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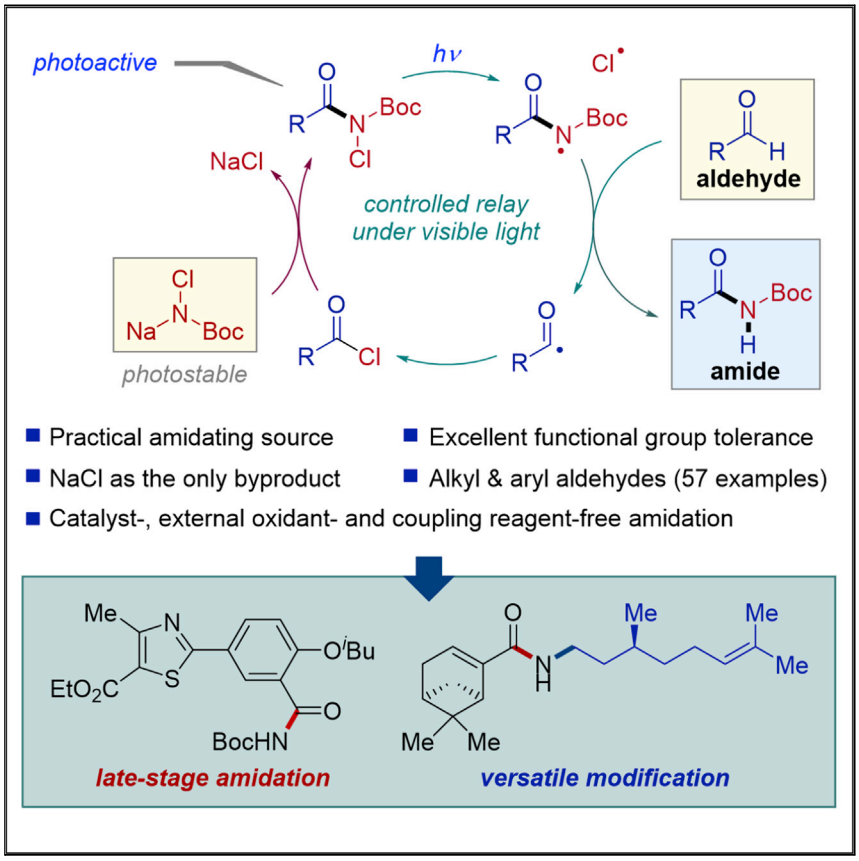
Controlled Relay Process to Access N-Centered Radicals for Catalyst-free Amidation of Aldehydes under Visible Light



A catalyst-free approach for controlled access to N-centered radicals is described, which enables the conversion of aldehydes to amides via an unconventional relay process harnessing visible light. The key tactic relies on the use of photostable *N*-chloro-*N*-sodio-carbamate amidating reagent that leads to slow incorporations of a photoactive radical source via C–N formation and other involved intermediates thereafter. This methodology displays excellent applicability and sustainable chemistry credentials and, thus, holds a promise for finding broad applications.

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HIGHLIGHTS

Relay process for the controllable formation of N-centered radicals under visible light

Amidation of aldehydes under catalyst-, oxidant-, and coupling-reagent-free conditions

Atom economic transformation that results in NaCl as the only byproduct

Broad scope and high functional group tolerance leading to excellent applicability

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Wongyu Lee,[1,2,3] Hyun Ji Jeon,[1,2,3] Hoimin Jung,[1,2] Dongwook Kim,[1,2] Sangwon Seo,[1,2,*] and Sukbok Chang[1,2,4,*]

SUMMARY

Nitrogen-centered radicals have attracted increasing attention as a versatile reactive intermediate for diverse C–N bond constructions. Despite the significant advances achieved in this realm, the controllable formation of such species under catalyst-free conditions remains highly challenging. Here, we report a new relay process involving the slow *in situ* generation of a photoactive *N*-chloro species via C–N bond formation, which subsequently enables mild and selective access to N-centered radicals under visible light conditions. The utility of this approach is demonstrated by the conversion of aldehydes to amides, employing *N*-chloro-*N*-sodio carbamates as a practical amidating source. This synthetic operation obviates the need for catalysts, external oxidants, and coupling reagents that are typically required in related processes, consequently allowing high functional group tolerance and excellent applicability for late-stage functionalization.

INTRODUCTION

The ubiquity of nitrogen-based motifs in high-value compounds has engendered the C–N bond formation as one of the most important organic transformations.[1,2] As a complementary method to the conventional transition-metal-catalyzed coupling reactions,[3–5] the construction of C–N bonds harnessing N-centered radicals has developed into a powerful synthetic tool.[6–9] In particular, recent advances in redox catalysis have led to a renaissance in this field, as this approach allows the mild and selective generation of N-centered radicals (Figure 1A). An array of new reaction modes have been developed by using single electron transfer (SET) or proton-coupled electron transfer (PCET) abilities of photoredox or transition-metal-based catalysts, which subsequently enabled diverse transformations, such as C–H amination,[10–15] hydroamination,[14,16–18] and remote C–H functionalization.[19–22] While redox catalysis remains as the most versatile strategy for N-centered radical chemistry, the simplest means to access such reactive intermediate relies on the thermal or photo-homolysis of nitrogen–halogen bonds (Figure 1A).[23] This method has been majorly utilized in the conversion of acyclic amines to pyrrolidines, known as the Hofmann-Löffler-Freytag (HLF) reaction,[24–26] via 1,5-hydrogen atom transfer (HAT), halogen abstraction, and base-induced intramolecular cyclization reactions. However, the inability to attain a delicate control over the homolysis process may lead to undesired degradation pathways, such as those arising from the side reactions with highly reactive halogen radical.[23]

Recently, iodine-based catalysis has been developed that offers solutions to some of the problems encountered in the classical homolysis approach.[9] For example, Muñiz[27–29]

The Bigger Picture

Amides are an important class of structural motifs prevalently found in bioactive compounds and synthetic materials of great significance. Amidation of aldehydes has been established as an atom-efficient strategy for amide synthesis; however, current methods lack in applicability mainly due to the requirement of troublesome reagents. In this article, we describe an unconventional relay process to convert aldehydes to amides under catalyst-, oxidant-, and coupling-reagent-free conditions, which is enabled by the development of a new mechanistic platform that gives efficient and controllable access to N-centered radicals under visible light. A wide range of (hetero)aromatic and aliphatic aldehydes can be employed, including those derived from biologically relevant complex molecules. We anticipate that the accomplished methodological advances, combined with the unique mechanistic features, will lead to the widespread application of the present strategy in broad research fields.

