abundant alkane feedstocks. At present, there are two main strategies for the amination of light alkanes. The first is that amine reagents (such as azo, nitro) containing unsaturated bonds react with alkyl radicals to realize the construction of C–N bonds by radical trapping (Figure 1a). For example, Zuo,¹³ Walsh and Schelter,¹⁴ Wu,¹⁵ Duan,¹⁶ and Fagnoni¹⁷ independently demonstrated an alkyl radical coupling with di-tert-butyl azodicarboxylate (DBAD) to forge a new C–N bond.

Furthermore, our group recently demonstrated that nitroarenes trapped alkyl radicals to furnish amination of a light alkane.¹⁸ Another is transition-metal-catalyzed Csp³–H amination via a nitrenoid transfer pathway (Figure 1a). Amination reactions feature C–H insertion or stepwise hydrogen atom transfer and a radical rebound process. For example, Meggers,¹⁹ Chang,^{20,21} Matsunaga,²² and Zhang²³ independently utilized Fe, Co, and Rh complexes for the transfer of in situ generated metal nitrenoids to enable the Csp³–H amination. Despite these notable benchmarks in the direct alkane amination, the strategy of reductive elimination from a high valence nickel complex has not been reported to the best of our knowledge.^{24–26} Previously, while nickel-catalyzed selective amination of unactivated alkanes with directing groups was showcased,^{27–31} an equivalent amount of oxidant or reductant agent is required.^{23–29} The ongoing need for new and complex amines through which to probe novel

reactivity has driven the development of innovative chemical methods for their synthesis.³² Therefore, the development of new and convenient strategies is in urgent demand. Recently, the decatungstate anion ([W₁₀O₃₂]^{4–}) has been broadly used as an efficient hydrogen atom transfer (HAT) photocatalyst in aliphatic C–H bonds.^{33–36} It has been proved in selective abstraction of electron-rich, sterically accessible C–H bonds.³⁷ Furthermore, amine electrophiles could serve as both the amine source and the internal oxidant.^{38–41} Thus, no external oxidant is required. We envision that alkyl radicals could be readily generated by the decatungstate anion. The site selectivity would be governed by varied BDEs and steric hindrances of secondary/tertiary C–H bonds. The subsequent oxidative addition of Ni^I-alkyl species to amine electrophiles forms the key C–Ni^{III}–N complex, which undergoes reductive elimination [RE] to furnish the amine product (Figure 1b). The commonly occurred protonation of Ni-alkyl species and β-hydride elimination is suppressed by carefully tuning the reactivity of Ni^{III} species with MCl_x additives (M = Li, Mg, Zn, Cr, etc.). Herein, we disclose a photoexcited W–Ni dual-catalyzed site-selective amination/amidation of inert Csp³–H bonds.

To pursue the goal, we explore the conditions for this C–H amination. As illustrated in Table 1, the treatment of cyclohexane **1** (0.5 mmol) and amine electrophile **2** (0.1

