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Synthesis of 3-Fluoropyridines via Photoredox-Mediated Coupling of α,α-Difluoro-β-iodoketones with Silyl Enol Ethers

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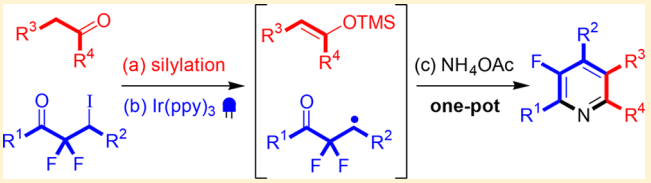
Supporting Information

ABSTRACT: A method for the synthesis of diversely substituted 3-fluoropyridines from two ketone components is described. The reaction involves photoredox coupling of α,α-difluoro-β-iodoketones with silyl enol ethers catalyzed by *fac*-Ir(ppy)$_3$ under blue LED irradiation with subsequent one-pot condensation with ammonium acetate. Based on cyclic voltammetry studies, it was determined that α,α-difluoro-β-iodoketones are reduced notably easier compared to 2,2,2-trifluoro-1-iodoethane, which may be ascribed to the influence of the carbonyl group.



INTRODUCTION

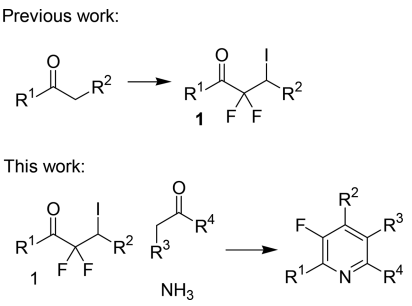
The pyridine unit plays an important role in medicinal chemistry with inclusion in more than 100 approved drugs.[1] Introduction of a single fluorine atom into a molecule can significantly modify its biological properties, and this tool is frequently used during the search of active compounds.[2] In particular, while substitution of hydrogen by fluorine may incur little steric effect, the fluorine substituent can decrease basicity of a nitrogen (for example, of the pyridine fragment) or increase metabolic stability by slowing down the rate of oxidation.

Concerning fluorinated pyridines,[3] 2- and 4-substituted derivatives are notably more susceptible to nucleophilic substitution of fluorine[4] compared to 3-fluoropyridines. Correspondingly, the 3-fluoropyridine fragment is a frequently utilized unit for the design of pharmaceuticals.[5]

Existing methods toward 3-fluoropyridines[3] rely on substitution of the diazonium group (Balz−Schiemann reaction),[6] whereas other transformations such as electrophilic fluorination of organometallics,[7] deoxofluorination,[8] and nucleophilic fluorination (transition-metal-catalyzed,[9] iodine(III) substitution,[10] uncatalyzed halogen substitution[11]) have been occasionally used. Several ring-forming reactions of narrow scope have also been described.[12] In this regard, reactions which provide diverse 3-fluoropyridines from readily available starting materials would be highly desirable.

Recently, we demonstrated that ketones can be easily transformed into α,α-difluoro-β-iodoketones **1** according to a halogenative difluorohomologation process[13] (Scheme 1). Herein, we report that ketones **1** can be coupled with another ketones and ammonia affording 3-fluoropyridines within one experimental step.[14] In this protocol, the key C−C bond-forming event involving a reaction of the iodide **1** with silyl enol ethers is performed under photoredox conditions. The use of visible light in combination with a photocatalyst[15] is the key feature of the method.

Scheme 1. Synthesis of 3-Fluoropyridines



RESULTS AND DISCUSSION

Because of the electron-withdrawing effect of fluorine atoms, perfluorinated compounds are good substrates for photoredox catalysis.[16,17] In particular, photoredox-mediated alkylation of enol ethers with perfluoroalkyl iodides (R_FI)[18] or with iodides bearing proximal difluoromethylene fragment (RCF_2I)[17e] were described.[19] However, moving two fluorine atoms away from iodine, as in compounds **1**, would likely decrease the efficiency of the reductive radical generation step.[20] As a starting point of our work, iodide **1a** and silyl enol ether **2a**, both originating

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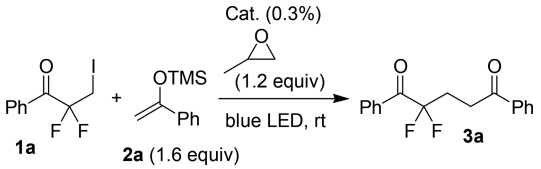
from acetophenone, were selected as model substrates, and their coupling was evaluated (Table 1). The mixture containing