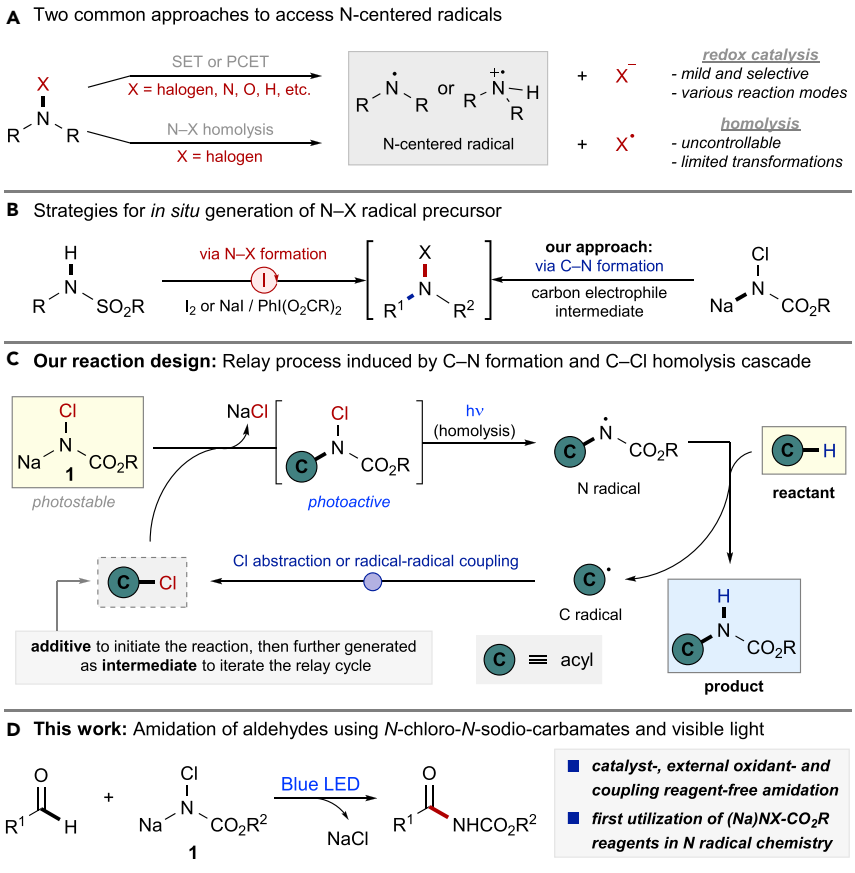

Figure 1. Synthetic Strategies for the Generation of N-centered Radicals

(A) Two common approaches to access N-centered radicals.

(B) Strategies for *in situ* generation of N–X radical precursor.

(C) Our reaction design of relay process for C–N formation via N-centered radical.

(D) Amidation of aldehydes using *N*-chloro-*N*-sodio-carbamates and visible light irradiation.

and Nagib[30–32] showed that a I_2 or NaI catalyst, in combination with a hypervalent iodine oxidant, is effective for the slow *in situ* generation of a *N*-iodoamine radical precursor by the iodination of amines (Figure 1B), which, in turn, enables the formation of N-centered radicals in a controlled manner. Not only does it preclude the requirement of nitrogen pre-functionalization, but this method has also been proven viable for intermolecular C–H amination.[33] Inspired by these elegant works, we envisaged developing a new C–N bond-forming strategy based on the *in situ* generation of a *N*-halo radical precursor via an alternative bond connection. While the previous methods provided impressive advances, their use in intermolecular reactions is still scarce, and the need for a large number of chemical oxidants may diminish their synthetic utilities. Moreover, the development of new strategies that could incorporate amino moieties other than those based on sulfonamides is highly desirable. To this end, we hypothesized that *N*-chloro-*N*-sodio-carbamate **1** may provide an alternative mechanistic platform for catalyst- and oxidant-free C–N constructions via a transposed sequence of the HLF-type process (Figure 1C). In this approach, the controlled generation of N-centered radicals would be achievable by the slow incorporation of a photoactive *N*-chloro intermediate from the photostable amidating reagent and a sparingly present organic chloride. The N–Cl homolysis would be followed by intermolecular HAT with a reactant to lead to the amidation product, while the translocation of N to C radical and chlorine abstraction would constantly provide the chloride species to enable the continuous relay process.

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Specifically, we were interested in attempting this reaction design in the amidation of aldehydes, given the significance of amides in broad research fields.[34] Although the conversion of aldehydes to amides have been enormously explored,[35] including by way of some visible-light-mediated approaches[36–39] and transition-metal-coordinated nitrene reactions,[40–42] there is a dearth of direct strategies to synthetically valuable N-protected amides.[43] In addition, we considered this as a desirable transformation worthy of further investigation since the existing methods are often hampered by the lack of applicability.[44] The competence to eliminate catalysts, oxidants, and highly reactive coupling reagents, thus, remains in high demand for aldehyde amidation, which may grant access to underexplored chemical space. Here, we report a visible-light-induced approach for amidation of aldehydes, utilizing **1** as a catalyst-free amidating reagent to afford N-protected amides under mild and convenient conditions (Figure 1D). This synthetic operation relies on a relay process that allows the controlled incorporation of a N-centered radical, which circumvents the limitations associated with the use of detrimental reagents, thereby leading to a broad scope, high functional group tolerance, and excellent applicability.

RESULTS AND DISCUSSION

Proof of Concept

N-Chloro-*N*-sodio-amino salts have been utilized for transition-metal-catalyzed C–N formation, for example, as a nitrene precursor.[45] Previously, our group also demonstrated that *N*-chloro-*N*-sodio-*tert*-butylcarbamate **1a** is a practical amino source for the Cu-catalyzed C–H amidation of (hetero)arenes.[46] This reagent can be readily prepared in multigram scales by treating *tert*-butylcarbamate (Boc-NH_2) with ^{t}BuOCl[47] or trichloroisocyanuric acid (TCCA),[46] followed by the salt formation using NaOH in MeOH. It is bench-stable, convenient to handle and additionally benefits from the ability to directly install a protected-amino moiety. In continuation of our research interests in C–N bond constructions,[4,48–50] we endeavored to evaluate the viability of **1a** for an unconventional reaction mode utilizing visible light.

