Organic Letters

Synthesis of Alkyl Halides from Aldehydes via Deformylative Halogenation

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Supporting Information

ABSTRACT: An unprecedented deformylative halogenation of aldehydes to alkyl halides is presented. Under oxidative conditions, 1,4-dihydropyridine (DHP), derived from an aldehyde, generated a C(sp3)- radical that coupled with a halogen radical that was generated from inexpensive and atom-economical halogen sources (NaBr, NaI, or HCl), to yield an alkyl halide. Because of the mild conditions, a wide range of functional groups were tolerated, and excellent site selectivity was achieved.



H alogenated organic compounds are ubiquitous in organic chemistry.¹ They not only play significant roles as synthetic intermediates and building blocks in organic transformations such as cross-coupling reactions and nucleophilic substitutions,² but they are also versatile precursors for most organometallic species, including Grignard, organozinc, and organocuprate reagents.³ Halogenated organic compounds have also been used as essential designer molecules in the pharmaceutical,⁴ agrochemical,⁵ and material science applications.⁶ Their syntheses have been carried out through substitutions,⁷ Markovnikov additions,⁸ and less common radical-based protocols⁹ such as the Hunsdiecker reaction¹⁰ and its variations.¹¹

Recently, the use of visible light as an efficient, clean, and inexpensive energy source for radical-based organic synthesis has received much attention.¹² However, halogenations using photocatalysis are very rare.¹³ In particular, the chlorination or bromination of arenes was usually restricted to electron-rich substrates,¹⁴ while the construction of alkyl chloride or bromide faced more challenges such as controlling site selectivity, choice of appropriate substrates, and halogen sources.¹⁵ Nicewicz and co-workers reported a photocatalyzed *anti*-Markovnikov hydrochlorination of styrenes.¹⁶ They utilized the stable benzylic radical to initiate the photoredox reaction and achieve the site-selective installation of chlorine, but only styryl substrates were showcased (Scheme 1a). The Glorius' group reported a Hunsdiecker decarboxylative halogenation strategy using diethyl bromomalonate, NCS, and NIS as halogen sources under photoirradiation (Scheme

1b).¹⁷ Alexanian and co-workers designed an amide-based halogenating reagent for aliphatic C–H halogenation (Scheme 1c).¹⁸

This protocol exhibited predominant δ -selectivity, but the formation of other regioisomers was also observed, in yields ranging from 18% to 46%. Roizen and co-workers reported a γ -selective intramolecular chlorination which required preinstallation of a chlorine-directing group, sulfamate ester (Scheme 1d).¹⁹

Aldehydes are among the most common functionalities in synthesis, and they are starting materials for a variety of organic transformations, among which deformylative transformation has significant synthetic value because it can integrate onecarbon degradation and further functionalization in a single step. However, such strategies are rare.²⁰ The reported methods relied on the generation of an acyl radical through hydrogen-atom transfer (HAT), followed by CO extrusion to form an alkyl radical for further functionalization. But the dissociation of an acyl radical to generate an alkyl radical is a high energy process, and acylated products are more commonly observed.²¹ An alternative is an oxidative process followed by elimination of CO₂ to furnish a one-carbon-shorter alkyl radical;²² however, the use of strong and stoichiometric oxidants is not desirable in synthesis. Recently, 1,4dihydropyridines (DHP)-easily prepared from aldehydes under neutral redox conditions-have been used in

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Scheme 1. Major Photoinduced Synthetic Methods for Alkyl Halides



deformylative transformations.²³ Its robustness allows for a wide range of structural derivatizations (see Supporting Information (SI)). Under photoirradiation, DHPs undergo homolysis to generate $C(sp^3)$ -centered alkyl radicals, which can be employed for further radical coupling reactions. However, these coupling reactions were primarily used in the construction of C–C bonds. Herein we report the first photoredox-catalyzed deformylative halogenation strategy to achieve the transformation of aldehydes to alkyl halides using readily available, inexpensive, and atom-economical NaBr and HCl as halogen sources. In addition, we have successfully developed a photocatalyst-free deformylative iodination using NaI as a halogen source (Scheme 1).

First, we established the conditions for the deformylative bromination using DHP 1a as the substrate (Table 1). After extensive screening, the optimized conditions furnished the desired brominated product 2a in 98% yield without the formation of the regioisomer derived from the more stable benzylic radical (Table 1, entry 1). H₂O was important to dissolve salts and achieve better yields (Table 1, entries 2-3). Other commonly used photocatalysts (B-D) exhibited lower efficacy (Table 1, entries 4-6). The use of organo-oxidants DTBP and TBN or the lack of an oxidant led to poor yields or no reaction (Table 1, entries 7-9). The yield was dramatically decreased when only half the amount of NaBr was used (Table 1, entry 10). Both blue LED irradiation and photocatalyst A were crucial to produce 2a in higher yields (Table 1, entries 11-13). A low yield was obtained when this reaction was conducted under air (Table 1, entry 14).