Table 1. Optimization of Photoredox Reaction



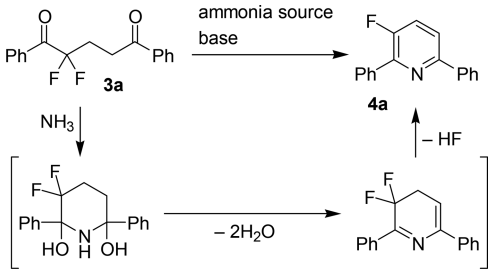
no.	cat.	solvent	additive (equiv)	time (h)	yield of 3a[a] (%)
1	$Ir(ppy)_3$	MeCN		3.5	81
2	$Ir(ppy)_3$	MeCN	PPh_3 (0.25)	3.5	97
3	$Ru(bpy)_3(BF_4)_2$	MeCN	PPh_3 (0.25)	3.5	30
4	Na_2-Eosin Y[b]	MeCN	PPh_3 (0.25)	15	47
5		MeCN	PPh_3 (0.25)	15	<5
6[c]	$Ir(ppy)_3$	MeCN	PPh_3 (0.25)	15	
7	$Ir(ppy)_3$	DMF	PPh_3 (0.25)	3.5	99
8	$Ir(ppy)_3$	DMF	PPh_3 (0.25)	0.5	69
9	$Ir(ppy)_3$	DMF		0.5	40
10		DMF		15	30
11		DMF	PPh_3 (0.5)	15	47
12[c]		DMF	PPh_3 (0.25)	15	

[a]Determined by ^{19}F NMR of reaction mixtures with 4-fluorotoluene as an internal standard. [b]5 mol %. [c]In the dark.

0.3 mol % of an iridium complex, *fac*-$Ir(ppy)_3$, was exposed to blue LED irradiation, and the reaction temperature was maintained at 25 °C by external cooling. Acetonitrile was used as solvent for primary optimization. Propylene oxide (PO) was added as a scavenger of iodotrimethylsilane (Me_3SiI),[17e,21] a highly reactive byproduct that can trigger side condensation reactions of diketone **3a**. After 3.5 h, the expected product **3a** was formed in good yield, though 19% of starting iodide **1a** remained unaffected (entry 1). Rewardingly, the addition of substoichiometric amounts (0.25 equiv) of triphenylphosphine provided notable acceleration leading to complete conversion of iodide **1a** (entry 2). Other photocatalysts such as $Ru(bpy)_3(BF_4)_2$ and Eosin Y were less effective (entries 3 and 4). For further applications of ketone **3a** under one-pot conditions (see below), we evaluated the photoredox coupling in dimethylformamide (DMF) as solvent. Fortunately, the reaction proceeded faster, leading to a virtually quantitative yield of the product as determined by ^{19}F NMR of the reaction mixture (entry 7). The phosphine has accelerating effect even in DMF, which is observable in experiments at reduced reaction time (see entries 8 and 9). Interestingly, in DMF the reaction can work even without the iridium catalyst, albeit at a slower rate (entries 10 and 11). To purify ketone **3a**, we had to recourse to preparative HPLC, since conventional flash chromatography did not allow to get rid of acetophenone formed after hydrolysis of excess of starting silyl enol ether **2a**.[22]

Then, the transformation of ketone **3a** into fluoropyridine **4a** was studied (Table 2). The reaction in DMF proceeded significantly faster than in acetonitrile (entries 1 and 2), and elevated temperatures were required for complete formation of the pyridine product.[23] Finally, the optimal conditions include the use of excess of ammonium acetate without base at 120 °C for 3 h. Importantly, a one-pot protocol, in which ammonium acetate was simply added to the reaction mixture from the

Table 2. Optimization of Cyclization Reaction



no.	reagents (equiv)	solvent	T (°C)	time (h)	yield[a] (%)
1	$AcONH_4$ (1.3), K_2CO_3 (2.5)	MeCN	80	2	<5
2	$AcONH_4$ (2.5), K_2CO_3 (4)	DMF	80	2	55
3	$AcONH_4$ (6)	DMF	120	3	98 (90[b])
4	HMDS (3.5), K_2CO_3 (2.5)	MeCN	80	2	<5
5	HMDS (3.5), K_2CO_3 (2.5)	DMF	140	2	71
6	HMDS (3.5)	DMF	140	1	<5

[a]Isolated yield. [b]Yield based on iodide **1a** in one-pot reaction.

photoredox coupling performed in DMF, afforded pyridine **4a** in 90% isolated yield based on iodide **1a** (entry 3). In fact, the opportunity to avoid the isolation of intermediate ketone **3a** greatly simplifies the procedure. Concerning the mechanism of the pyridine ring formation, we believe that ammonia attacks at the carbonyl groups followed by temperature promoted elimination of water and dehydrofluorination.