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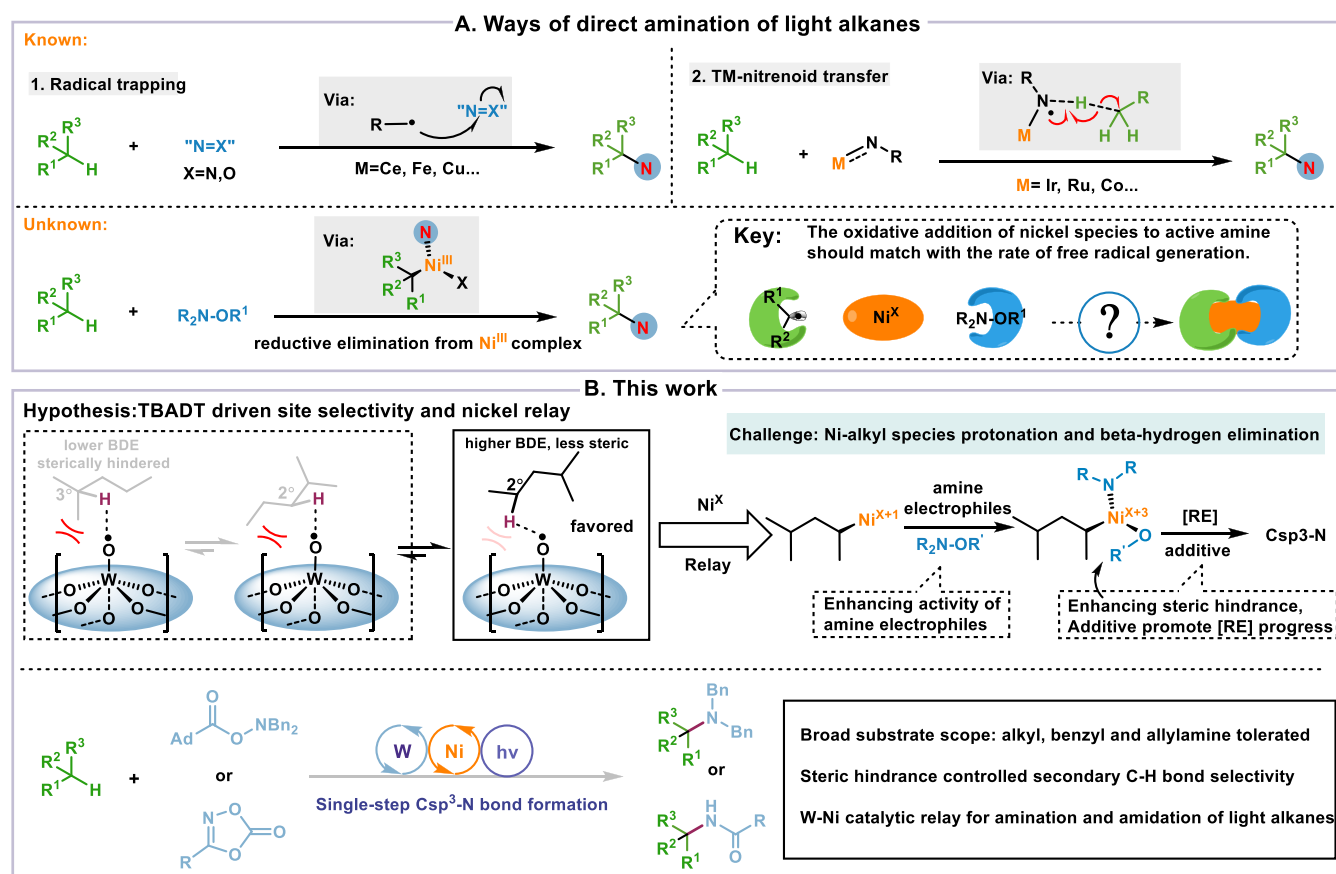


Figure 1. Strategies for selective amination/amidation of simple alkanes.

Table 1. Optimizations of the Reaction Conditions

Entry	Deviation from standard conditions	Yield % ^{a,b}
1	none	82(78)
2	NiBr ₂ instead of NiI ₂	62
3	Ni(PPh ₃) ₂ Cl ₂ instead of NiI ₂	trace
4	NH ₄ Cl instead of LiCl	31
5	NaCl instead of LiCl	34
6	MeCN	53
7	10 mol % NiI ₂	35
8	1a/2a/5a/6a	ND
9	4a instead of 3a	57
10	w/o LiCl	trace
11	w/o NiI ₂	ND

