OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Formylation of Fluoroalkyl Imines through Visible-Light-Enabled H-Atom Transfer Catalysis: Access to Fluorinated α-Amino Aldehydes

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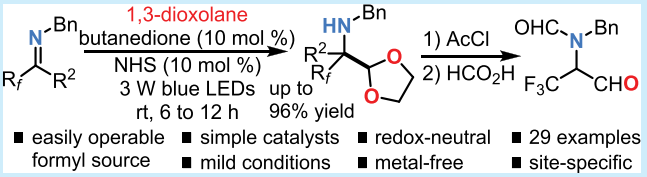
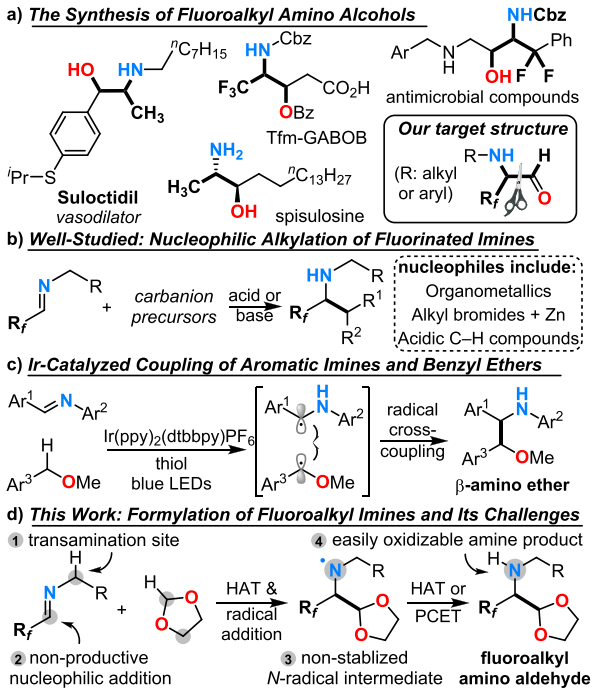
Supporting Information

ABSTRACT: A visible-light-enabled catalytic formylation of fluoroalkyl imines is developed. With readily accessible starting materials and organocatalysts, this method provides a general approach to masked fluoroalkyl amino aldehydes. A synergistic catalytic effect between the photosensitizer and the H atom transfer agent was proven pivotal to this transformation. After removing the mask, free aldehydes can be obtained and further converted to various β-fluoroalkyl β-amino alcohols, which are attractive building blocks in the synthesis of bioactive and pharmaceutical compounds.



β-Amino alcohols are ubiquitous structural motifs in natural and pharmaceutical compounds. Their fluorinated analogues could find great potentials in drug discovery, because of the unique electronic, lipophilic, and metabolic properties[1] (Scheme 1a). Nonetheless, the difficulties in synthesizing β-fluoroalkyl β-amino alcohols have undoubtedly limited the research in this area.[2] α-Amino aldehydes are versatile precursors to different β-amino alcohols.[3] Therefore, a general synthetic method of fluoroalkyl α-amino aldehydes is highly desirable but remains underdeveloped.[4]

Scheme 1. Synthetic Aims, Strategy, and Challenges of This Study



Fluoroalkyl imines are readily prepared from fluorinated hemiacetals[5] and have been proven useful in fluoroalkyl amine synthesis, mostly acting as electrophiles in polar reactions (Scheme 1b).[6] As an easily operable formyl source, 1,3-dioxolane has recently been demonstrated to be practical in aldehyde preparations.[7] Since its C−H bonds are nonacidic, homolytic C−H cleavage becomes an alternative way to activate 1,3-dioxolane toward electron acceptors. C(sp^3)−H functionalization of ethers through H atom abstraction has recently achieved great development; however, most of the previous works required a stoichiometric amount of strong oxidants to produce and regenerate the H-abstractors.[8] These methods are less suitable for the redox-neutral catalytic reaction of imines, especially those with alkyl substituents.[9] *To the best of our knowledge, there has been no precedent for the addition of oxyalkyl radicals to fluoroalkyl imines, catalytic or noncatalytic.*

Photoredox catalysis has set an ideal platform for the redox-neutral reactions of imines,[10] by creating transient single-electron oxidant/reductant under mild conditions.[11] MacMillan's group reported a photoredox coupling of aromatic imines with benzylic ethers with an Ir complex and a thiol as the catalyst (Scheme 1c).[10a] This Ir catalyst was subsequently applied in other photoredox reactions of imines, mostly through a single-electron reduction of the C═N bond, followed by a radical cross-coupling event.[10b,c,g,h,12] Therefore, this strategy is limited to conjugated imines that could form