With the optimized conditions established, we proceeded to evaluate the scope of the deformylative bromination process. As shown in Scheme 2, a myriad of DHPs were suitable substrates, giving the corresponding brominated products in good to excellent yields. Notably, no regioisomeric products were observed even when active benzylic positions were available (2a-2c). A diverse range of functional groups were well tolerated, such as hydroxyl, ether, ester, ketone, aldehyde,

Table 1. Optimization of Visible-Light-MediatedDeformylative Bromination of $1a^a$

X	NaBr (3 equiv) K ₂ S ₂ O ₈ (1.5 equiv) Ru(bpy) ₃ Cl ₂ ·6H ₂ O (1 mol %) (A) MeCN/H ₂ O (v/v=9/1), blue LEDs, rt, 24 h	2a
entry	variations from the standard conditions	yield (%) ^b
1	none	98
2	$MeCN/H_2O(v/v = 1/1)$	89
3	MeCN	9
4	B instead of A	13
5	C instead of A	53
6	D instead of A	9
7	DTBP instead of K ₂ S ₂ O ₈	0
8	TBN instead of K ₂ S ₂ O ₈	11
9	Without K ₂ S ₂ O ₈	0
10	NaBr (1.5 equiv)	16
11	CFL as a light source	47
12	no light	0
13	without A	18
14	under air	17

^{*a*}Reaction conditions: **1a** (0.1 mmol), NaBr (0.3 mmol), $K_2S_2O_8$ (0.15 mmol), **A** (1 mol %), MeCN/H₂O (v/v = 9/1) [0.2 M], blue LEDs, rt, 24 h, Ar atmosphere. ^{*b*}Yields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.**A** = Ru(bpy)₃Cl₂· 6H₂O, **B** = Ir(ppy)₃, **C** = Eosin Y (Green LEDs), **D** = 9-Mesityl-10-methylacridinium perchlorate, DTBP = Di-*tert*-butyl peroxide, TBN = *tert*-butyl nitrite.





^aReaction conditions: as in Table 1 (entry 1); isolated yields.

thioether, nitro, and nitrile groups (2d-2m). Heterocyclic compounds such as furan (2n), thiophene (2o), thiazole (2p), benzotriazole (2q), indole (2r), and *N*-Boc-piperidine (2s) were suitable substrates. Benzylic DHPs also succeeded in delivering the brominated products in good yields (2t-2x).

Once the versatility of the deformylative bromination was demonstrated, we focused our attention on deformylative chlorination. Our newly developed HCl/DMPU^{24,8b} was superior to other inorganic chloride salts (Table 2, entries 1-7), while Ir(ppy)₃ (**B**) was a more efficient photocatalyst

Table 2. Screening of Chlorine Source and Photocatalyst for Deformylative Chlorination of $1a^a$

	1a	3a		
entry	[Cl]	photocatalyst	yield (%) ^b	
1	LiCl	А	37	
2	NaCl	Α	31	
3	KCl	А	16	
4	CsCl	А	22	
5	NH ₄ Cl	А	54	
6	$CaCl_2$	Α	21	
7	HCl/DMPU (43% w/w)	Α	62	
8	HCl/DMPU (43% w/w)	В	84	
9	HCl/DMPU (43% w/w)	С	44	
10	HCl/DMPU (43% w/w)	В	47 ^c	
11	HCl/DMPU (43% w/w)	В	18 ^d	

^{*a*}Reaction conditions: as in Table 1 (entry 1). ^{*b*}Yields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. DMPU = N,N'-Dimethylpropyleneurea. ^{*c*}Without **B**. ^{*d*}No light.

(Table 2, entries 7–9). Both light and photocatalyst were crucial in the production of 3a (Table 2, entries 10–11). With these modified conditions in hand, we examined the scope of the deformylative chlorination protocol. As illustrated in Scheme 3, our method produced the corresponding chlorinated products in good to excellent yields. Various functional groups (3a-3p) as well as heterocyclic arenes (3q-3t) were tolerated.



^aReaction conditions: as in Table 1 (entry 1); isolated yields.

The scalability of our deformylative halogenation was evaluated using 3 mmol of DHP substrate 1a. The halogenated products were generated in yields of 79% and 67%, respectively (Figure 1a). To highlight the excellent site selectivity of this protocol, two similar but distinguishable DHPs (1x and 1y) were prepared and subjected under the standard conditions to both parallel and crossover experiments (Figure 1b). In the



Figure 1. (a) Gram-scale synthesis; (b) Light on/off experiment; (c) Selectivity study; (d) Radical quenching experiment.

former, only *in situ* DHP-substituted products were observed, while, in the latter, two brominated products (2y and 2z) were formed with the same mole ratio as the starting DHPs, indicating that the reactivities of 1x and 1y were the same and that no isomerization occurred during this reaction.