The structure of **1a** was first analyzed by X-ray crystallography, which revealed that it has an interesting 2D sheet connectivity in its solid state (Figure 2A). The rigid sodium-based framework consists of the organic anionic parts being held together through multiple Na–O and Na–N coordinations, each ion being surrounded by four ions of the opposite charge. The length of the Na–O bonds is slightly shorter than that of the Na–N bonds, which is indicative of similar charge distribution between the two atoms. Interestingly, the N–Cl bond of **1a** (1.763 Å) was determined to be relatively longer than those of certain *N*-chloro species (1.700–1.715 Å) that were reported to homolytically dissociate under photolytic conditions.[51] With the recognition of these structural aspects, the photostability of **1a** was tested under visible light irradiation in MeCN (Figure 2B). Despite the comparably longer N–Cl bond length, **1a** was found to be inert to homolysis under the photo conditions, in which the stability might have resulted from the structural rigidity or the incapability to absorb the light energy. This is in stark contrast to the photochemical lability of its protonated variant **1b**, which decomposed to the corresponding carbamate **2** (32%) and a chlorinated derivative **3** (40%) under the same conditions, presumably via a HLF-type process.

With **1a** revealed to be resistant to uncontrollable photo-decompositions, we further carried out experimental investigations to prove the conceptual viability of our reaction design (Figure 2C). We proposed that an acid chloride additive **I** would initiate

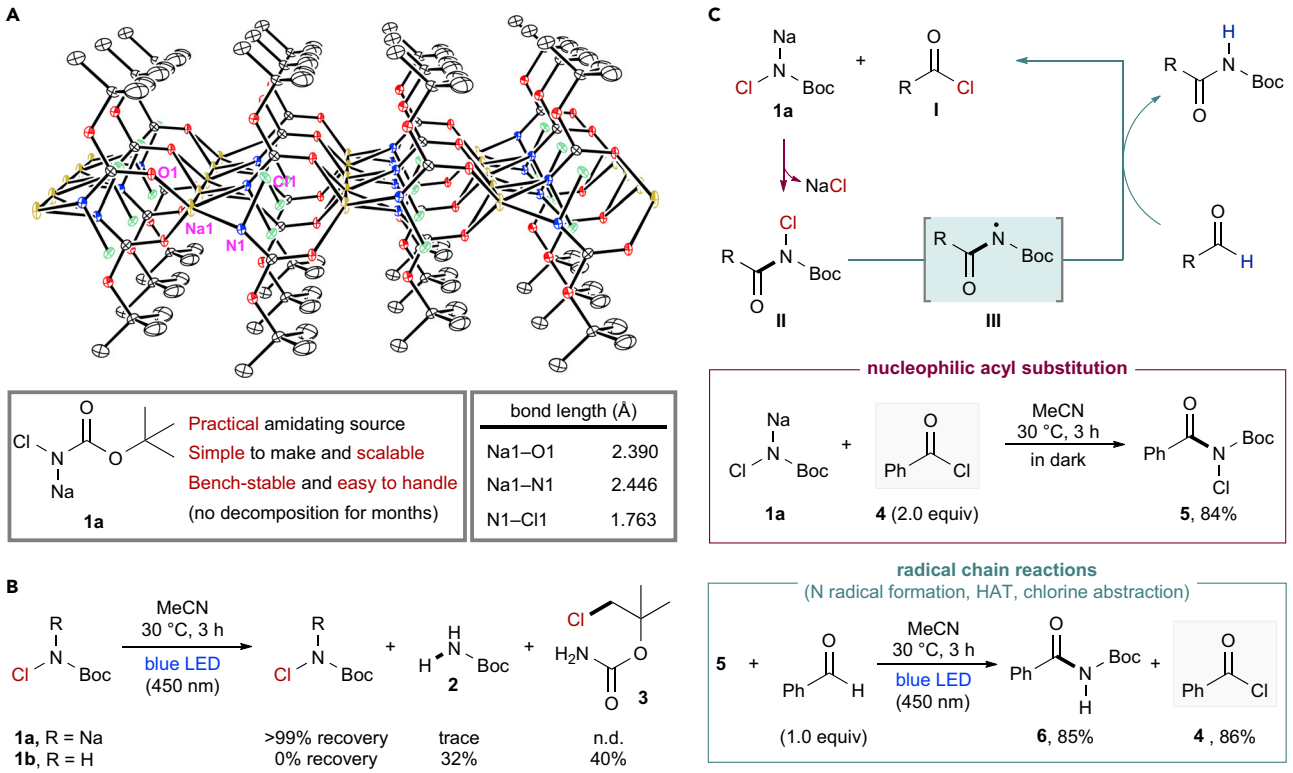

Figure 2. Proof of Concept for the Proposed Amidation of Aldehydes Using Visible Light

(A) X-ray structure of *N*-chloro-*N*-sodio-*tert*-butylcarbamate **1a**: minor disorder and hydrogen atoms were omitted for clarity.

(B) Photochemical stabilities of *N*-chloro amino sources.

(C) Proposed relay cycle and the feasibilities of each step of the reaction sequence.

the relay cycle by first reacting with **1a** to give *N*-chloroamide species **II**. Alexanian et al., recently reported compelling strategies for site-selective intermolecular halogenation of aliphatic C–H bonds by using specifically designed *N*-haloamides and visible light.[52,53] Based on the structural similarity, we envisioned that **II** could react with aldehyde to furnish the amide product and further generate acid chloride **I** for the next relay cycle. To validate this working mode, each step of the reaction sequence was investigated. First, the nucleophilic acyl substitution of **1a** with benzoyl chloride **4** in the dark successfully gave *N*-chloroamide **5** in an 84% yield. The obtained amide **5** was subsequently found to afford amide **6** (85%) along with benzoyl chloride **4** (86%) upon treatment with benzaldehyde under visible light irradiation. These results demonstrated that the designed amidation would be highly feasible, whereby the conversion of aldehydes to amides would be achieved through a relay process involving the aforementioned reactions.

