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Visible-Light-Induced Aminochlorination of Alkenes

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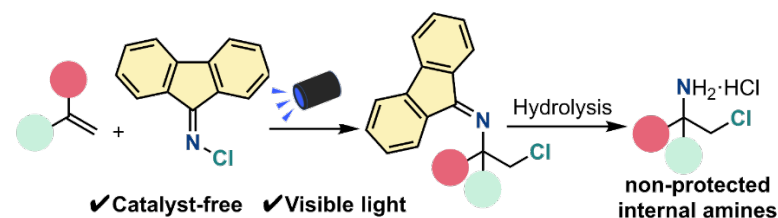
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Supporting Information Placeholder



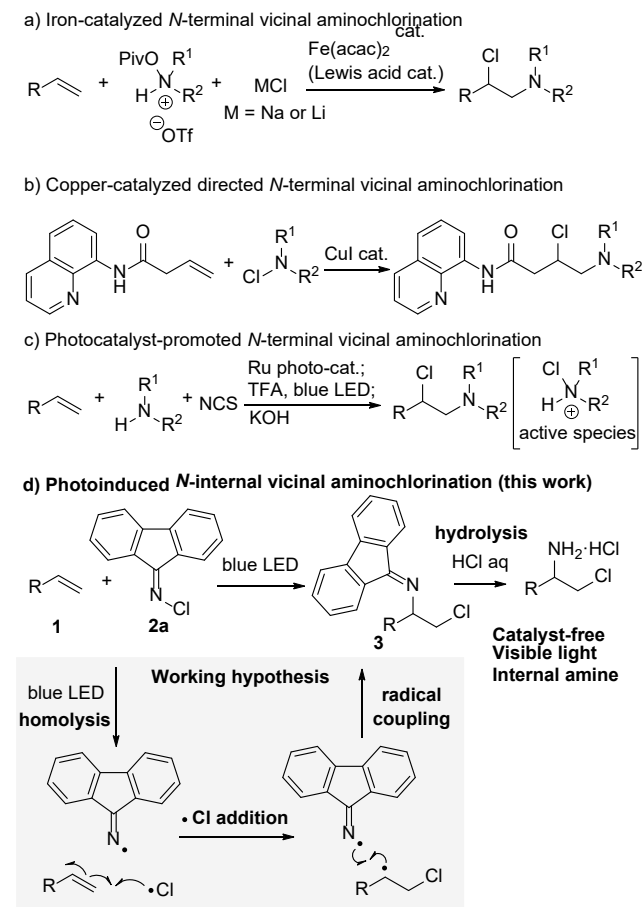
ABSTRACT: Photoinduced *N*-internal vicinal aminochlorination of styrene-type terminal alkenes was developed. The reaction proceeded without any catalyst, and the use of *N*-chloro(flourenone imine) as both a photoactivatable aminating agent and a chlorinating agent was essential. The imine moiety, introduced at the internal position of the alkenes, could be hydrolyzed under mild conditions to provide versatile β -chlorinated primary amines, the synthetic utility of which was demonstrated by several transformations.

Nitrogen-containing molecules are ubiquitous in natural products and artificial functional molecules. Hence, the development of a useful reaction that enables installation of nitrogen atoms on simple and readily available feedstock materials to provide valuable building blocks has been a long-standing research subject in synthetic organic chemistry. Vicinal chloroamines are attractive targets that serve as competent platform compounds, taking advantage of the reactivity of the alkyl chloride moiety.¹ One of the most powerful methods for preparing vicinal chloroamines is the aminochlorination of readily available alkenes.² Important progress toward this transformation has been made in the past decade with metal catalysts³ and photocatalysts.⁴ Nevertheless, the nitrogen sources for the reaction have been mostly limited to those leading to protected amines, which are difficult to deprotect under mild reaction conditions. Hence, a mild and convenient method for aminochlorination of alkenes giving non-protected amines or amines with readily cleavable *N*-protecting groups is highly demanded. In this