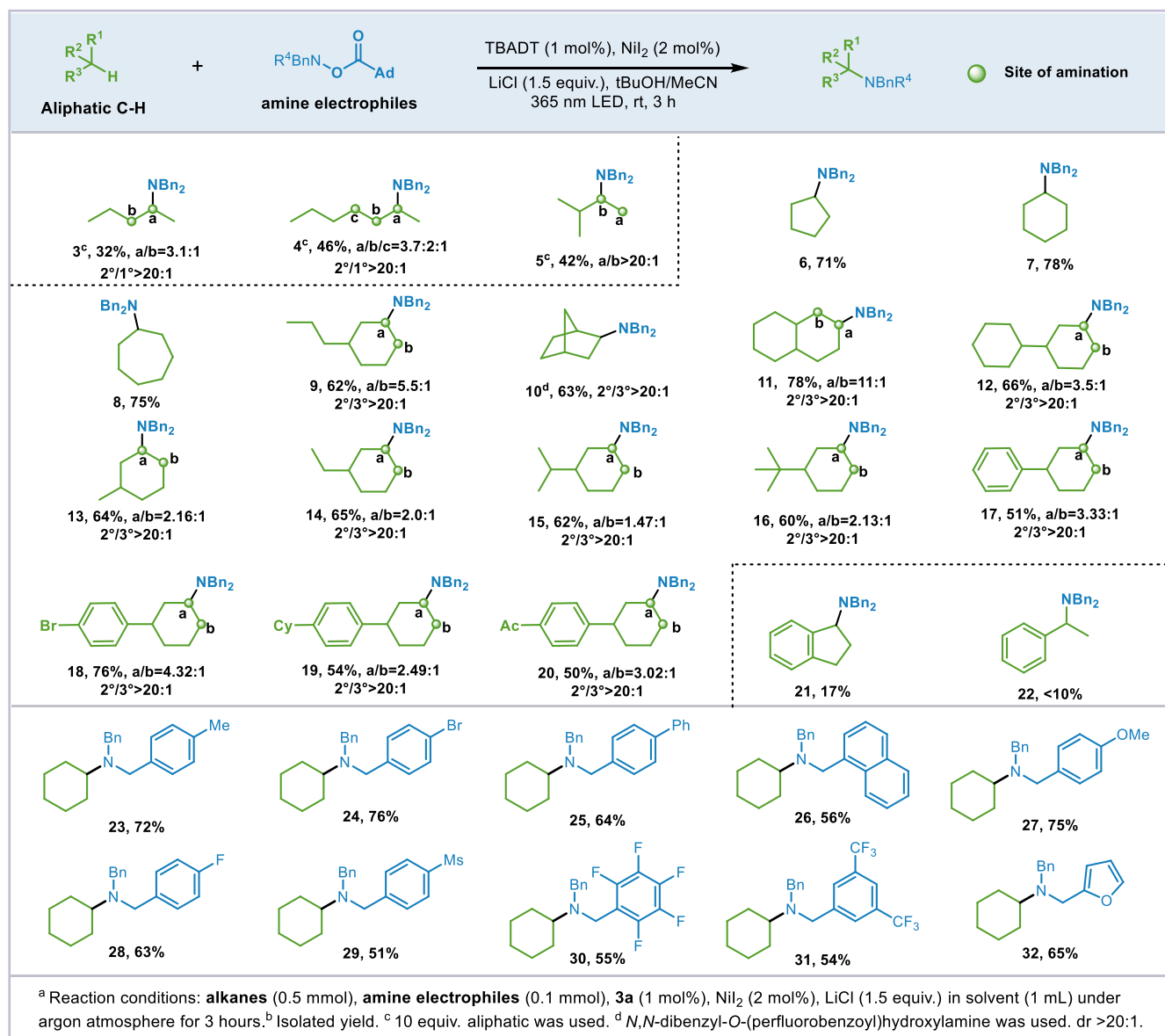
^aReaction conditions: 1 (0.5 mmol), 2 (0.1 mmol), 3a (1 mol %), NiI₂ (2 mol %), LiCl (1.5 equiv.), in solvent (1 mL) under argon atmosphere for 3 h. benzophenone (1a), 9H-fluoren-9-one (2a), TBADT (3a), NaDT (4a), biacetyl (5a), [UO₂](NO₃)₂·H₂O (6a). ^bIsolated yield.

mmol) in the presence of tetrakis(tetrabutylammonium) decatungstate (TBADT 3a, 1 mol %), NiI₂ (2 mol %), LiCl (1.5 equiv) in MeCN/tBuOH (3:1, 0.1 M) under Ar for 3 h furnished the desired product 7 in 78% isolated yield (entry 1).