Received: January 10, 2019

DOI: 10.1021/acs.orglett.9b00128
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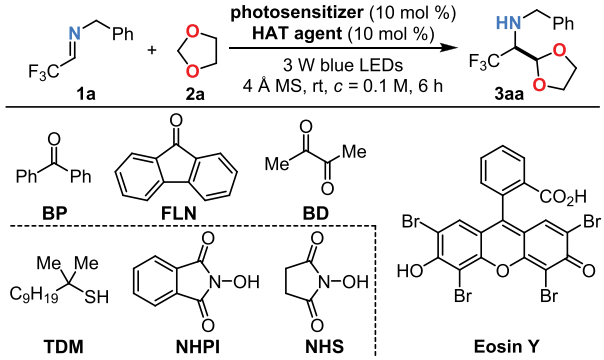
long-lived carbon radicals intermediate after a single-electron reduction.

Our group has recently developed an AIBN/thiol/O_2 co-mediated reaction that selectively functionalizes 1,3-dioxolane with aromatic and glyoxylate aldimines through a radical chain process.[13] However, this method was inefficient when applied to fluoroalkyl imines, which may be ascribed to a few potential challenges: (1) transamination for *N*-alkyl substrates;[14] (2) nonproductive nucleophilic addition;[15] (3) the generation of nonconjugated *N*-centered radical requires high energy;[16] and (4) the secondary amine products are unstable to single-electron oxidants.[17] (Scheme 1d) To tackle these problems, a neutral, mild, and oxidant-free H atom transfer (HAT) catalytic system has to be developed.[18] Herein, we disclose an organo photoredox catalytic functionalization of 1,3-dioxolane with a broad range of fluoroalkyl imines, providing an approach to various masked fluoroalkyl α-amino aldehydes.

N-Benzyltrifluoroacetaldimine **1a** was chosen as the model substrate for the reaction optimization, because it produces a masked α-amino aldehyde **3aa** with a readily removable *N*-benzyl group. For reference purposes, we first test **1a** with our previous method. Most of the starting material decomposed when heated at 65 °C in the presence of AIBN and *tert*-dodecyl mercaptan (TDM), affording **3aa** in only 29% yield (Table 1, entry 1). Then, we started exploring the photoredox reaction with a few organic photosensitizers that are reported[11c] to be capable of H-atom abstraction. With a commercial blue LED strip (3 W, 1 m) as the light source, 2,3-butanedione (**BD**) exhibited noticeably higher reactivity among the ketones we tested (entries 2−4 in Table 1). Having long been used as a photosensitizer, Eosin Y was recently reported to act as an excellent direct HAT catalyst.[18f] However, the same loading of Eosin Y was proven inactive, whereas lowering its loading to 2 mol % offered a small amount of **3aa** (entries 5 and 6 in Table 1). Based on our previous observations, a polarity reversal catalyst that serves as an H-atom shuttle might also be able to improve the efficiency of the photoredox reaction.[13,19] A brief survey of a mercaptan and *N*-hydroxyimides approved the practicability of this strategy (entries 7−9 in Table 1), and *N*-hydroxysuccinimide (**NHS**) showed the most prominent acceleration effect, affording **3aa** with excellent isolated yield (entry 9 in Table 1). Notably, this effect is far less prominent when **NHS** was applied to the Eosin Y-catalyzed case (entry 10). Notably, control experiments revealed that NHS alone does not promote this reaction, while no desired product was detected in darkness (entries 11 and 12 in Table 1).

Table 1. Catalysts Discovery[a]



entry	catalysts and conditions	conversion[b] (%)	yield[c] (%)
1	**AIBN** + **TDM**, 65 °C[d]	>95	29
2	**BP** only	52	10
3	**FLN** only	39	8
4	**BD** only	37	25
5	**Eosin Y** (10 mol %)	<10	<5
6	**Eosin Y** (2 mol %)	31	12
7	**BD** + **TDM**	92	56
8	**BD** + **NHPI**	>95	88
9	**BD** + **NHS**	>95	94 (90)[e]
10	**Eosin Y** (2 mol %) + **NHS**	53	20
11	**NHS** only	<10	<5
12	**BD** + **NHS**[d]	<10	nd[f]

[a]Unless otherwise stated, the reaction was performed with **1a** (0.2 mmol), a photosensitizer (0.02 mmol), a co-catalyst (0.02 mmol), and 4 Å molecular sieves (20 mg) in freshly distilled 1,3-dioxolane (2 mL) under the irradiation of 3 W blue LEDs at room temperature for 6 h. [b]The conversions were determined by quantitative ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard. [c]Yield determined by quantitative ^{19}F NMR. [d]The reaction was performed without blue light irradiation. [e]Isolated yield. [f]Not detected.