context, Morandi reported an iron-catalyzed aminochlorination of alkenes affording non-protected vicinal chloroamines (Scheme 1a).⁵ An *O*-pivaloylhydroxyamine and an alkali metal chloride were used as nitrogen and chlorine sources, respectively. Guan, Bi, and Fu employed *N*-chloroamines as both nitrogen and chlorine sources for copper-catalyzed aminochlorinations directed by an 8-aminoquinoline amide group (Scheme 1b).⁶ Leonori developed a photoinduced aminochlorination with direct use of various amines (Scheme 1c).⁷ An *in situ* generated protonated *N*-chloroamine reagent acted as the active species in this reaction. These reactions all introduce a nitrogen atom at the terminal position. A vicinal aminochlorination installing an amino group at the internal position was achieved using electrophilic *N*-chloroamine-based reagents. However, the protecting groups on the nitrogen atom were difficult to remove.⁸ Herein, we report visible-light-induced aminochlorination of styrene-type alkenes with a fluorenone-derived *N*-chloroimine reagent⁹ (Scheme 1d). An imino group was

introduced at the internal position of the alkene, and the hydrolysis of the imine moiety proceeded under mild conditions to give the corresponding primary amine. Importantly, no catalyst was required, and the reaction was promoted only by visible light irradiation.

Scheme 1. Various aminochlorinations of alkenes for the preparation of non-protected amines

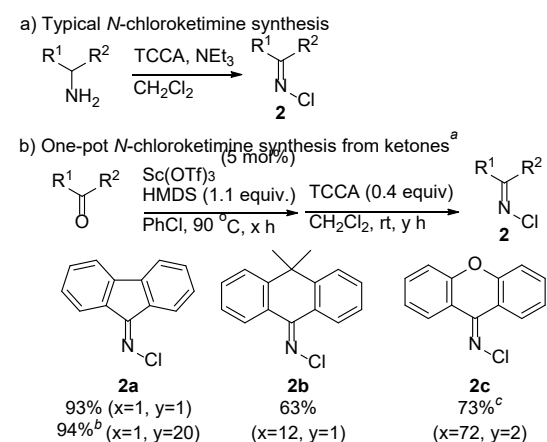


Our reaction design for the *N*-internal vicinal aminochlorination of terminal alkenes is as follows. An *N*-chloroimine prepared from an aromatic ketone with an extended π -system would be photoexcited by visible light irradiation. Subsequent homolysis of the N–Cl bond via the excited state of the *N*-chloroimine would enable simultaneous generation of an *N*-centered iminyl radical and a Cl radical. Since simple alkenes are prone to react with electrophilic radicals, the highly electrophilic Cl radical would react preferentially in the presence of the nucleophilic *N*-centered iminyl radical.¹⁰ The Cl radical addition would proceed at the terminal position of the alkene rather than the internal position, generating a stable internal carbon radical. The carbon radical would couple with the *N*-centered iminyl radical to furnish the internal amine product. Finally, hydrolysis of the installed imine moiety would occur under mild conditions to provide the corresponding primary amine.¹¹

Since the synthesis of *N*-chloroimines relies on the oxidation and chlorination of the corresponding free amines (Scheme 2a),¹² structural diversity was limited by the

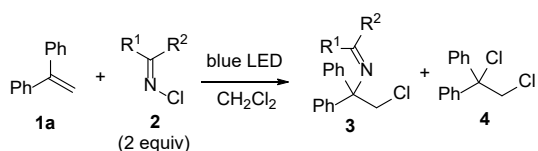
availability of the amines. To have a broad scope of the *N*-chloroimines, we envisaged their synthesis from readily available ketones via the formation of unprotected imines followed by *N*-chlorination. With this in mind, a new method for the synthesis of fluorenone-derived *N*-chloroimine **2a** was developed. Thus, Sc(OTf)₃-catalyzed imine formation using hexamethyldisilazane (HMDS, 1.1 equiv) as a nitrogen source¹³ was followed by *N*-chlorination with 0.4 equivalent of trichloroisocyanuric acid (TCCA) to afford *N*-chloro(fluorenone imine) **2a** in 93% yield in a one-pot process (Scheme 2b). Scale-up to 10 mmol was possible without a decrease in the yield, albeit with a longer reaction time for the *N*-chlorination step. Dimethylantracene was also reactive to afford **2b** in 63% yield. Although xanthone was less reactive than fluorenone and dimethylantracene, the corresponding *N*-chloroimine (**2c**) was obtained in good yield by stirring for 72 h at 110 °C with 2 equiv of HMDS for imine formation and subsequent *N*-chlorination using 0.7 equiv of TCCA.