Optimization of the Reaction Conditions

The proven viabilities of each reaction step led us to investigate the desired transformation of aldehydes to amides. We initially hypothesized that a substoichiometric amount of acid chloride would be required as an additive to induce the proposed reaction. With this in mind, we carried out the reaction between **1a** and benzaldehyde under visible light irradiation using an integrated photoreactor[54] (blue LED, 450 nm; Figure 3A). Pleasingly, the use of **1a**, benzaldehyde (2.0 equiv), benzoyl chloride additive **4** (1 mol %) and MeCN solvent yielded the amidation product **6** in a 97% yield in 3 h. However, to our surprise, the formation of **6** was also achieved

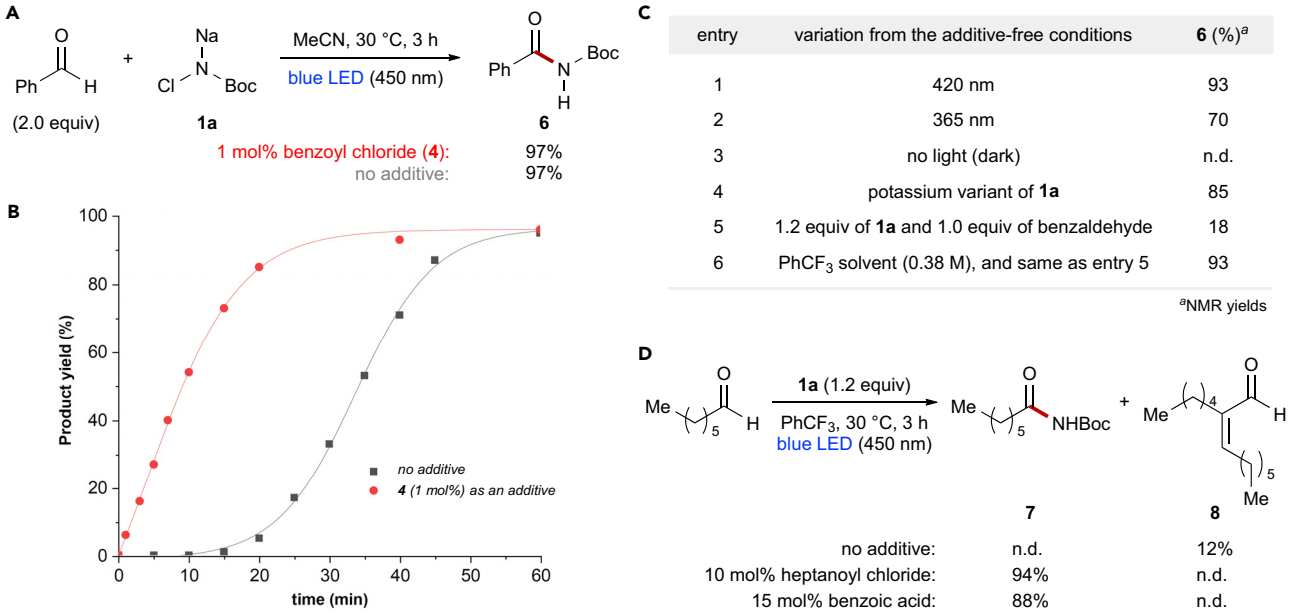

Figure 3. Optimization of the Reaction Conditions

(A) Preliminary results for the amidation of benzaldehyde with **1a** under visible light.

(B) Changes in the product yields along the reaction time for the reactions in the absence and presence of benzoyl chloride **4** additive.

(C) Selected conditions for further optimization of the reaction between benzaldehyde and **1a**.

(D) Optimization of the reaction between 1-heptanal and **1a**.

in the same efficiency even in the absence of any additives (97%). We speculated that a little decomposition of **1a** could promote the aldehyde chlorination in a manner similar to the previous reports,[55] which would convert a sacrificial amount of aldehyde to acid chloride for the initiation process. This hypothesis could be supported by monitoring the changes in product yields along the reaction times in both reaction conditions (Figure 3B). It was observed that the amidation took place smoothly, reaching a full conversion within 30 min in the presence of 1 mol % of benzoyl chloride **4**, whereas the additive-free system displayed an induction period during which **4** is presumed to be formed.

Further optimization was carried out, and control experiments showed that higher-energy light sources could also furnish **6**, albeit in slightly lower yields (Figure 3C, entries 1–2), whereas the reaction was completely inactive in the dark (Figure 3C, entry 3). A potassium derivative of the carbamate source was less effective than **1a** (Figure 3C, entry 4). Finally, a change of solvent from MeCN to $PhCF_3$ allowed the reaction to be carried out at an almost equimolar ratio of the two reactants (Figure 3C, entries 5–6), which would be beneficial for late-stage applications.

In contrast to the success with benzaldehyde, aliphatic substrates were found to be ineffective under the additive-free conditions, mainly due to their propensity to form aldol side products. For instance, the reaction of 1-heptanal suffered from the rapid formation of undesired aldol product **8** along with unknown decompositions (Figure 3D). We reasoned that an acid chloride additive would, thus, be necessitated in this case, as the initiatory *in situ* formation of such species might not be operative for aliphatic substrates, or it might be that the undesired side reactions are comparably faster than its generation. Indeed, we could overcome this issue by employing the corresponding acid chloride additive (10 mol %), which furnished the desired

amide **7** in a 94% yield while obviating the generation of unwanted side products. Further optimizations revealed that benzoic acid could be alternatively utilized as a practical additive (15 mol %), which is assumed to promote the initiatory generation of acid chloride (see Tables S2–S8 for detailed optimizations).