We also examined amine electrophiles with different substituents (see SI). In general, aliphatic carboxylic acid-activated amine electrophiles are superior to aromatic carboxylic acids. Using the adamantane carboxylic acid-activated amine electrophile, the target product can be

obtained in 82% yield. Further investigation revealed that NiBr₂ gave decreased results (entry 2). when Ni(PPh₃)₂Cl₂ was used, only trace amounts of the product was observed (entry 3). Chloride salts are known to be beneficial for the reductive cross-coupling. However, additives such as NH₄Cl and NaCl inhibit the reaction (entries 4 and 5). Lithium chloride was found to promote the reduction and elimination of high-valent nickel, while MgCl₂ and ZnCl₂ would inhibit such transformation.^{42,43} For the optimization of solvents,

Scheme 1. Substrate Scope for Amination of Simple Alkanes

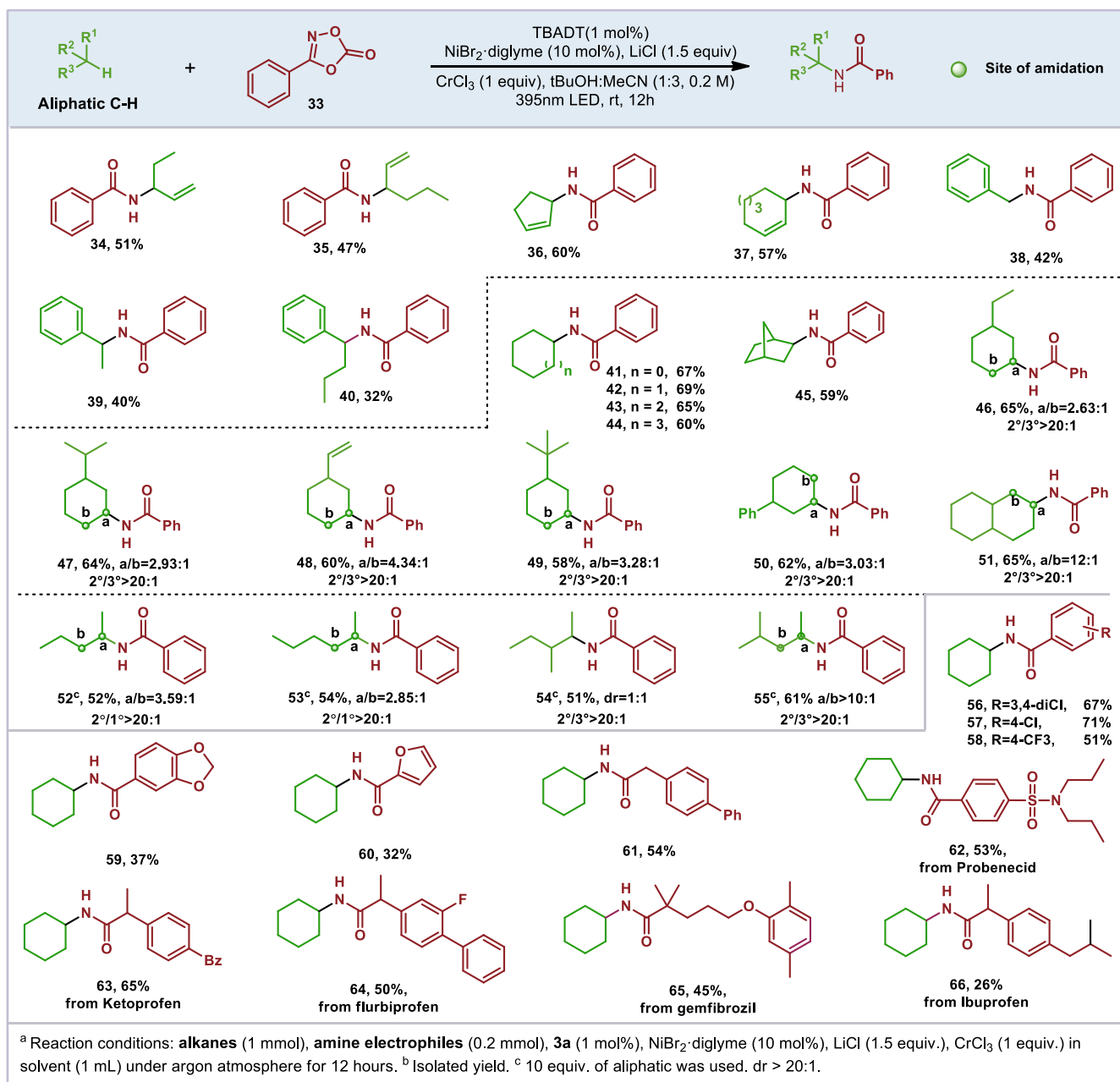


dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF) did not improve the yield (entry 6). When the amount of the nickel catalyst was increased, the yield of the target product decreased significantly (entry 7). For the optimization of the photocatalyst, ketones and uranyls did not furnish the desired product. NaDT only provided decreased yields (entries 8 and 9). Without LiCl or NiI₂, the reaction was prohibited (entries 10 and 11).

Under the optimized reaction conditions, we examined the substrate generality of the cross C–N bond coupling (CCNC) with various alkanes and amine electrophiles (Scheme 1). This CCNC delivers a protected primary amine in an operationally simple and scalable way from various alkanes. First, we explored the CCNC of a simple alkane. The present tungsten/nickel system demonstrated a high degree of methylene selectivity in the amination of linear aliphates (3–5), which is in good agreement with the proposed HAT mechanism.²¹ In general, the 2° carbon radicals have better thermodynamic stability than the primary. The primary C–H bonds, owing to the higher BDEs, were barely functionalized in the presence of