Scheme 2. Synthetic methods for *N*-chloroimines

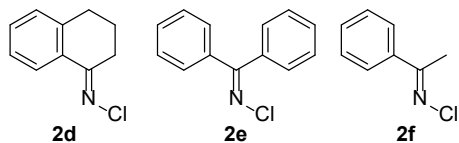


^aKetone (1 mmol), Sc(OTf)₃ (0.05 mmol), HMDS (1.1 mmol), PhCl (1 mL), 90 °C; TCCA (0.4 mmol), CH₂Cl₂, room temperature. ^b10 mmol scale. ^cHeated to 110 °C in a sealed tube with HMDS (2.0 mmol) for imine formation, with TCCA (0.7 mmol) for *N*-chlorination.

Next, vicinal aminochlorination was investigated with 1,1-diphenylethylene as an alkene substrate under blue LED irradiation (Table 1). Photolabile *N*-chloro(fluorenone imine) (**2a**)⁹ provided desired vicinal aminochlorination product **3a** in 64% yield along with vicinal dichlorination product **4a** in 17% yield (entry 1). In addition, a fluorenone azine was detected in the crude mixture, suggesting the generation of *N*-centered iminyl radical. On the other hand, anthracene-type (**2b**) and xanthone-type (**2c**) *N*-chloroimines were barely reactive, giving **3b** and **3c**, respectively, in low yields (entries 2 and 3). A bicyclic derivative, *N*-chloro(tetralone imine) **2d**, also showed low reactivity, giving **3a** in only 16% yield (entry 4). *N*-Chloroimines with flexible carbon frameworks, such as benzophenone-type (**2e**) and acetophenone-type (**2f**) *N*-chloroimines, were totally unreactive (entries 5 and 6).

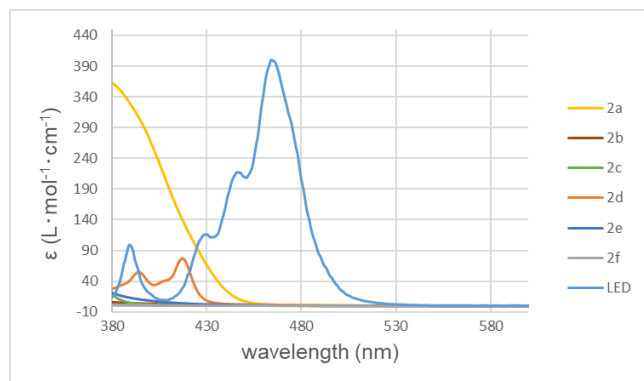
Table 1. Optimization of aminochlorination.^a

entry	2	yield (%) of 3	yield (%) of 4
1	2a	64	17
2	2b	13	9
3	2c	8	10
4	2d	16	5
5	2e	0	0
6	2f	0	0



^a**1a** (0.1 mmol), **2** (0.2 mmol), CH₂Cl₂ (0.05 M), blue LED, 12 h. Yields were determined by ¹H NMR analysis using tetrachloroethane as an internal standard.

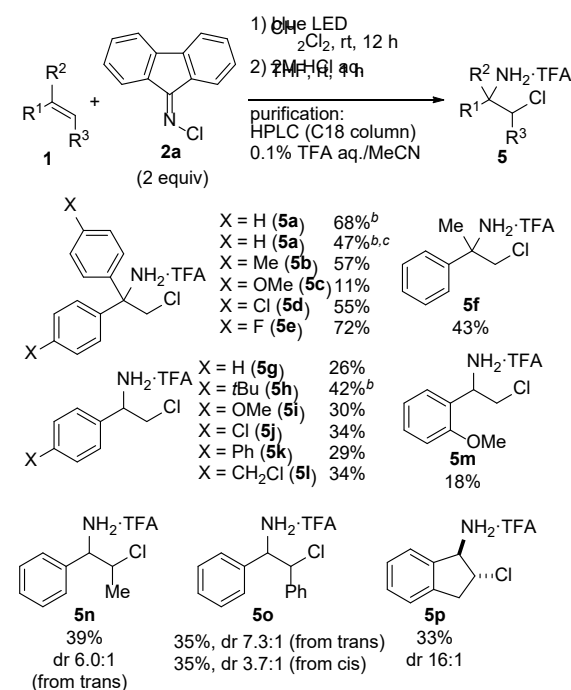
The critical effect of the fluorene scaffold of *N*-chloroimine was ascribed to its photo-absorption ability. In fact, the UV-Vis spectrum of **2a** showed significant absorption in the blue LED emission range, while those of the other *N*-chloroimines showed much less or no absorption in the same region (Figure 1).