Silyl enol ethers **2** can be obtained from ketones using a combination of chlorosilane/sodium iodide/triethylamine.[24] For some ketones, the isolation of enol ethers **2** by distillation is simple and can be performed on a gram scale, and these individual enol ethers were used for the synthesis of pyridines according to the optimized one-pot procedure (Table 3). For the generality, the photoredox reactions were performed for a longer time (15 h), which is required for less reactive substrates.

Given that silylation is a virtually quantitative process, we decided to develop a procedure in which the crude unpurified silyl enol ether is directly involved into the synthesis of fluoropyridines (Table 4). The advantage of the latter protocol is that it can be conveniently performed on a millimole scale of the ketone. As follows from the results presented in Tables 3 and 4, the reaction is quite general. Various iodides **1** bearing iodine at the primary or secondary carbon were employed effectively. The macrocyclic iodide **1g** furnished product **4t** featuring a bridge-type ring junction. Concerning the ketone component, methyl-substituted ketones uniformly provided good yields of 5-unsubstituted 3-fluoropyridines **4** (R^3 = H for structure **4** in the scheme of Table 4). The ketone can have aromatic or heteroaromatic (furyl, thienyl, pyridyl) groups. Notably, the ester group remained unaffected in the presence of ammonia (Table 4, entry 9). The reaction of benzalacetone gave the expected product with the erosion of the double-bond geometry, which can be associated with reversible conjugate addition of ammonia under forcing conditions (Table 4, entry 3). However, for ketones leading to enol ethers with terminally substituted double bond, the photoredox step turned out to be less predictable. Thus, enol ethers derived from α-tetralone, indanone and propiophenone afforded corresponding pyridines **4f,i,o** in decreased yields of 56–60%. At the same time, in photoredox reactions of silyl enolates of cyclohexanone,

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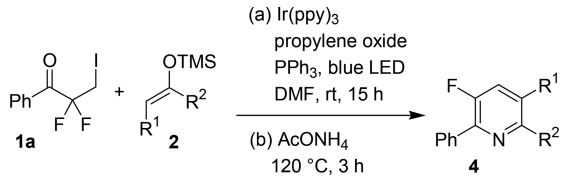
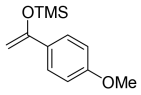
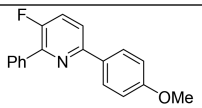
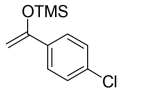
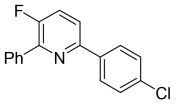
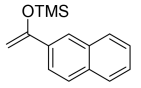
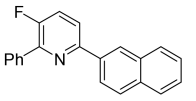
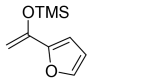
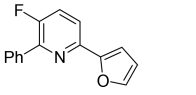
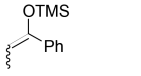
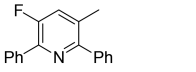
Table 3. Synthesis of Pyridines 4 from Iodide 1a



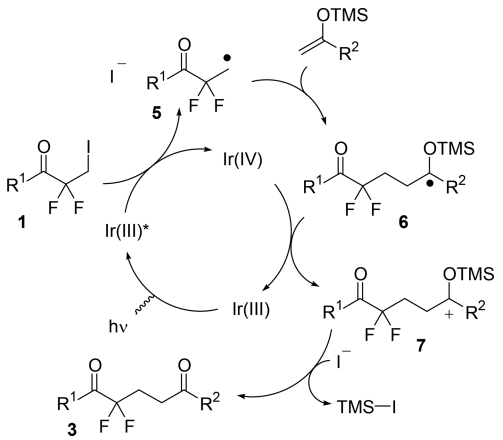
Enol ether		Product		Yield of **4**, %[a]
	**2b**		**4b**	82
	**2c**		**4c**	79
	**2d**		**4d**	57
	**2e**		**4e**	60
	**2f**		**4f**	60

[a]Isolated yield.

cyclododecanone, and propionaldehyde, less than 25% of diketones were formed. These results may be explained by decreased reactivity of corresponding enol ethers toward addition of the fluorinated radicals. Indeed, in photoredox reactions of these enol ethers, noticeable amounts of protodeiodinated products were observed resulting from the hydrogen atom transfer to the free radicals either from allylic position of the silyl enol ether or from solvent.