Reaction Scopes

The established mild photo conditions led us to explore the substrate scope of various aromatic and aliphatic aldehydes in reaction with 1.2 equiv of amidating reagent **1a** (Figure 4). Electron-neutral, electron-donating, and electron-withdrawing substituents on benzaldehydes were equally viable: alkyl and aryl (**9**–**15**), alkoxy (**16**–**19**), halo (**20**–**23**), nitro (**24**), trifluoromethyl (**25**), cyano (**26**), sulfide (**27**), sulfonyl (**28**), ester (**29**), and boronic ester (**30**) were all fully compatible, thereby delivering the amide products in good to excellent yields (54%–93%). Notably, aromatic C–H chlorination was not observed in all substrates, which is often a favored pathway for reactions involving conventional chlorinating reagents.[55,56]

The high amidation efficiency was further demonstrated in reactions of polyaromatic (**31**–**32**, 73% and 67%) and heterocyclic aldehydes irrespective of their electronic nature (**33**–**36**, 61%–72%), including a nicotinamide derivative **35**. Interestingly, a benzoic acid additive (15 mol %) was beneficial in obtaining satisfactory results in certain aldehydes (**33**, **34** and **36**), while slightly lower yields (~20%) were obtained in the absence of such additive in those cases. The reaction also proceeded smoothly for vanillin isobutyrate, an aldehyde widely used in fragrance industries, resulting in an amide derivative **37** in a 70% yield.

A range of aliphatic aldehydes could also be efficiently amidated in reaction with **1a** (1.2 equiv) in the presence of benzoic acid additive (15 mol %): linear (**7**, **38**–**41**) and sterically more demanding branched aldehydes (**42**–**44**), as well as cyclic substrates (**45**–**51**), were all feasible. As in the case of benzaldehydes, labile functional groups such as alkyl bromide (**39**) and α,β-unsaturated olefinic units (**50**–**51**) were found to be compatible. Given that (1*R*)-(–)-Myrtenal is more readily available than its carboxylic acid derivative, the successful formation of amide **51** proves that the current photo-procedure is an attractive alternative to the classical coupling reaction of carboxylic acids[57] for accessing certain classes of amides. Finally, the flexibility of amino precursors was briefly examined. Derivatives of *O*-benzyl (Cbz, **52**–**54**, 57%–93%), *O*-methyl (**55**, 85%) and *O*-ethyl carbamate (**56**, 88%), and sulfonamide (**57**, 60%) readily reacted.

Synthetic Utility

We next investigated the feasibility of our amidation reaction in late-stage functionalization (Figure 5), which is a highly desirable feature scarcely explored by the existing aldehyde amidation strategies. We envisioned that the mild reaction conditions accomplished by obviating the need for strong oxidants and highly reactive coupling reagents would grant such capability. In particular, we paid attention to the modification of biologically relevant compounds via the direct installation of a formyl moiety and subsequent amidation to show that the unconventional retrosynthetic approaches can be utilized in late-stage construction of amide functionality. The ease of our reaction and a wide variety of transformations available for installation of a formyl group would render the present strategy highly attractive.

The manipulation of olefins is of particular significance since they can be divergently converted to aldehydes, for example, by means of oxidation,[58] homologative hydroformylation[59] or dehomologative ozonolysis.[60] As a demonstration, Camphene

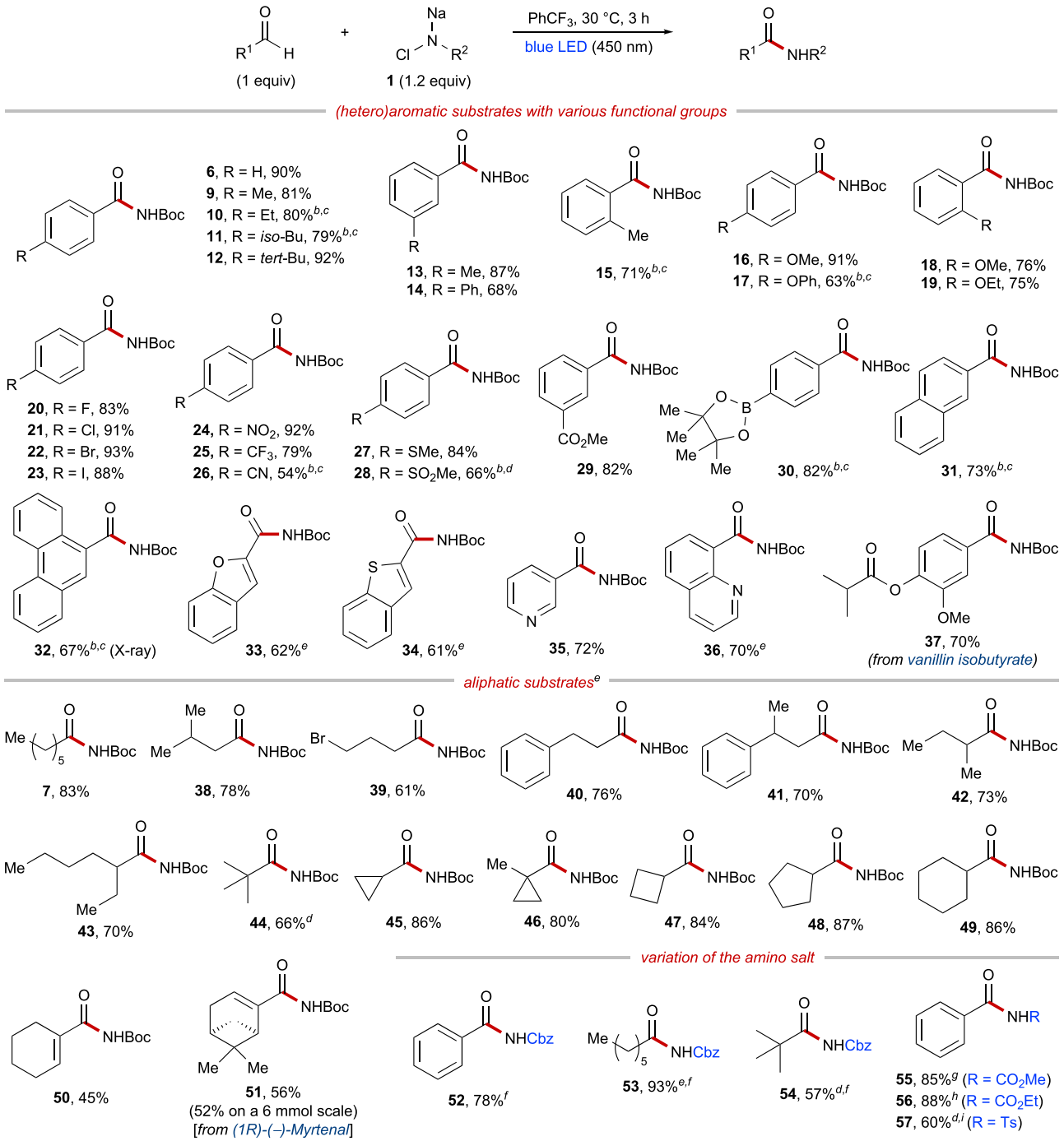

Figure 4. Reaction Scope

[a]Reaction conditions: Performed on Penn PhD Photoreactor M2 using 450 nm blue LED, with aldehyde (1.0 equiv), *N*-chloro-*N*-sodio-carbamate **1a** (1.2 equiv), and $PhCF_3$ (0.38 M) at 30°C for 3 h: isolated yields.