Figure 1. UV-Vis spectra of 2 and emission spectra of blue LED^a

^aUV-Vis spectra of **2** in CH₂Cl₂ (3 mM).

Using **2a** as the optimum aminochlorination reagent, the scope of alkenes was investigated (Scheme 3). After the photoinduced aminochlorination, crude materials were hydrolyzed to the corresponding primary amine·HCl salts. When necessary, purification was conducted using a reversed-phase (C18) HPLC column under 0.1% aq. TFA/MeCN eluent conditions to provide the products as TFA salts. The product **5a** derived from 1,1-diphenylethylene **1a** was isolated without HPLC purification in 68% yield as the HCl salt. The reaction at the 1 mmol scale proceeded in 47% yield. Although a 4-methyl substituent on the

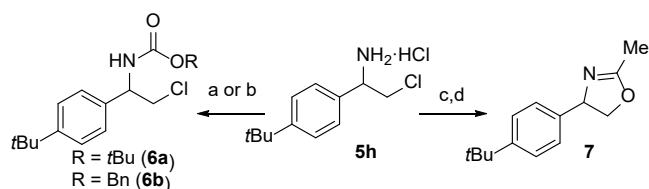
benzene ring was tolerated (**5b**, 57% yield), an electron-donating 4-methoxy substituent significantly decreased the yield (**5c**, 11% yield). *p*-Chloro and fluoro substituents were competent to afford the corresponding products in good yields (**5d**, 55% yield; **5e**, 72% yield). α -Methylstyrene **1f** also reacted to give **5f** in 43% yield. Aminochlorination of monoaryl styrene derivatives also proceeded under the reaction conditions albeit with generally lower yields. The reaction tolerated various substituents at the *para* position of the aryl group including electron-donating *tert*-butyl (**5h**, 42% yield) and methoxy (**5i**, 30% yield) groups, electron-deficient chloro (**5j**, 34% yield) and phenyl (**5k**, 29% yield) groups, and a potentially reactive chloromethyl group (**5l**, 34% yield). On the other hand, an *ortho*-methoxy substituent (**5m**) decreased the yield to 18%. Methyl or phenyl substituents at the β -position of the styrene were compatible, affording the products with moderate diastereoselectivities (**5n**, 39% yield, dr 6.0:1; **5o**, 35% yield, dr 7.3:1 from *trans*-stilbene and 3.7:1 from *cis*-stilbene). A cyclic substrate, indene **1p**, afforded the product **5p** with high *trans*-selectivity (33% yield, dr 16:1). However, when allylbenzene was used as an aliphatic alkene, only trace amount of the product was observed.

Scheme 3. Substrate Scope

^a**1** (0.3 mmol), **2** (0.6 mmol), CH₂Cl₂ (0.05 M), blue LED, 12 h. Yields of isolated products. ^bIsolated as HCl salt without HPLC purification. ^c1 mmol scale.

To assess the reactivity of the obtained aminochlorination products, transformations of **5h** were examined (Scheme 4). First, Boc and Cbz groups were introduced to the nitrogen atom in good yields without affecting the C-Cl bond. Second, an oxazoline (**7**) was produced by a two-step acylation-cyclization procedure in 59% overall yield.