To gain insight into the reaction mechanism, the bromination of 1a was monitored with the light on/off over time. A smooth transformation under irradiation by blue LEDs and no further production of 2a in the dark suggested that the reaction proceeded through a photoredox catalytic pathway rather than a radical chain pathway (Figure1c). A radical quenching experiment was also conducted by adding the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the reaction of 1a. We observed that the bromination was completely inhibited (Figure 1d). Based on the above observations, we proposed a plausible mechanism for this bromination process, shown in Scheme 4a. Upon visible light irradiation the excited photocatalyst *Ru(bpy)₃²⁺ is oxidized by $K_2S_2O_8$ $(E_{red}(S_2O_8^{-2}/SO_4^{-2})) = +2.01 \text{ V vs}$ SCE)²⁵ through single electron transfer (SET), resulting in the formation of SO₄²⁻, SO₄⁻⁻, and a strong oxidative Ru(bpy)₃³⁺ ($E_{\text{red}}^{\text{III/II}} = +1.29 \text{ V vs SCE}$) species.^{12o} Then the singleelectron oxidization of DHP 1 $(\vec{E}_{red} = +1.03 \text{ V vs SCE})^{26,23g}$ yields radical II and reductively quench the photocatalyst. The resulting radical II then fragments to an alkyl radical IV along with pyridine derivative III, driven by aromatization. The high reduction potential of the generated $SO_4^{\bullet-}$ ($E_{red}(SO_4^{\bullet-}/SO_4^{2-}) = +2.6 \text{ V vs SCE})^{25}$ enables the further oxidization of Br⁻ ($E_{red}(Br^{\bullet}/Br^{-} = +0.8 \text{ V vs SCE})^{27}$ to its radical form, thus rendering the radical coupling with alkyl radical IV to furnish the brominated product 2. In the chlorination process, however, the single electron transfer (SET) from the ground state of DHP 1 ($E_{red} = +1.03$ V vs SCE)^{26,23g} to either the photoexcited Ir(III) ($E_{red} *^{III/II} = +0.31$ V vs SCE)^{12o} or the oxidized Ir(IV) ($E_{red} *^{IV/III} = +0.77$ V vs SCE)^{12o} is not favored. Therefore, the possibility of generating radical V via photoexcited DHP 1* was suggested, which has been experimentally proved.^{23f} This different radical initiation is also evident by the formation of the chlorinated product in moderate yield when only the blue LED was employed (Table 2, entry 10). The radical V would reductively quench the oxidized photocatalyst Ir(IV) to form the pyridine derivative III. The resulting alkyl radical IV would follow a similar radical coupling route as the bromination, giving rise to chlorinated product 3 (Scheme 4b).

Scheme 4. Plausible Reaction Mechanism





Subsequently, we examined the deformylative iodination using NaI as a halogen source.

Unlike in the case of bromination and chlorination, a photoredox catalyst was not required in this protocol because a iodine radical is generated from the NaI/K₂S₂O₈ system.²⁸ After extensive optimization (see SI), we found that 95% of the product could be obtained in the presence of 1.5 equiv each of NaI/K₂S₂O₈. As shown in Scheme 5, various DHPs were suitable substrates, giving the desired iodinated products in good to excellent yields (4a–4l) although benzylic DHP 4m showed less reactivity.

In conclusion, we have developed a highly efficient visiblelight-mediated deformylative halogenation protocol using inexpensive and atom-economical halogen sources. This





^{*a*}Reaction conditions: 1 (0.1 mmol), NaI (0.15 mmol), $K_2S_2O_8$ (0.15 mmol), H_2O [0.2 M], rt, 24 h, under air; isolated yields.

protocol exhibited excellent site selectivity and functional group tolerance, which are highly desired in late-stage functionalization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01337.

Experimental detail and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Petrone, D. A.; Ye, J.; Lautens, M. Modern Transition-Metal-Catalyzed Carbon-Halogen Bond Formation. *Chem. Rev.* 2016, *116*, 8003-8104.

(2) (a) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides. Angew. Chem., Int. Ed. **2005**, 44, 674–688. (b) Kambe, N.; Iwasaki, T.; Terao, J. Pd-catalyzed cross-coupling reactions of alkyl halides. Chem. Soc. Rev. **2011**, 40, 4937–4947. (c) Littke, A. F.; Fu, G. C. Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. Angew. Chem., Int. Ed. **2002**, 41, 4176–4211. (d) Rudolph, A.; Lautens, M. Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions. Angew. Chem., Int. Ed. **2009**, 48, 2656–2670. (e) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent advances in homogeneous nickel catalysis. Nature **2014**, 509, 299. (f) Terao, J.; Kambe, N. Cross-Coupling Reaction of Alkyl Halides with Grignard Reagents Catalyzed by Ni, Pd, or Cu Complexes with π -Carbon Ligand(s). Acc. Chem. Res. **2008**, 41, 1545–1554.

(3) (a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. New Applications of Polyfunctional Organometallic Compounds in Organic Synthesis. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435. (b) Kim, J. H.; Ko, Y. O.; Bouffard, J.; Lee, S.-g. Advances in tandem reactions with organozinc reagents. *Chem. Soc. Rev.* **2015**, *44*, 2489–2507. (c) Sun, C.-L.; Shi, Z.-J. Transition-Metal-Free Coupling Reactions. *Chem. Rev.* **2014**, *114*, 9219–9280.