[b]2.0 equiv of aldehyde and 1.0 equiv of **1a** were used.

[c]MeCN (0.75 M) instead of $PhCF_3$.

[d]MeCN (0.38 M) instead of $PhCF_3$. [e]Benzoic acid (0.15 equiv) was added as an additive.

[f]Na(Cl)NCbz (1.2 equiv) instead of **1a**.

[g]$Na(Cl)NCO_2Me$ (1.2 equiv) instead of **1a**.

[h]$Na(Cl)NCO_2Et$ (1.2 equiv) instead of **1a**.

[i]Na(Cl)NTs (1.0 equiv) instead of **1a** and 2 equiv of benzaldehyde.

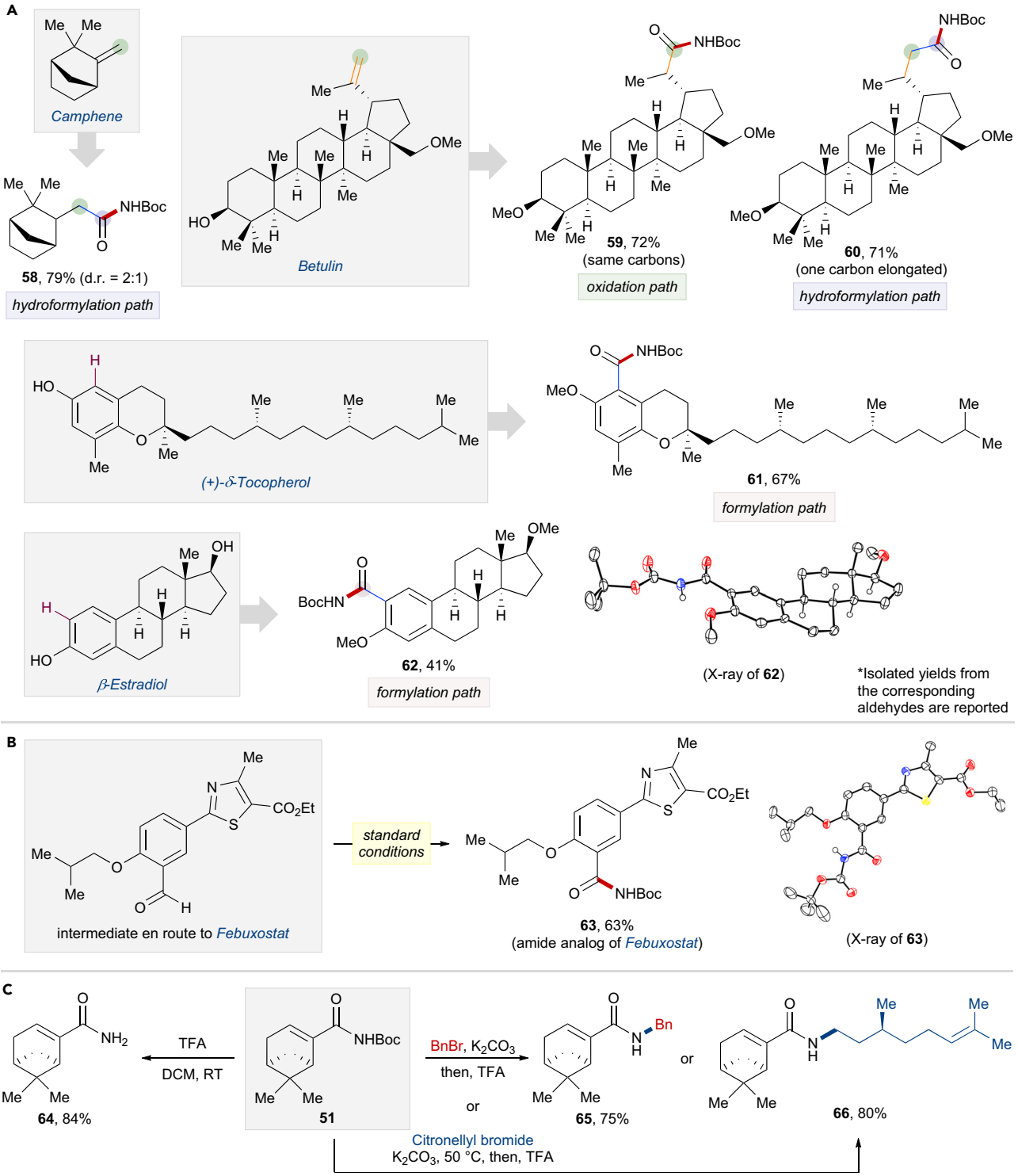

Figure 5. Synthetic Utility

(A) Late-stage amidation of biologically relevant compounds via installation of a formyl group and subsequent amidation (see Supplemental Information for detailed reaction conditions).

(B) Amidation of a key intermediate en route to febuxostat to access its amide analog.

(C) Modification of amide **51**.

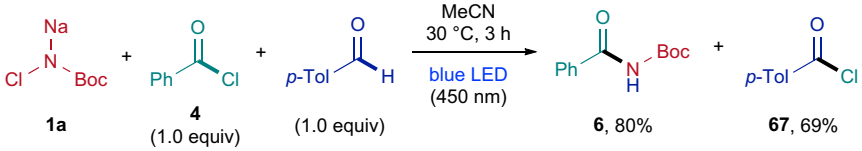

Figure 6. Control Experiments with a Mixture of Benzoyl Chloride and *p*-Tolualdehyde

underwent efficient hydroformylation to give one carbon-elongated aldehyde by using Rh-catalysis, and the successive treatment with **1a** under the currently developed conditions furnished amide **58** (Figure 5A). Likewise, the modification of an olefin functionality in Betulin by oxidation or hydroformylation granted access to two diversified aldehydes, and subsequently the amide analogs **59** and **60**, respectively, under our reaction conditions. Moreover, aromatic aldehydes readily obtained by directed *ortho*-formylation could be successfully employed under the standard conditions. For instance, amide derivatives of (+)-δ-Tocopherol and β-Estradiol were effectively obtained through this approach (**61** and **62**, respectively). In addition, we could intercept a key aldehyde intermediate en route to a drug molecule Febuxostat, affording an amide variant of the bioactive compound (**63**, Figure 5B).