Scheme 4. Transformations of chloroamine 5h

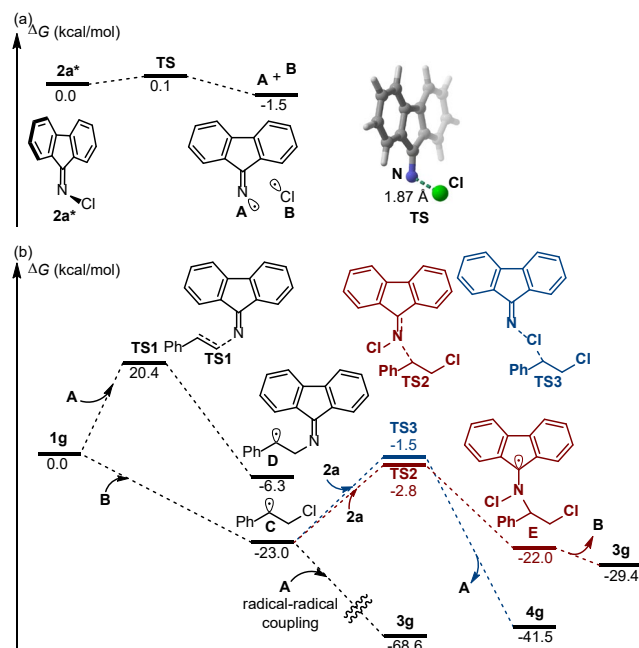


^aBoc₂O (2 equiv), NEt₃ (2.2 equiv), CH₂Cl₂, rt, 17 h, 72% yield; ^bCbzCl (2 equiv), NaHCO₃ (2 equiv), THF, 0 °C, 15 min, 55% yield; ^cAc₂O (3 equiv), NEt₃ (3.5 equiv), THF, rt, 1.5 h, 74% yield; ^dNEt₃ (2 equiv), TBAI (0.5 equiv), THF, 80 °C, 7 h, 80% yield.

To obtain mechanistic insights, DFT calculations were performed using the Gaussian 16 C.01 package¹⁴ at the U ω B97X-D/6-31+G(d,p)/SMD(DCM) level of theory (Figure 2). First, the photoinduced N–Cl scission was assessed (Figure 2a). The N–Cl bond of the optimized structure of triplet state **2a***, which would be generated through photoexcitation and intersystem crossing, is oriented perpendicular to the π -plane of the fluorene backbone. The N–Cl homolysis from **2a*** proceeded through **TS** as an essentially barrierless process (0.1 kcal/mol), and an *N*-centered iminyl radical (**A**) and a chlorine radical (**B**) were generated in a slightly exergonic process (–1.5 kcal/mol relative to **2a***).

The addition of the Cl radical (**B**) to styrene (**1g**) proceeds in a barrierless manner to produce chloromethylated benzyl radical (**C**), while the addition of the iminyl radical (**A**) requires 20.4 kcal/mol to afford an aminomethylated benzyl radical (**D**) (Figure 2b). The requirement of higher energy for the iminyl radical addition than that for the Cl radical addition is consistent with our reaction design, in which the electrophilic Cl radical was expected to react preferentially in the presence of the nucleophilic *N*-centered iminyl radical. For the subsequent process, we examined two pathways that incorporate the imine moiety at the benzylic position. One is radical-radical coupling between the benzyl radical **C** and the iminyl radical **A** to produce **3g** in a highly exergonic manner. For this process, we failed to locate a transition state as expected due to the general difficulty of computations for radical-radical coupling processes. The other possibility is attack of the radical center of **C** at the nitrogen atom of **2a**. The corresponding transition state (**TS2**) is 20.2 kcal/mol higher in Gibbs free energy relative to **C**, and subsequent elimination of the Cl radical (**B**) proceeds via a transient fluorenyl radical (**E**) to propagate a radical chain process. It should be noted that the addition of **C** to **2a** can happen at the Cl atom to produce **4g** through **TS3** (1.3 kcal/mol higher in Gibbs free energy relative to **TS2**). Since vicinal dichloride side product **4g** was obtained in meaningful amounts in the experiments, the C–Cl bond formation process at the benzylic position should be competitive with the C–N bond formation process. Although the radical chain process requires higher energy than the radical-radical coupling process, the former process cannot be excluded considering that **2a** was present in much higher concentration than iminyl radical (**A**).

Figure 2. Energy diagrams for (a) radical generation and (b) radical addition to styrene.