Having established the optimal reaction conditions, we thereby examined the substrate scope of this catalytic protocol, and the results are summarized in Figure 1. First, imine **1b** formed with (*R*)-1-phenylethylamine that possesses a very labile C−H bond was tolerated, furnishing the masked amino aldehydes **3ba** with decent yield and diastereomerix ratio (dr) (entry 1 in Figure 1). Next, a series of 1°, 2°, or 3° *N*-alkyl groups were also evaluated under the reaction conditions (entry 2 in Figure 1). The substrates with hindered substituents underwent slower reactions than the linear ones did. Memantine, which is a bulky amine that is used to treat Alzheimer's disease, was successfully incorporated into amino aldehyde **3ga** (entry 3 in Figure 1). Then, several *N*-substituents with potential reactive sites toward an N-centered radical[20] were investigated. Satisfyingly, the anticipated masked amino aldehydes **3ha**−**3la** are obtained selectively, without the detection of potential intramolecular Minisci, 1,5-H shift or cyclization products (entries 4−7 in Figure 1). Also, *N*-aryl imines were efficiently converted to corresponding amino aldehydes **3ma** and **3na** in good yields (entry 8 in Figure 1). Beside the trifluoromethyl imines, a few other fluorinated alkyl groups were then taken into consideration. A gem-difluoromethyl-, a chlorodifluoromethyl-, as well as a pentafluoroethyl-substituted imine are all excellent radical acceptors, giving products **3oa**−**3qa** in satisfactory yields (entry 9 in Figure 1). In addition, a masked propanal and tetrahydrofuran also participated the reaction smoothly with imines **1a** and **1j** to give aminoketones and amino ethers, respectively (see entries 10 and 11 in Figure 1). Moreover, the ketimines prepared from ethyl trifluoropyruvate are great reaction partners, offering structurally diversified fluoroalkyl amino acid derivatives with a quaternary carbon center (entries 12−14 in Figure 1). Last, a less-active ketimine **1w**, formed with trifluoroacetone and aniline, was also made into desired product **3wa** at elevated temperature after extended reaction time (entry 15 in Figure 1).

To verify the synthetic applications of this light-promoted transformation, we performed the reaction of **1a** on a 10 mmol scale and isolated **3aa** in 86% yield, and the excess 1,3-dioxolane was easily recovered by distillation. The hydrolysis of the cyclic acetal unit was difficult for the masked amino aldehydes, since most reported procedures are not effective for

DOI: 10.1021/acs.orglett.9b00128
Org. Lett. XXXX, XXX, XXX−XXX

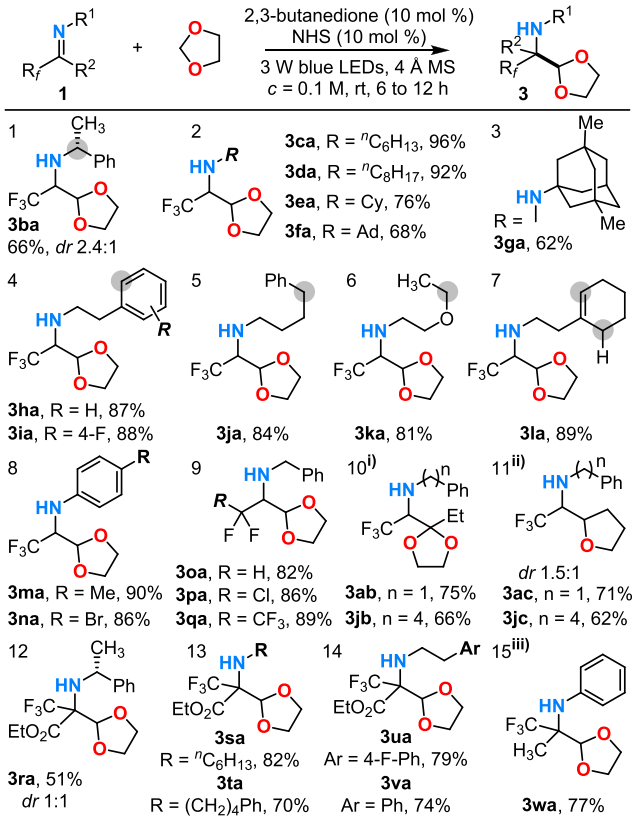
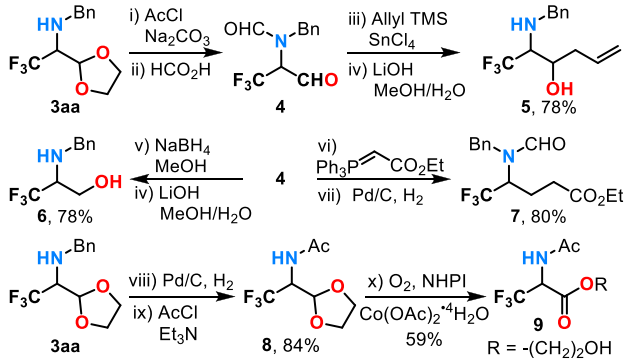