The synthetic utility of our protocol was further demonstrated by transforming the obtained amide **51** to synthetically valuable derivatives (Figure 5C). While N-protected amides have been broadly utilized as a versatile intermediate for various transformation,[61,62] the ready-removability of the Boc-group is also beneficial. For example, a primary amide **64** was readily obtained by deprotection of the Boc-group using trifluoroacetic acid (TFA) (84%). In addition, *N*-alkylation of the obtained amide **51** was performed under mild conditions, which was enabled presumably by the increased acidity of the NH bond. Treatment of **51** with benzyl or bio-relevant citronellyl bromide, followed by deprotection, furnished secondary amides **65** and **66**, respectively. These versatile modifications showcased that our strategy can be applied for accessing distinctive amides via alternative retrosynthetic C–N bond disconnections.

Mechanistic Investigations

With proven synthetic values, we carried out further investigations to corroborate the proposed reaction mechanism. The reaction progress via photoexcitation of aldehyde could be excluded, as it has been well established that aldehydes or related carbonyl compounds require higher-energy light (UV) to get excited to the triplet state.[63–65] Furthermore, the photo-reaction of **1a** with an equal mixture of benzoyl chloride **4** and *p*-tolualdehyde afforded an amide product **6** and an acid chloride **67** via a crossover chlorine transfer (Figure 6). Notably, the direct amidation of *p*-tolualdehyde was not observed, indicating that the proposed relay process induced by the reaction with *in situ* generated acid chloride would likely be the reaction pathway.

To realize how acid chloride is initially formed, we turned our attention to the role of a carboxylic acid additive in reactions with aliphatic aldehydes. Interestingly, when *N*-sodio salt **1a** was treated with a stoichiometric amount of benzoic acid, the protonated carbamate **1b** was obtained in 82% (Figure 7A). The reaction of **1b** with 1-heptanal under the standard conditions resulted in the formation of carbamate **2** and heptanoyl chloride **68** at poor yields, but no amidation product was formed. These outcomes indicated that the protonated carbamate **1b**, which is generated in a small amount with the aid of benzoic acid additive, or presumably by moisture

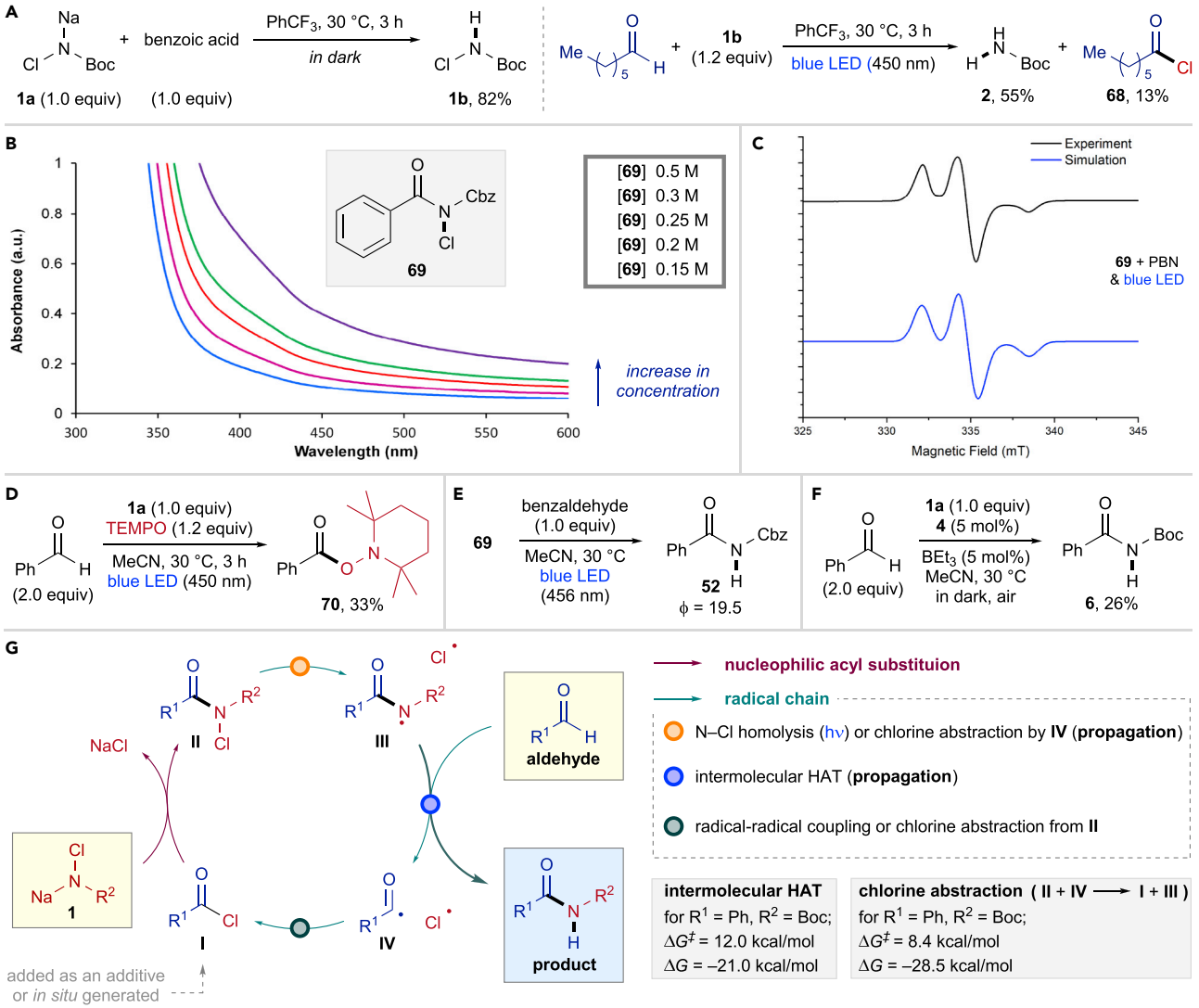

Figure 7. Mechanistic Investigations

(A) The role of benzoic acid additive.