secondary C–H bonds. According to the characteristic ¹H nuclear magnetic resonance peaks of the products, no sign of tertiary C–H amination was observed, possibly due to its considerable steric hindrance. The degree of selectivity between two competing secondary C–H bonds followed the statistic ratios. Different sizes of simple cycloalkanes could furnish the target amination products in high efficiency (6–9). The amine products of the bridged bicyclic alkane (10) and decahydronaphthalene (11) were afforded in high regioselectivity distereoselectivity. For different alkyl or aryl substituted cyclohexanes, the amination occurs with high selectivity (12–20). For substituted cyclohexanes containing benzylic active sites, no benzylic amination products were detected, but meta-substituted products were obtained with higher regioselectivity (17–20). The benzylic amination products all obtained lower yields under standard reaction conditions, but most of them were self-coupling products and simultaneously along with the decomposition of the amine electrophile (21 and 22). Second, we explored the CCNC of different amine electrophiles. The amination products were furnished in good yield (23–32).

Scheme 2. Substrate Scope for Amidation of Simple Alkanes



Amine electrophiles with electron-withdrawing and electron-donating substituents were tolerated in the reaction. Functional groups such as methyl (**23**), halogen (**24**, **28**, **30**), aryl (**25**), methoxy (**27**), mesylate (**29**), and trifluoromethyl (**31**) remained intact during the CCNC reaction. The heterocyclic substrate also furnished the product in moderate yield (**32**).