Figure 1. Substrate scope. Unless otherwise stated, the reaction was performed with an imine **1** (0.2 mmol), 2,3-butanedione (0.02 mmol), NHS (0.02 mmol), and 4 Å molecular sieves (20 mg) in freshly distilled 1,3-dioxolane (2 mL) under the irradiation of 3 W blue LEDs at room temperature for 6−12 h. The dr values were measured by ^{1}H NMR with crude products and the yields were obtained after flash column chromatography. Notes: (i) for **3ab** and **3jb**, 2-ethyl-1,3-dioxolane (2 mL) was used as the solvent; (ii) for **3ac** and **3jc**, THF (2 mL) was used as the solvent; (iii) for **3wa**, 40 °C, 36 h.

3aa. This might be caused by the presence of more Lewis basic sites beside the etheric oxygen, as well as the subsequent enolization of the aldehyde product.[13] After screening various protection and deprotection methods, we were able to obtain compound **4** with a free aldehyde group after a practical two-step procedure (Scheme 2). Through the Hosomi−Sakurai reaction, this valuable synthon was readily derived to a *β*-fluoroalkyl-*β*-amino homoallylic alcohol **5**, which is not easy to prepare through alternative approaches.[2a] Besides, typical transformations of aldehyde like $NaBH_4$ reduction and Wittig reaction are also applicable to **4** to afford fluoroalkyl amine derivatives **6** and **7**, respectively. In addition, after the *N*-benzyl group was switched to acetyl, the masked aldehyde **8** can be converted to an amino ester **9** via catalytic aerobic oxidation.

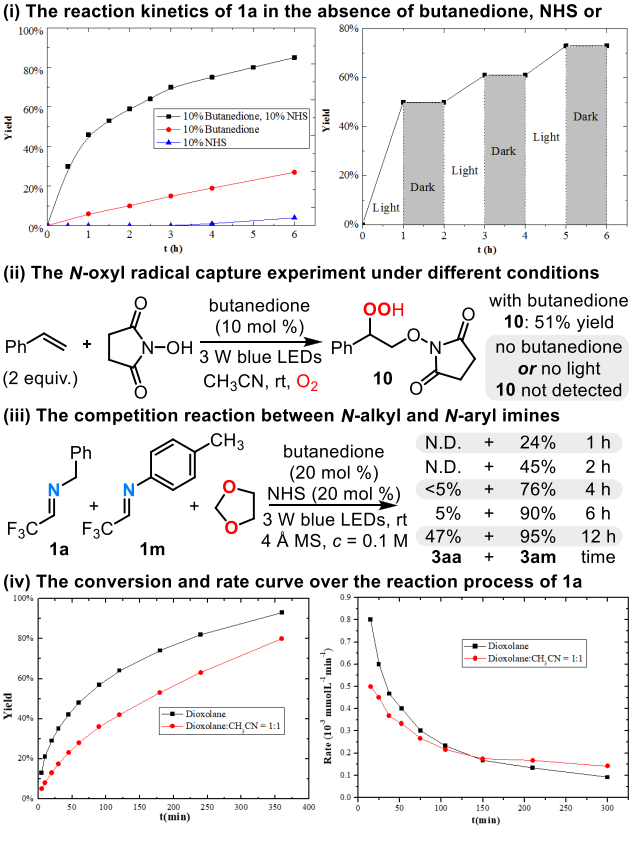
To gather information for a mechanistic working hypothesis, we performed a series of control experiments and kinetic studies. First, the processes involved in the reactions of **1a** in 1,3-dioxolane with different catalysts were monitored. As depicted in Scheme 3(i), the reaction was remarkably accelerated by the addition of NHS, while NHS alone is almost catalytically inactive. Also, the lights on/off experiment suggested that the irradiation of blue light is indispensable for the reaction to proceed. Second, we employed styrene and oxygen as a probe to test if a *N*-oxyl radical was generated