(B) UV-vis spectra of *N*-chloroamide **69**.

(C) Experimental (black) X-band EPR spectrum of a mixture of **69** and a spin-trapping reagent (PBN) in benzene measured at 100 K after irradiation with Blue LED (456 nm) and simulated (blue) EPR spectrum; simulation parameters: g = [2.0068 2.0073 2.0021], A = [19 0 89]; see also Figure S5.

(D) Radical trap experiment with 2,2,6,6-tetramethylpiperidin-1-yl (TEMPO).

(E) Measurement of the quantum yield for the product formation from **69**.

(F) Control experiment using the combination of BEt_3 and air as a radical initiator.

(G) Proposed relay cycle and DFT calculations.

in the case of additive-free conditions, would act as a radical chlorinating reagent to convert a sacrificial amount of aldehyde to acid chloride. The relay process would then be commenced by its reaction with *N*-chloro-*N*-sodio-carbamate salt **1**.

The feasibilities of the rest of the relay steps were already discussed and shown in Figure 2C. To further support the experimental evidence, the photoactivity of *N*-chloroamide intermediate was first affirmed by ultraviolet-visible (UV-vis) absorption spectra of *N*-chloroamide **69**, which showed absorption bands tailing into the visible region (Figure 7B). Upon the absorption of light, we proposed that the N–Cl bond of

the *N*-chloroamide intermediate would be homolytically cleaved to initiate radical chains, and this photolytic pathway was investigated by electron paramagnetic resonance (EPR) spectroscopy. The X-band EPR spectrum of an irradiated solution of **69** in benzene did not yield a characteristic signal of N-centered radical, presumably due to the short lifetime of such species. On the other hand, signals corresponding to a spin adduct (persistent nitroxide radical) were obtained by spin-trapping[66] with α-phenyl *N*-*tert*-butyl nitrone (PBN), which is indicative of radical generation from the photo-conversion of **69** (Figure 7C). The homolytic nature of N–Cl cleavage could be further confirmed by a radical trap experiment with 2,2,6,6-tetramethylpiperidin-1-yl (TEMPO), which afforded a TEMPO adduct **70** as the only product, probably via the translocation of N to C radical (HAT) and subsequent trap with TEMPO (Figure 7D).

Moreover, the quantum yield for the product formation from **69** (Φ = 19.5) proved that chain reactions are operative in certain extents in these radical processes (Figure 7E),[67] indicating that N-centered radical can also be formed via radical propagation (chlorine abstraction). Control experiments also verified the association of such chain reactions that can be initiated by organoborane as an alternative radical initiator (Figure 7F),[68] even though the low conversion suggested that the involved propagations are likely to be short chains with the participation of radical termination. In our photo-system, constant irradiation of visible light ensures that the terminated process would be persistently reinitiated, thereby contrarily giving excellent efficiency. The possibilities of propagation reactions were additionally supported by the density functional theory (DFT) calculations (Figure 7G, bottom right), in which both HAT and chlorine abstraction processes for benzaldehyde substrate were computed to be exergonic by –21.0 and –28.5 kcal/mol, respectively, with low activation barriers of 12.0 and 8.4 kcal/mol.

With these results, we summarize the reaction mechanism in Figure 7G. The photochemical stability of **1** combined with its low capability for direct N–Cl homolysis prevents undesired side reactions such as oxidation and aromatic chlorination,[55,56] while its partially protonated form gives rise to acid chloride **I** as kinetically competent species to trigger the relay process. The photoactive radical source **II** is formed by the reaction between acid chloride **I** and the amidating reagent **1**, followed by a series of radical reactions involving imidyl radical **III** and acyl radical **IV** to produce the amide product. Acid chloride **I** is further generated either by radical propagation (chlorine abstraction) or radical termination (radical-radical coupling). An interesting mechanistic feature of this strategy is that, unlike the conventional radical chain reactions, the substrate itself is not the radical precursor. One of the end products from the chain reactions (**I**) is transformed to the starting radical source (**II**) by a cascade C–N bond formation, thus rendering this relay process iterated in a highly efficient and controllable fashion by slow incorporation of the radical precursor.

Conclusions

In conclusion, a new reaction model has been developed for controllable access to N-centered radicals, which enabled the conversion of aldehydes to amides under visible light conditions with *N*-chloro-*N*-sodio-carbamates as the amidating reagent. A broad range of (hetero)aromatic and aliphatic aldehydes could be employed, delivering synthetically useful N-protected amides under extremely mild conditions with high functional group tolerance. The virtue of this methodology has been demonstrated by successful applications on biologically relevant compounds, and the post-modification of obtained products to diverse amide analogs. The reaction was revealed to proceed via an unprecedented relay process, whereby highly efficient radical chain reactions are

enabled by the controlled *in situ* generation of a photoactive radical precursor via C–N bond formation. The distinct features in the reaction mechanism, along with the synthetic advantages accomplished by low waste generation and excellent applicability, should allow the developed protocol to find widespread applications in both academic and industrial research. Expansion of this chemistry to other types of transformations is currently under investigation in our laboratory.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Sukbok Chang (sbchang@kaist.ac.kr).

Materials Availability

All unique reagents generated in this study are available from the Lead Contact without restriction.

Data and Code Availability

Crystallographic data generated during this study have been deposited in the Cambridge Crystallographic Data Centre (CCDC) under accession numbers CCDC: 1983504 (**32**), 1983505 (**62**), 1983506 (**63**), and 2011508 (**1a**). These data can be obtained free of charge from the CCDC at http://www.ccdc.cam.ac.uk/data_request/cif.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.12.004.

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AUTHOR CONTRIBUTIONS

S.S. and S.C. conceived, designed, and organized the project. W.L. and H.J.J. performed and analyzed all experiments for reaction optimization, scope, synthetic application, and mechanistic investigations. W.L. and H.J. conducted the DFT calculations. D.K. analyzed the X-ray crystal structures. S.S. and S.C. wrote the manuscript. All authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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