The proposed mechanism of photoredox reaction is shown in Scheme 2. The reduction of idodide **1** by the photoexited iridium(III) catalyst generates radical **5**, which adds across the enol ether double bond. Silyloxy-substituted radical **6** is then oxidized by iridium(IV) to cation **7**, which expels the silyl group leading to diketone **3**.

Scheme 2. Proposed Photoredox Cycle



To confirm the radical character of the process, the photoredox reaction of **1a** and **2a** was performed in the presence of 1 equiv of TEMPO. The desired reaction was completely blocked, as no expected product **3a** was observed. Instead, a compound arising from the trapping of difluorinated radical **5** by TEMPO was detected by ^{19}F NMR and GC–MS. Furthermore, the interaction of the photoexcited iridium catalyst with iodoketone **1a** was confirmed by Stern–Volmer fluorescence quenching experiments.

The accelerating effect of triphenylphosphine deserves a special comment. Previously, we observed such an effect, which on the basis of electrochemical data, was ascribed to reductive quenching of the excited state by the phosphine leading to a stronger reductive complex (for $Ru(bpy)_3^{2+}$ photocatalyst).[17b,25] However, for *fac*-Ir(ppy)$_3$, the reductive quenching of the photoexited complex by triphenylphosphine seems unlikely because of the mismatch of reduction potentials (Ir(III)*/Ir(II) + 0.31 V;[26] $Ph_3P/Ph_3P^{+\bullet}$ + 1.10 V vs SCE; see the Supporting Information for cyclic voltammetry).

Another opportunity is the formation of halogen-bonded species between iodide **1** and the phosphine followed by light-promoted homolysis and/or reduction of C–I bond.[27] However, for an equimolar mixture of iodide **1a** and triphenylphosphine, there were no signs of complex formation according to ^{19}F and ^{31}P NMR and UV–vis spectroscopy. For compound **1a**, the reduction potential of −1.20 V (vs SCE) was determined by cyclic voltammetry (CV), and the CV curve of **1a** was unaffected by the addition of a stoichiometric amount of triphenylphosphine. For comparison, the reduction potential of 2,2,2-trifluoro-1-iodoethane (CF_3CH_2I) was found to be −1.70 V. Apparently, more facile reduction of **1a** relative to CF_3CH_2I is associated with the presence of the benzoyl group.[28] Since we could not detect associative interaction between **1a** and the phosphine, the latter would likely not affect the electron transfer event. Similarly, no interaction between triphenylphosphine and silyl enol ether **2a** was observed by ^{31}P NMR.

In summary, a convenient protocol for the synthesis of diversely substituted 3-fluoropyridines is described. The method is based on the visible-light-mediated coupling of two derivatives of ketones followed by condensation with ammonia, and the whole sequence can be performed in a one-pot manner. Given that starting difluorinated iodides themselves are readily obtained from ketones by halogenative difluorocarbene insertion, the presented method allows for assembling of the 3-fluoropyridine structure from two simple ketones.

EXPERIMENTAL SECTION

Dimethylformamide (under vacuum) and acetonitrile were distilled from CaH_2 and stored over MS 4A. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer. The measurements were done in a positive-ion mode (interface capillary voltage −4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to 3000. Column chromatography was carried out employing silica gel 230–400 mesh. Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. For preparative HPLC, a reversed-phase column (C18-kromasil, 5 μ, 21.2 × 250 mm) was used. For irradiation, a strip of light-emitting diodes (2835-120LED 1M-Blue, 12 V) was used. Compounds **1b**,**f**[13a] and **2a**–**f**[24] were prepared according to literature procedures.