Scheme 2. Product Derivatization[a]



[a]Conditions: (i) AcCl (3 equiv), Na_2CO_3 (3 equiv), CH_2Cl_2, 0 °C to rt, 5 h, 96%; (ii) HCO_2H (88%, aq.), rt, 36 h; (iii) $SnCl_4$ (1.5 equiv), allyltrimethylsilane (2 equiv), CH_2Cl_2, −78 °C to rt; (iv) LiOH (2 equiv), CH_3OH/H_2O (4:1), 50 °C, 4 h; (v) $NaBH_4$ (1 equiv), MeOH, 0 °C to rt, 10 min; (vi) $Ph_3P=CHCO_2Et$ (1.5 equiv), THF, rt, 6 h; (vii) Pd/C, H_2, EtOH, 80 °C, 24 h; (viii) Pd/C, H_2, EtOH, 80 °C, 4 h; (ix) AcCl (2 equiv), NEt_3 (2.0 equiv), 0 °C to rt; (x) $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), NHPI (20 mol %), O_2, MeCN, 30 °C, 8 h.

Scheme 3. Mechanistic Studies



under certain conditions.[21] Alkene dioxygenation product **10** was only observed in the presence of both butanedione and light irradiation, implying the *N*-oxyl radical generation with these two factors (Scheme 3(ii)). In addition, when an *N*-alkyl (**1a**) and an *N*-aryl (**1m**) imine were subjected into the same reaction, the latter one was overwhelmingly more active while the *N*-alkyl substrate **1a** only started to involve after the consumption of **1m** (Scheme 3(iii)). Its superior reactivity

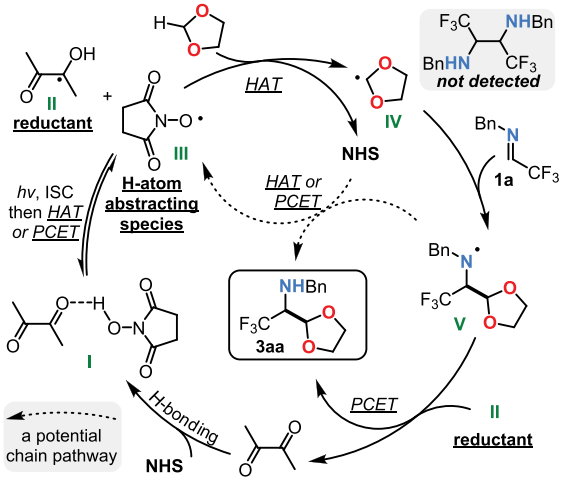
DOI: 10.1021/acs.orglett.9b00128
Org. Lett. XXXX, XXX, XXX−XXX

might be explained by the conjugation effect brought by the aryl group, which lowers the energy of the *N*-radical intermediate. It is noteworthy that a reductive homocoupling product of imine was not detected throughout our investigation. The observations described above suggest that the C−C bond-forming step likely goes through a radical addition manner, rather than a radical cross-coupling fashion in most of the previous works.[10a−c,g,h,12]

Furthermore, to verify whether the C−H abstraction from 1,3-dioxolane is involved in the rate-determining step, we monitored the reaction progress of **1a** in pure 1,3-dioxolane and in 1,3-dioxolane/MeCN mixture (1:1 (v/v)), respectively. The curves of yield and reaction rate (calculated by Δyield/Δt) over time are presented in Scheme 3(iv). As we can see, the concentration of 1,3-dioxolane has a direct impact on the reaction rate in the early stage, while this impact diminishes and even reverses as the reaction proceeds, which could be caused by the decreasing concentration of **1a**. Based on these data, we speculate that the rate of the H atom abstraction and the radical addition step may be of the same order of magnitude, so the rate-determining step is altered during the reaction. In the beginning, when imine is sufficient, the H-abstraction is rate-limiting. As the rate of H-abstraction remains almost constant (1,3-dioxolane is in large excess), the declining concentration of imine **1a** makes the radical addition an even slower step during the late stage of the reaction, especially for the *N*-alkyl imines.