(4) (a) Hernandes, M.; Cavalcanti, S. M.; Moreira, D. R.; de Azevedo, W., Jr.; Leite, A. C. Halogen Atoms in the Modern Medicinal Chemistry: Hints for the Drug Design. *Curr. Drug Targets* **2010**, *11*, 303–314. (b) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. Principles and Applications of Halogen Bonding in Medicinal Chemistry and Chemical Biology. *J. Med. Chem.* **2013**, *56*, 1363–1388.

(5) Jeschke, P. The unique role of halogen substituents in the design of modern agrochemicals. *Pest Manage. Sci.* **2010**, *66*, 10–27.

D

(6) (a) Amanchukwu, C. V.; Harding, J. R.; Shao-Horn, Y.; Hammond, P. T. Understanding the Chemical Stability of Polymers for Lithium-Air Batteries. *Chem. Mater.* 2015, 27, 550-561.
(b) Tang, M. L.; Bao, Z. Halogenated Materials as Organic Semiconductors. *Chem. Mater.* 2011, 23, 446-455.

(7) (a) Huy, P. H.; Motsch, S.; Kappler, S. M. Formamides as Lewis Base Catalysts in SN Reactions—Efficient Transformation of Alcohols into Chlorides, Amines, and Ethers. *Angew. Chem., Int. Ed.* **2016**, 55, 10145–10149. (b) Munyemana, F.; George, I.; Devos, A.; Colens, A.; Badarau, E.; Frisque-Hesbain, A.-M.; Loudet, A.; Differding, E.; Damien, J.-M.; Rémion, J.; Van Uytbergen, J.; Ghosez, L. A mild method for the replacement of a hydroxyl group by halogen. 1. Scope and chemoselectivity. *Tetrahedron* **2016**, 72, 420–430. (c) Senaratne, P. A.; Orihuela, F. M.; Malcolm, A. J.; Anderson, K. G. Recyclable Lucas Reagent in Converting Aliphatic Alcohols to Chlorides1. *Org. Process Res. Dev.* **2003**, 7, 185–186.

(8) (a) Kropp, P. J.; Daus, K. A.; Tubergen, M. W.; Kepler, K. D.; Wilson, V. P.; Craig, S. L.; Baillargeon, M. M.; Breton, G. W. Surfacemediated reactions. 3. Hydrohalogenation of alkenes. *J. Am. Chem. Soc.* **1993**, *115*, 3071–3079. (b) Liang, S.; Hammond, G. B.; Xu, B. Metal-free regioselective hydrochlorination of unactivated alkenes via a combined acid catalytic system. *Green Chem.* **2018**, *20*, 680–684. (c) Schevenels, F. T.; Shen, M.; Snyder, S. A. Isolable and Readily Handled Halophosphonium Pre-reagents for Hydro- and Deuteriohalogenation. *J. Am. Chem. Soc.* **2017**, *139*, 6329–6337. (d) Yadav, V. K.; Babu, K. G. A Remarkably Efficient Markovnikov Hydrochlorination of Olefins and Transformation of Nitriles into Imidates by Use of AcCl and an Alcohol. *Eur. J. Org. Chem.* **2005**, *2005*, 452– 456.

(9) (a) Gaspar, B.; Carreira, E. M. Catalytic Hydrochlorination of Unactivated Olefins with para-Toluenesulfonyl Chloride. *Angew. Chem., Int. Ed.* 2008, 47, 5758–5760. (b) Liu, W.; Groves, J. T. Manganese Porphyrins Catalyze Selective C–H Bond Halogenations. *J. Am. Chem. Soc.* 2010, 132, 12847–12849. (c) Podgoršek, A.; Zupan, M.; Iskra, J. Oxidative Halogenation with "Green" Oxidants: Oxygen and Hydrogen Peroxide. *Angew. Chem., Int. Ed.* 2009, 48, 8424–8450.

(10) (a) Hunsdiecker, H.; Hunsdiecker, C. Über den Abbau der Salze aliphatischer Säuren durch Brom. Ber. Dtsch. Chem. Ges. B **1942**, 75, 291–297. (b) Das, P. J.; Roy, S. Catalytic Hunsdiecker Reaction of α , β -Unsatuated Carboxylic Acids: How Efficient Is the Catalyst? J. Org. Chem. **2002**, 67, 7861–7864.