In summary, we have developed an *N*-internal vicinal aminochlorination of terminal alkenes using *N*-chloro(fluorenone imine) as both aminating and chlorinating agents. The reaction does not require any catalyst, and only visible-light irradiation is necessary for the reaction. This simple protocol introduces an imine moiety at the internal position exclusively and affords the corresponding free primary amines after imine hydrolysis under mild conditions. Functionalization of the amino group and transformation of the alkyl chloride moiety were possible, demonstrating the potential utility of the products.

ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and NMR spectra (PDF)

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 7, pp 469–513.
(2) (a) Chemler, S. R.; Bovino, M. T. Catalytic Aminohalogenation of Alkenes and Alkynes. *ACS Catal.* **2013**, *3*, 1076–1091. (b) Wu, Z.; Hu, M.; Li, J.; Wu, W.; Jiang, H. Recent Advances in Amination Difunctionalization of Alkenes. *Org. Biomol. Chem.* **2021**, *19*, 3036–3054.
(3) (a) Cai, Y.; Liu, X.; Jiang, J.; Chen, W.; Lin, L.; Feng, X. Catalytic Asymmetric Chloroamination Reaction of α,β -Unsaturated γ -Keto Esters and Chalcones. *J. Am. Chem. Soc.* **2011**, *133*, 5636–5639. (b) Arteaga, G. C.; Saavedra-Olavarría, J.; Almendras, S.; Hermosilla-Ibáñez, P.; Almodovar, I.; Pérez, E. G. Copper-Catalyzed Intermolecular Aminochlorination of Alkenes. *Tetrahedron Lett.* **2018**, *59*, 1091–1093. (c) Li, Q.; Shi, M.; Timmons, C.; Li, G. FeCl_3 -Catalyzed Aminochlorination of Arylmethylenecyclopropanes and Arylvinylidenecyclopropanes and Corresponding Mechanistic Studies. *Org. Lett.* **2006**, *8*, 625–628. (d) Zhu, C.-L.; Tian, J.-S.; Gu, Z.-Y.; Xing, G.-W. Xu, H. Iron(II)-Catalyzed Asymmetric Intramolecular Olefin Aminochlorination using Chloride Ion. *Chem. Sci.* **2015**, *6*, 3044–3050. (e) Brogini, G.; Beccalli, E. M.; Borelli, T.; Brusa, F.; Gazzola, S.; Mazza, A. Intra-Intermolecular Palladium-Catalyzed Domino Reactions of Glycine Allylamides for the Synthesis of Diversely Functionalized Piperazinones. *Eur. J. Org. Chem.* **2015**, 4261–4268.
(4) (a) Qin, Q.; Ren, D.; Yu, S. Visible-light-promoted Chloroamination of Olefins with *N*-chlorosulfonamide as Both Nitrogen and Chlorine Sources. *Org. Biomol. Chem.* **2015**, *13*, 10295–10298. (b) Mo, J.-N.; Yu, W.-L.; Chen, J.-Q.; Hu, X.-Q.; Xu, P.-F. Regiospecific Three-Component Aminofluorination of Olefins via Photoredox Catalysis. *Org. Lett.* **2018**, *20*, 4471–4474.
(5) (a) Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. Efficient Access to Unprotected Primary Amines by Iron-Catalyzed Aminochlorination of Alkenes. *Science* **2018**, *362*, 434–439. (b) Falk, E.; Makai, S. Decaillau, T.; Gürtler, L.; Morandi, B.

Desing and Scalable Synthesis of *N*-Alkylhydroxylamine Reagents for the Direct Iron-Catalyzed Installation of Medicinally Relevant Amines. *Angebot. Chem. Int. Ed.* **2020**, *59*, 21064–21071.

(6) Li, Y.; Liang, Y.; Dong, J.; Deng, Y.; Zhao, C.; Su, Z.; Guan, W.; Bi, X.; Liu, Q.; Fu, J. Directed Copper-Catalyzed Intermolecular Amination Difunctionalization of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 18475–18485.

(7) Gavaerts, S.; Angelini, L.; Hampton, C.; Malet-Sanz, L.; Ruffoni, A.; Leonori, D. Photoinduced Olefin Di-amination with Alkylamines. *Angew. Chem. Int. Ed.* **2020**, *59*, 15021–15028.