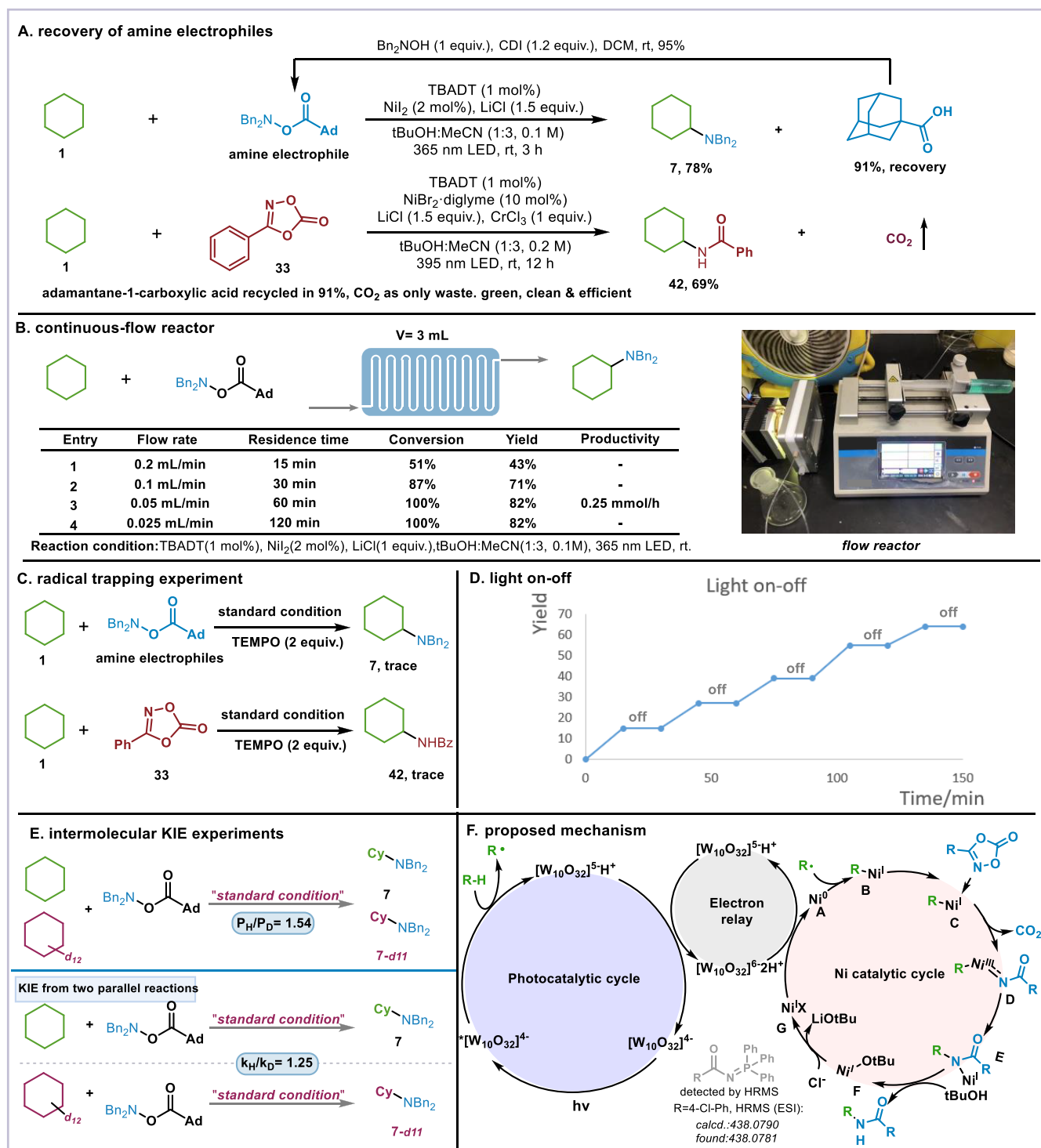
Next, we examined amide electrophiles for this Ni-catalyzed CCNC reaction (Scheme 2). First, the CCNC of alkyl olefins furnished the amidation products at the allylic position with high regioselectivity (**34–37**). The amidation of the benzylic C–H could also be achieved in moderate yields (**38–40**). Second, cycloalkanes in different sizes furnished the corresponding amide products in high efficiency (**41–44**).