(11) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. A practical alternative to the hunsdiecker reaction. Tetrahedron Lett. 1983, 24, 4979-4982. (b) Camps, P.; Lukach, A. E.; Pujol, X.; Vázquez, S. Hunsdiecker-Type Bromodecarboxylation of Carboxylic Acids with Iodosobenzene Diacetate-Bromine. Tetrahedron 2000, 56, 2703-2707. (c) Cristol, S.; Firth, W., Jr. Communications. A Convenient Synthesis of Alkyl Halides from Carboxylic Acids. J. Org. Chem. 1961, 26, 280-280. (d) Kochi, J. K. A. New Method for Halodecarboxylation of Acids Using Lead(IV) Acetate. J. Am. Chem. Soc. 1965, 87, 2500-2502. (e) McKillop, A.; Bromley, D.; Taylor, E. C. Thallium in organic synthesis. VI. Synthesis of primary aliphatic bromides. J. Org. Chem. 1969, 34, 1172-1173. (f) Tan, X.; Song, T.; Wang, Z.; Chen, H.; Cui, L.; Li, C. Silver-Catalyzed Decarboxylative Bromination of Aliphatic Carboxylic Acids. Org. Lett. 2017, 19, 1634-1637. (g) Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. Silver-Catalyzed Decarboxylative Chlorination of Aliphatic Carboxylic Acids. J. Am. Chem. Soc. 2012, 134, 4258-4263.

(12) (a) Arora, A.; Weaver, J. D. Visible Light Photocatalysis for the Generation and Use of Reactive Azolyl and Polyfluoroaryl Intermediates. Acc. Chem. Res. 2016, 49, 2273–2283. (b) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. Controlled Fluoroalkylation Reactions by Visible-Light Photoredox Catalysis. Acc. Chem. Res. 2016, 49, 2284–2294. (c) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Visible light photoredox-controlled reactions of N-radicals and radical ions. Chem. Soc. Rev. 2016, 45, 2044–2056. (d) Fabry, D. C.; Rueping, M. Merging Visible Light Photoredox Catalysis with Metal Catalyzed C–H Activations: On the Role of Oxygen and Superoxide

Ions as Oxidants. Acc. Chem. Res. 2016, 49, 1969-1979. (e) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; König, B. Visible Light Mediated Photoredox Catalytic Arylation Reactions. Acc. Chem. Res. 2016, 49, 1566-1577. (f) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. Merging Visible Light Photoredox and Gold Catalysis. Acc. Chem. Res. 2016, 49, 2261-2272. (g) Jin, Y.; Fu, H. Visible-Light Photoredox Decarboxylative Couplings. Asian J. Org. Chem. 2017, 6, 368-385. (h) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. ACS Catal. 2017, 7, 4999-5022. (i) Koike, T.; Akita, M. A versatile strategy for difunctionalization of carbon-carbon multiple bonds by photoredox catalysis. Org. Chem. Front. 2016, 3, 1345-1349. (j) König, B. Photocatalysis in Organic Synthesis - Past, Present, and Future. Eur. J. Org. Chem. 2017, 2017, 1979-1981. (k) Lee, K. N.; Ngai, M.-Y. Recent developments in transition-metal photoredox-catalysed reactions of carbonyl derivatives. Chem. Commun. 2017, 53, 13093-13112. (1) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. ACS Catal. 2017, 7, 2563-2575. (m) Morris, S. A.; Wang, J.; Zheng, N. The Prowess of Photogenerated Amine Radical Cations in Cascade Reactions: From Carbocycles to Heterocycles. Acc. Chem. Res. 2016, 49, 1957-1968. (n) Narayanam, J. M. R.; Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. Chem. Soc. Rev. 2011, 40, 102-113. (o) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. Chem. Rev. 2013, 113, 5322-5363. (p) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. Chem. Rev. 2016, 116, 10075-10166. (q) Roslin, S.; Odell, L. R. Visible-Light Photocatalysis as an Enabling Tool for the Functionalization of Unactivated C(sp3)-Substrates. Eur. I. Org. Chem. 2017, 2017, 1993-2007. (r) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. Chem. Rev. 2016, 116, 10035-10074. (s) Srivastava, V.; Singh, P. P. Eosin Y catalysed photoredox synthesis: a review. RSC Adv. 2017, 7, 31377-31392. (t) Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A. Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for sp3-sp2 Cross-Coupling. Acc. Chem. Res. 2016, 49, 1429-1439. (u) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The merger of transition metal and photocatalysis. Nat. Rev. Chem. 2017, 1, 0052. (v) Xuan, J.; Xiao, W.-J. Visible-Light Photoredox Catalysis. Angew. Chem., Int. Ed. 2012, 51, 6828-6838.

(13) (a) Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. A Scalable Procedure for Light-Induced Benzylic Brominations in Continuous Flow. J. Org. Chem. 2014, 79, 223–229.
(b) Kim, H. J.; Kim, M. Visible Light-Mediated Installation of Halogen Functionalities into Multiple Bond Systems. ChemistrySelect 2017, 2, 9136–9146. (c) Tu, H.; Zhu, S.; Qing, F.-L.; Chu, L. Visiblelight-induced halogenation of aliphatic CH bonds. Tetrahedron Lett. 2018, 59, 173–179.