Measurement of Redox Potentials by Cyclic Voltammetry. Voltammetric studies were carried out in a temperature-controlled (25 °C) cell (V = 10 mL) under nitrogen atmosphere with a scan rate of

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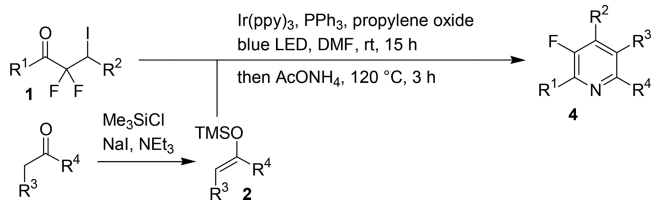
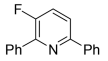
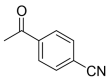
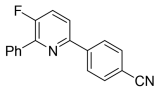
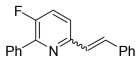
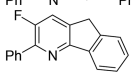
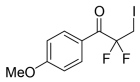
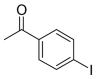
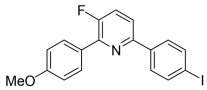
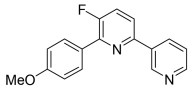
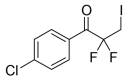
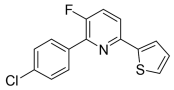
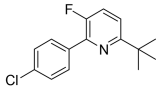
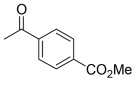
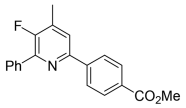
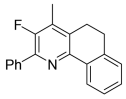
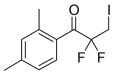
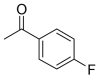
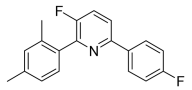
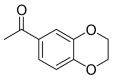
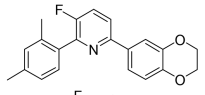
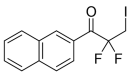
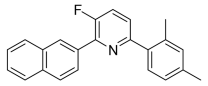
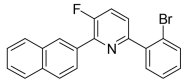
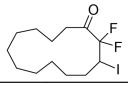
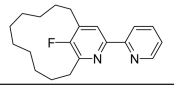
Table 4. Synthesis of Pyridines from Iodides 1 and Ketones



no	Iodide **1**		Ketone	Product		Yield of **4**, %[a]
1		**1a**			**4a**	89
2					**4g**	68
3					**4h**[b]	76
4					**4i**	59
5		**1b**			**4j**	80
6					**4k**	84
7		**1c**			**4l**	57
8					**4m**	61
9		**1d**			**4n**	76
10					**4o**	56
11		**1e**			**4p**	69
12					**4q**	76
13		**1f**			**4r**	62
14					**4s**	88
15		**1g**			**4t**	92

[a]Isolated yield. [b]*E*/*Z* mixture, ratio 70:30.

0.1 V·s^{-1}. A glassy carbon disk (diameter 2 mm) was used as a working electrode. Experiments were performed with the concentration of a studied compound of 1 mM in dry acetonitrile containing Et_4NClO_4 (0.1 M). A saturated calomel electrode (SCE) separated from the solution being studied by a salt bridge filled with the supporting electrolyte (0.1 M Et_4NClO_4) was used as a reference electrode. A platinum plate (S = 3 cm^2) was used as a counter electrode.

Preparation of *α,α*-Difluoro-*β*-iodoketones 1a,c−e,g. The tube containing silyl enol ether **2** (1 mmol, 1 equiv) was evacuated and filled with argon. Then, MeCN (1 mL), Me_3SiCF_2Br (305 mg, 1.5 mmol, 1.5 equiv), and Bu_4NBr (64.5 mg, 0.2 mmol, 0.2 equiv) were successively added at room temperature. The mixture was stirred for 1.5 h at 80 °C, and then cooled to room temperature. Iodine monochloride (0.68 mL, 1.3 mmol, 1.3 equiv) was added, and the mixture was stirred for 10 min at room temperature. For the workup, the mixture was diluted with saturated solution of Na_2SO_3 (8 mL), and the aqueous phase was extracted with hexane (3 × 5 mL). The combined organic layers were filtered through Na_2SO_4 and

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concentrated under vacuum, and the residue was purified by column chromatography.

2,2-Difluoro-3-iodo-1-phenylpropan-1-one (**1a**). Yield: 290 mg (98%). Colorless oil. R_f: 0.30 (hexane/EtOAc, 30/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 3.76 (t, J = 16.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 186.9 (t, J = 31.3 Hz), 134.9, 131.4, 130.3, 128.9, 115.7 (t, J = 255.1 Hz), 0.9 (t, J = 27.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.2 (t, J = 16.0 Hz, 2F). HRMS (ESI): calcd $C_9H_8F_2IO$ (M + H) 296.9582, found 296.9583.