Amidation of (1*s*,4*s*)-bicyclo[2.2.1]heptane afforded product **45** with a high dr value. For different substituted cyclohexanes, the amidation reaction occurred on the ring

with high selectivity (**46–51**). Functional groups such as alkyl (**46**, **47**), vinyl (**48**), and aryl (**50**) were all tolerated. Finally, we explored the CCNC of a simple alkane. The amidation products were furnished toward secondary C–H bonds with highly selectivity (**52–55**). Subsequently, we examined dioxazolones with different substituents. The amidation products were furnished in good yield (**56–66**). Dioxazolones with electron-withdrawing and electron-donating substituents were tolerated in the reaction (**56–59**). The furan substituted electrophile gave the corresponding heterocyclic product (**60**). To further extend the reaction feasibility, the natural products and drug molecules were assigned to the standard conditions to furnish the amidated products in moderate yield (**62–66**).

With the diversified reactions in hand, we conducted additional experiments to improve the practicability of this strategy (Scheme 3A). The adamantane acid reagent can be

Scheme 3. Synthetic Application and Proposed Mechanism



recovered in 91% yield after the reaction. Only CO₂ is exhausted. Subsequently, we investigated the C–H amination of alkanes in continuous-flow reactors (Scheme 3B). The reaction solution was injected by a syringe pump with the flow rate of 0.2 mL/min for the mixture solution stream. The amination product was obtained in 43% yield with a residence time of 15 min. Under the flow rate of 0.1 mL/min, the reaction yield was increased to 71% with a residence time of 30 min. At 0.05 mL/min, the yield reached 82% with a residence time of 60 min, affording remarkable productivity of 0.25

mmol/hour. The addition of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) completely inhibited the reaction, suggesting that the reaction may undergo a free radical pathway (Scheme 3C). A light on–off experiment proves that the reaction does not occur in darkness. When light is turned back on, the reaction reboots (Scheme 3D). Furthermore, the overall kinetic isotope effect (KIE) studies suggested the process of homolytic C–H bond cleavage may not be the rate-determining step (Scheme 3E, see SI for details).⁴⁴ To gain more insight into the reaction pathway of

this W–Ni dual-catalyzed reaction, we conducted the kinetic studies using the reaction between cyclohexane **1** and amine electrophiles **2** as the model reaction. The kinetic profiles were obtained by measuring the initial reaction rates at different concentrations of catalyst or reactants (see SI for details). The observation of positive kinetic orders in TBADT and NiI₂ indicate regeneration of TBADT and NiI₂ as the rate-limiting step. Positive kinetic orders in LiCl supports the crucial role that is experimentally observed for the additives. Thus, LiCl probably serves a role in facilitating Ni reduction.

According to previous reports,^{45–49} a plausible catalytic cycle is proposed (Scheme 3F). Under irradiation, photoexcitation of the photocatalyst would produce the triplet excited state. Subsequent hydrogen atom abstraction from an alkane by an excited state photocatalyst would readily afford a reduced photocatalyst and a carbon-centered radical R. The Ni^I species G reduced by the photocatalyst could initially afford Ni⁰ species A, which captures the alkyl radical to furnish Ni^I-alkyl species B. The coordination of dioxazolone to B should form the Ni complex C, which transforms to the electrophilic metal nitrenoid D that was captured by PPh₃ (Scheme 3F, see SI for details) and release molecular CO₂.³³ Facile nitrene insertion should afford the Ni-amide complex E, which is readily protonated to give the product and F for the next cycle.

In conclusion, we have developed a highly selective C(sp³)–N coupling reaction with unactivated light alkanes by using the cheap and accessible TBADT photocatalyst and nickel(III) catalysis. Compared with the traditional amine formation methods, this protocol benefits from improved atom efficiency, decreased waste generation, and reduced synthetic steps, which provides a powerful tool for the rapid construction of aliphatic amines and amides.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.2c03456>.

The synthetic procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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