(14) (a) Hering, T.; König, B. Photocatalytic activation of N-chloro compounds for the chlorination of arenes. Tetrahedron 2016, 72, 7821-7825. (b) Hering, T.; Mühldorf, B.; Wolf, R.; König, B. Halogenase-Inspired Oxidative Chlorination Using Flavin Photocatalysis. Angew. Chem., Int. Ed. 2016, 55, 5342-5345. (c) Kawakami, K.; Tsuda, A. Brominated Methanes as Photoresponsive Molecular Storage of Elemental Br2. Chem. - Asian J. 2012, 7, 2240-2252. (d) Li, R.; Wang, Z. J.; Wang, L.; Ma, B. C.; Ghasimi, S.; Lu, H.; Landfester, K.; Zhang, K. A. I. Photocatalytic Selective Bromination of Electron-Rich Aromatic Compounds Using Microporous Organic Polymers with Visible Light. ACS Catal. 2016, 6, 1113-1121. (e) Ohkubo, K.; Mizushima, K.; Fukuzumi, S. Oxygenation and chlorination of aromatic hydrocarbons with hydrochloric acid photosensitized by 9-mesityl-10-methylacridinium under visible light irradiation. Res. Chem. Intermed. 2013, 39, 205-220. (f) Ohkubo, K.; Mizushima, K.; Iwata, R.; Fukuzumi, S. Selective photocatalytic

aerobic bromination with hydrogen bromidevia an electron-transfer state of 9-mesityl-10-methylacridinium ion. *Chem. Sci.* **2011**, *2*, 715–722. (g) Petzold, D.; König, B. Photocatalytic Oxidative Bromination of Electron-Rich Arenes and Heteroarenes by Anthraquinone. *Adv. Synth. Catal.* **2018**, *360*, *626*–630. (h) Zhang, L.; Hu, X. Room temperature C(sp2)-H oxidative chlorination via photoredox catalysis. *Chem. Sci.* **2017**, *8*, 7009–7013.

(15) (a) Cristol, S. J.; Seapy, D. G. New procedure for the transformation of alcohols to alkyl halides via xanthate esters and freeradical intermediates. J. Org. Chem. 1982, 47, 132-136. (b) Griffin, J. D.; Cavanaugh, C. L.; Nicewicz, D. A. Reversing the Regioselectivity of Halofunctionalization Reactions through Cooperative Photoredox and Copper Catalysis. Angew. Chem., Int. Ed. 2017, 56, 2097-2100. (c) Han, L.; Xia, J.-B.; You, L.; Chen, C. Ketone-catalyzed photochemical C(sp3)-H chlorination. Tetrahedron 2017, 73, 3696-3701. (d) Kee, C. W.; Chan, K. M.; Wong, M. W.; Tan, C.-H. Selective Bromination of sp3 C H Bonds by Organophotoredox Catalysis. Asian J. Org. Chem. 2014, 3, 536-544. (e) Manabe, Y.; Kitawaki, Y.; Nagasaki, M.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. Revisiting the Bromination of C H Bonds with Molecular Bromine by Using a Photo-Microflow System. Chem. -Eur. J. 2014, 20, 12750-12753. (f) Nishina, Y.; Ohtani, B.; Kikushima, K. Bromination of hydrocarbons with CBr4, initiated by light-emitting diode irradiation. Beilstein J. Org. Chem. 2013, 9, 1663-1667. (g) Qin, Q.; Yu, S. Visible-Light-Promoted Remote C(sp3)-H Amidation and Chlorination. Org. Lett. 2015, 17, 1894-1897. (h) Shibatomi, K.; Kitahara, K.; Sasaki, N.; Kawasaki, Y.; Fujisawa, I.; Iwasa, S. Enantioselective decarboxylative chlorination of β ketocarboxylic acids. Nat. Commun. 2017, 8, 15600. (i) Su, J. Y.; Grünenfelder, D. C.; Takeuchi, K.; Reisman, S. E. Radical Deoxychlorination of Cesium Oxalates for the Synthesis of Alkyl Chlorides. Org. Lett. 2018, 20, 4912-4916. (j) Wang, Y.; Li, G.-X.; Yang, G.; He, G.; Chen, G. A visible-light-promoted radical reaction system for azidation and halogenation of tertiary aliphatic C-H bonds. Chem. Sci. 2016, 7, 2679-2683. (k) Zhao, M.; Lu, W. Visible Light-Induced Oxidative Chlorination of Alkyl sp3 C-H Bonds with NaCl/Oxone at Room Temperature. Org. Lett. 2017, 19, 4560-4563. (1) Zhao, M.; Lu, W. Catalytic Bromination of Alkyl sp3C-H Bonds with KBr/Air under Visible Light. Org. Lett. 2018, 20, 5264-5267.

(16) Wilger, D. J.; Grandjean, J.-M. M.; Lammert, T. R.; Nicewicz, D. A. The direct anti-Markovnikov addition of mineral acids to styrenes. *Nat. Chem.* **2014**, *6*, 720.

(17) Candish, L.; Standley, E. A.; Gómez-Suárez, A.; Mukherjee, S.; Glorius, F. Catalytic Access to Alkyl Bromides, Chlorides and Iodides via Visible Light-Promoted Decarboxylative Halogenation. *Chem. - Eur. J.* **2016**, *22*, 9971–9974.