(8) (a) Song, Lu.; Luo, S.; Cheng, J.-P. Visible-light Promoted Intermolecular Halofunctionalization of Alkenes with *N*-halogen Saccharins. *Org. Chem. Front.* **2016**, *3*, 447–452. (b) Pu, X.-Q.; Zhao, H.-Y.; Lu, Z.-H.; He, X.-P.; Yang, X.-J. Aminochlorination of Alkenes with CFBSA. *Eur. J. Org. Chem.* **2016**, 4526–4533. (c) Martínez, C.; Muñoz, K. A Versatile Metal-Free Intermolecular Aminochlorination of Alkenes. *Adv. Synth. Catal.* **2014**, *356*, 205–211. (d) Zhu, N.; Li, Y.; Bao, H. Metal-Free Intermolecular Aminochlorination of Unactivated Alkenes. *Org. Chem. Front.* **2018**, *5*, 1303–1307.

(9) Pinck, L. A.; Hilbert, G. E. Preparation and Decomposition of 9-Fluorylchloramines. *J. Am. Chem. Soc.* **1947**, *69*, 470–471.

(10) Pratley, C.; Fenner, S.; Mrphy, J. A. Nitrogen-Centered Radicals in Functionalization of sp^2 Systems: Generation, Reactivity, and Applications in Synthesis. *Chem. Rev.* **2022**, *122*, 8181–8260.

(11) (a) Patra, T.; Das, M.; Daniliuc, C. G.; Glorius, F. Metal-Free Photosensitized Oxymination of Unactivated Alkenes with Bifunctional Oxime Carbonates. *Nat. Catal.* **2021**, *4*, 54–61. (b) Li, J.; Yuan, Y.; Bao, X.; Sang, T.; Yang, J.; Huo, C. Visible-Light-Induced Intermolecular Oxymination of Alkenes. *Org. Lett.* **2021**, *23*, 3712–3717. (c) Tan, G.; Paulus, F.; Rentería-Gómez, Á.; Lalis, R. F.; Daniliuc, C. G.; Gutierrez, O.; Glorius, F. Highly Selective Radical Relay 1,4-Oxymination of Two Electronically Differentiated Olefins. *J. Am. Chem. Soc.* **2022**, *144*, 21664–21673. (d) Tan, G.; Das, M.; Keum, H.; Bellotti, P.; Daniliuc, C.; Glorius, F. Photochemical Single-Step Synthesis of β -Amino Acid Derivatives from Alkenes and (Hetero)arenes. *Nat. Chem.* **2022**, *14*, 1174–1184. (e) Patra, T.; Bellotti, P.; Strieth-Kalthoff, F.; Glorius, F. Photosensitized Intermolecular Carboamination of Alkenes through the Persistent Radical Effect. *Angew. Chem. Int. Ed.* **2020**, *59*, 3172–3177.

(12) (a) Luca, L. D.; Giacomelli, G. An Insight of the Reactions of Amines with Trichloroisocyanuric Acid. *Synlett* **2004**, 2180–2184. (b) Qi, B.; Li, L.; Wang, Q.; Zhang, W.; Fang, L.; Zhu, J. Rh(III)-Catalyzed Coupling of *N*-Chloroimines with α -Diazo- α -phosphonoacetates for the Synthesis of 2*H*-Isoindoles. *Org. Lett.* **2019**, *21*, 6860–6863.

(13) (a) Kondo, Y.; Kadota, T.; Hirazawa, Y.; Morisaki, K.; Morimoto, H. Ohshima, T. Scandium(III) Triflate Catalyzed Direct Synthesis of *N*-Unprotected Ketimines. *Org. Lett.* **2020**, *22*, 120–125. (b) Kondo, Y.; Hirazawa, Y.; Kadota, T.; Yamada, K.; Morisaki, K.; Morimoto, H.; Ohshima, T. One-Pot Catalytic Synthesis of α -Tetrasubstituted Amino Acid Derivatives via In Situ Generation of *N*-Unsubstituted Ketimines. *Org. Lett.* **2022**, *24*, 6594–6598.

(14) Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallin