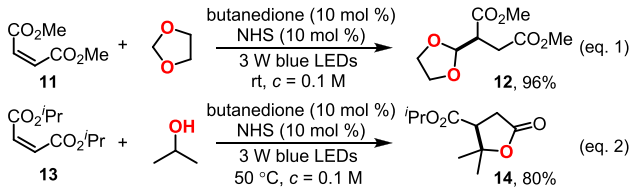
Based on these obtained results, we proposed a plausible catalytic mechanism, as depicted in Scheme 4. First, according

Scheme 4. A Plausible Reaction Mechanism



to previous studies, 2,3-butanedione and NHS could form a complex **I** through hydrogen bonding in aprotic solvents.[21a] Butanedione has an absorbance peak at ∼420 nm.[22] The excitation of an electron from a nonbonding orbital to a corresponding π^*-orbital (C═O bond, n, π^*), followed by intersystem crossing (ISC), generates a triplet ketyl diradical.[23] Through either an HAT or a proton-coupled electron transfer (PCET) event,[24] the catalyst pair turns into a reducing radical **II** and an H-abstracting *N*-oxyl radical **III**. Radical **III** then plays a key role in the HAT step to facilitate the generation of a nucleophilic 1,3-dioxolan-2-yl radical **IV**. Because of the lack of stabilizing effect, the radical addition to *N*-alkyl substrates may be relatively slower than to the *N*-aryl ones (as presented in Scheme 3(iii)). The resulted *N*-radical **V** could be either reduced by radical **II** or another molecule of NHS. If it was quenched by **II**, butanedione was regenerated together with the product **3aa**, completing the photoredox catalytic cycle (solid arrows). On the other hand, if **V** was reduced by NHS (dashed arrows), the resulted *N*-oxyl radical **III** would continue to promote the reaction (radical chain manner).

The radical addition of 1,3-dioxolane to imines provides us with a facile and selective approach to masked fluoroalkyl amino aldehydes. However, the direct utilization of alcohols as hydroxyalkyl sources to synthesize amino alcohols was ultimately found to be difficult. To determine whether it is limited by the H-abstraction activity of this catalytic manifold, or by the compatibility issue between alcohols and imines, we thereby tested this catalytic reaction with dialkyl maleate as a radical acceptor. As a reference, the addition of 1,3-dioxolane to dimethyl maleate was equally efficient under the same conditions (eq 1). Gratifyingly, isopropanol was also reactive at



slightly elevated temperature, providing lactone **14** in 80% isolated yield (eq 2). These results manifested that this photoredox HAT catalytic method is also reactive toward the α(C−H) bonds of alcohols. The incompatibility between imines and alcohols might be ascribed to the potential nucleophilic O-addition, or the mismatching reactivity between hydroxyalkyl radicals and fluoroalkyl imines.

In summary, we have established a metal-free and redox-neutral method for the catalytic synthesis of masked fluoroalkyl amino aldehydes, which are versatile precursors to a series of fluorinated β-amino alcohols. A broad range of fluoroalkyl aldimines and ketimines are tolerated with this procedure, even those possessing sensitive *N*-alkyl groups. According to the results of mechanistic studies, this reaction features a synergistic catalytic effect that is empowered by two small organic molecules and visible light. Synthetic applications of this method in the preparation of fluorine-labeled bioactive molecules and further exploration of this catalytic manifold in other types of reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website10.1021/acs.orglett.9b00128.

Detailed experimental procedures and NMR data for all compounds (PDF)

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DOI: 10.1021/acs.orglett.9b00128
Org. Lett. XXXX, XXX, XXX−XXX

Funding

National Natural Science Foundation of China (No. 21801083, to D. Lu, and No. 21472053, to Y. Gong) and Hubei Provincial Natural Science Foundation of China (No. 0216013067, to D. Lu) provided funding of this research work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Huazhong University of Science & Technology and the Natural Science Foundation of Hubei Committee (No. 2016CFA001) are gratefully acknowledged. We also thank Huazhong University of Science & Technology Analytical & Testing Center for characterizing new compounds.

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DOI: 10.1021/acs.orglett.9b00128
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