(18) (a) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. Site-Selective Aliphatic C-H Chlorination Using N-Chloroamides Enables a Synthesis of Chlorolissoclimide. J. Am. Chem. Soc. 2016, 138, 696-702. (b) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. Site-Selective Aliphatic C-H Bromination Using N-Bromoamides and Visible Light. J. Am. Chem. Soc. 2014, 136, 14389-14392.

(19) Short, M. A.; Blackburn, J. M.; Roizen, J. L. Sulfamate Esters Guide Selective Radical-Mediated Chlorination of Aliphatic C-H Bonds. *Angew. Chem., Int. Ed.* **2018**, *57*, 296–299.

(20) (a) Guo, X.; Wang, J.; Li, C.-J. An Olefination via Ruthenium-Catalyzed Decarbonylative Addition of Aldehydes to Terminal Alkynes. J. Am. Chem. Soc. 2009, 131, 15092–15093. (b) Harris, E. F. P.; Waters, W. A. Thiol Catalysis of the Homolytic Decomposition of Aldehydes. Nature 1952, 170, 212. (c) Jung, Y.; Kim, I. Deformylative Intramolecular Hydroarylation: Synthesis of Benzo[e]pyrido[1,2-a]indoles. Org. Lett. 2015, 17, 4600–4603. (d) Patra, T.; Manna, S.; Maiti, D. Metal-Mediated Deformylation Reactions: Synthetic and Biological Avenues. Angew. Chem., Int. Ed. 2011, 50, 12140–12142. (e) Paul, S.; Guin, J. Dioxygen-Mediated Decarbonylative C□H Alkylation of Heteroaromatic Bases with Aldehydes. Chem. - Eur. J. 2015, 21, 17618–17622. (f) Shuai, Q.; Yang, L.; Guo, X.; Baslé, O.; Li, C.-J. Rhodium-Catalyzed Oxidative C-H Arylation of 2-Arylpyridine Derivatives via Decarbonylation of Aromatic Aldehydes. J. Am. Chem. Soc. 2010, 132, 12212-12213. (g) Tang, R.-J.; He, Q.; Yang, L. Metal-free oxidative decarbonylative coupling of aromatic aldehydes with arenes: direct access to biaryls. Chem. Commun. 2015, 51, 5925-5928.

(21) (a) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. Chemistry of Acyl Radicals. Chem. Rev. 1999, 99, 1991-2070. (b) Esposti, S.; Dondi, D.; Fagnoni, M.; Albini, A. Acylation of Electrophilic Olefins through Decatungstate-Photocatalyzed Activation of Aldehydes. Angew. Chem., Int. Ed. 2007, 46, 2531-2534. (c) Matcha, K.; Antonchick, A. P. Metal-Free Cross-Dehydrogenative Coupling of Heterocycles with Aldehydes. Angew. Chem., Int. Ed. 2013, 52, 2082-2086. (d) Mukherjee, S.; Patra, T.; Glorius, F. Cooperative Catalysis: A Strategy To Synthesize Trifluoromethyl-thioesters from Aldehydes. ACS Catal. 2018, 8, 5842-5846. (e) Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. The radicalchain addition of aldehydes to alkenes by the use of Nhydroxyphthalimide (NHPI) as a polarity-reversal catalyst. Chem. Commun. 2001, 2352-2353. (f) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C-H Activation/Radical Cross-Coupling. Chem. Rev. 2017, 117, 9016-9085. (g) Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C-H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. J. Am. Chem. Soc. 2017, 139. 11353-11356

(22) (a) Ellington, B. R.; Paul, B.; Das, D.; Vitek, A. K.; Zimmerman, P. M.; Marsh, E. N. G. An Unusual Iron-Dependent Oxidative Deformylation Reaction Providing Insight into Hydrocarbon Biosynthesis in Nature. ACS Catal. 2016, 6, 3293–3300. (b) Shokri, A.; Que, L. Conversion of Aldehyde to Alkane by a Peroxoiron(III) Complex: A Functional Model for the Cyanobacterial Aldehyde-Deformylating Oxygenase. J. Am. Chem. Soc. 2015, 137, 7686–7691. (c) Watanabe, E.; Kaiho, A.; Kusama, H.; Iwasawa, N. Cobalt–Salen Complex-Catalyzed Oxidative Generation of Alkyl Radicals from Aldehydes for the Preparation of Hydroperoxides. J. Am. Chem. Soc. 2013, 135, 11744–11747.

(23) (a) Badir, S. O.; Dumoulin, A.; Matsui, J. K.; Molander, G. A. Synthesis of Reversed C-Acyl Glycosides through Ni/Photoredox Dual Catalysis. Angew. Chem., Int. Ed. 2018, 57, 6610-6613. (b) Buzzetti, L.; Prieto, A.; Roy, S. R.; Melchiorre, P. Radical-Based C-C Bond-Forming Processes Enabled by the Photoexcitation of 4-Alkyl-1,4-dihydropyridines. Angew. Chem., Int. Ed. 2017, 56, 15039-15043. (c) Chen, W.; Liu, Z.; Tian, J.; Li, J.; Ma, J.; Cheng, X.; Li, G. Building Congested Ketone: Substituted Hantzsch Ester and Nitrile as Alkylation Reagents in Photoredox Catalysis. J. Am. Chem. Soc. 2016, 138, 12312-12315. (d) de Assis, F. F.; Huang, X.; Akiyama, M.; Pilli, R. A.; Meggers, E. Visible-Light-Activated Catalytic Enantioselective β -Alkylation of $\alpha_{,\beta}$ -Unsaturated 2-Acyl Imidazoles Using Hantzsch Esters as Radical Reservoirs. J. Org. Chem. 2018, 83, 10922-10932. (e) Dumoulin, A.; Matsui, J. K.; Gutiérrez-Bonet, Á.; Molander, G. A. Synthesis of Non-Classical Arylated C-Saccharides through Nickel/Photoredox Dual Catalysis. Angew. Chem., Int. Ed. 2018, 57, 6614-6618. (f) Gu, F.; Huang, W.; Liu, X.; Chen, W.; Cheng, X. Substituted Hantzsch Esters as Versatile Radical Reservoirs in Photoredox Reactions. Adv. Synth. Catal. 2018, 360, 925-931. (g) Gutiérrez-Bonet, A.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. 1,4-Dihydropyridines as Alkyl Radical Precursors: Introducing the Aldehyde Feedstock to Nickel/Photoredox Dual Catalysis. ACS Catal. 2016, 6, 8004-8008. (h) Li, G.; Chen, R.; Wu, L.; Fu, Q.; Zhang, X.; Tang, Z. Alkyl Transfer from C Cleavage. Angew. Chem., Int. Ed. 2013, 52, 8432-8436. (i) Nakajima, K.; Nojima, S.; Nishibayashi, Y. Nickel- and Photoredox-Catalyzed Cross-Coupling Reactions of Aryl Halides with 4-Alkyl-1,4-dihydropyridines as Formal Nucleophilic Alkylation Reagents. Angew. Chem., Int. Ed. 2016, 55, 14106-14110. (j) Verrier, C.; Alandini, N.; Pezzetta, C.; Moliterno, M.; Buzzetti, L.; Hepburn, H. B.; Vega-Peñaloza, A.; Silvi, M.; Melchiorre, P. Direct Stereoselective Installation of Alkyl Fragments at the β -Carbon of Enals via Excited Iminium Ion

Organic Letters

Catalysis. ACS Catal. 2018, 8, 1062–1066. (k) Zhang, H.-H.; Yu, S. Radical Alkylation of Imines with 4-Alkyl-1,4-dihydropyridines Enabled by Photoredox/Brønsted Acid Cocatalysis. J. Org. Chem. 2017, 82, 9995–10006.

(24) (a) Ebule, R.; Liang, S.; Hammond, G. B.; Xu, B. Chloride-Tolerant Gold(I)-Catalyzed Regioselective Hydrochlorination of Alkynes. ACS Catal. 2017, 7, 6798–6801. (b) Liang, S.; Ebule, R.; Hammond, G. B.; Xu, B. A Chlorinating Reagent Yields Vinyl Chlorides with High Regioselectivity under Heterogeneous Gold Catalysis. Org. Lett. 2017, 19, 4524–4527.

(25) (a) Gutiérrez-Bonet, Á.; Remeur, C.; Matsui, J. K.; Molander, G. A. Late-Stage C–H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines. *J. Am. Chem. Soc.* **2017**, 139, 12251–12258. (b) Schweizer, S.; Tresse, C.; Bisseret, P.; Lalevée, J.; Evano, G.; Blanchard, N. Stereodivergent Hydrogermylations of α -Trifluoromethylated Alkynes and Their Applications in Cross-Coupling Reactions. *Org. Lett.* **2015**, *17*, 1794–1797.

(26) Cheng, J.-P.; Lu, Y.; Zhu, X.-Q.; Sun, Y.; Bi, F.; He, J. Heterolytic and Homolytic N-H Bond Dissociation Energies of 4-Substituted Hantzsch 2,6-Dimethyl-1,4-dihydropyridines and the Effect of One-Electron Transfer on the N-H Bond Activation. J. Org. Chem. 2000, 65, 3853-3857.

(27) Zhang, P.; Le, C. C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. J. Am. Chem. Soc. 2016, 138, 8084–8087.

(28) (a) Semwal, R.; Ravi, C.; Kumar, R.; Meena, R.; Adimurthy, S. Sodium Salts (NaI/NaBr/NaCl) for the Halogenation of Imidazo-Fused Heterocycles. J. Org. Chem. 2019, 84, 792–805. (b) Tonnar, J.; Lacroix-Desmazes, D. P. Use of Sodium Iodide as the Precursor to the Control Agent in Ab Initio Emulsion Polymerization. Angew. Chem., Int. Ed. 2008, 47, 1294–1297.