1-(4-Chlorophenyl)-2,2-difluoro-3-iodopropan-1-one (**1c**). Yield: 294 mg (89%). White crystals. Mp: 52−53 °C. R_f: 0.28 (hexane/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 3.75 (t, J = 15.9 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 185.9 (t, J = 31.8 Hz), 141.7, 131.7 (t, J = 3.3 Hz), 129.7 (t, J = 3.1 Hz), 129.4, 115.7 (t, J = 255.0 Hz), 0.4 (t, J = 27.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.2 (t, J = 15.9 Hz, 2F). HRMS (ESI): calcd for $C_9H_6ClF_2IONa$ (M + Na) 352.9012, found 352.9010.

2,2-Difluoro-3-iodo-1-phenylbutan-1-one (**1d**). Yield: 273 mg (88%). Colorless oil. R_f: 0.23 (hexane/EtOAc, 28/1).^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 4.68 (ddq, J = 15.4, 12.7, 7.2 Hz, 1H), 1.99 (d, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 187.6 (t, J = 30.6 Hz), 134.7, 132.3 (t, J = 2.3 Hz), 130.2 (t, J = 3.4 Hz), 129.0, 116.8 (t, J = 257.5 Hz), 21.0 (t, J = 3.4 Hz), 19.4 (t, 25.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −97.3 (dd, J = 272.8, 12.7 Hz, 1F), −103.4 (dd, J = 272.8, 15.4 Hz, 1F). HRMS (ESI): calcd for $C_{10}H_{10}F_2IO$ (M + H) 310.9739, found 310.9742.

1-(2,4-Dimethylphenyl)-2,2-difluoro-3-iodopropan-1-one (**1e**). Yield: 217 mg (67%). White crystals. Mp: 51−52 °C. R_f: 0.25 (hexane/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (d, J = 8.0 Hz, 1H), 7.16−7.05 (m, 2H), 3.75 (t, J = 15.3 Hz, 2H), 2.50 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 189.5 (t, J = 29.5 Hz), 143.9, 141.0, 133.1, 130.1 (t, J = 6.1 Hz), 128.6, 126.3, 115.5 (t, J = 256.7 Hz), 21.6, 21.4, 1.0 (t, J = 28.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: − 94.9 (t, J = 15.3 Hz, 2F). HRMS (ESI): calcd for $C_{11}H_{11}F_2IONa$ (M + Na) 346.9715, found 346.9704.

2,2-Difluoro-3-iodocyclotridecan-1-one (**1g**). Yield: 354 mg (99%). White crystals. Mp: 58−59 °C. R_f: 0.10 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.23 (dd, J = 28.7, 9.8 Hz, 1H), 2.99 (ddt, J = 19.5, 10.3, 2.1 Hz, 1H), 2.64 (ddd, J = 19.2, 7.1, 1.8 Hz, 1H), 2.02−1.82 (m, 1H), 1.82−1.50 (m, 4H), 1.50−1.05 (m, 13H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 200.1 (dd, J = 32.3, 27.3 Hz), 115.8 (dd, J = 259.7, 254.3 Hz), 36.7, 31.7 (d, J = 3.3 Hz), 29.6 (dd, J = 24.9, 22.8 Hz), 26.4, 25.6, 25.3, 24.6, 24.6, 24.2, 23.2, 21.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −87.6 (d, J = 239.4 Hz, 1F), −119.4 (dd, J = 239.3, 28.7 Hz, 1F). HRMS (ESI): calcd for $C_{13}H_{21}F_2IONa$ (M + Na) 381.,497; found 381.0482.

2,2-Difluoro-1,5-diphenylpentane-1,5-dione (**3a**). A reaction tube with a stir bar was evacuated and filled with argon. Then, iodoketone **1a** (296 mg, 1 mmol, 1 equiv), MeCN (2 mL), PPh_3 (65.5 mg, 0.25 mmol, 0.25 equiv), propylene oxide (69.6 mg, 1.2 mmol, 1.2 equiv), *fac*-Ir(ppy)$_3$ (0.2 mg, 0.003 mmol, 0.003 equiv), and silyl enol ether **2a** (307 mg, 1.6 mmol, 1.6 equiv) were successively added at room temperature. The reaction vessel was irradiated with a strip of blue LED for 15 h; during irradiation, the mixture was cooled with room temperature water. The reaction mixture was quenched with water and extracted with MTBE (3 × 5 mL), and the combined organic layers were filtered through Na_2SO_4 and concentrated under vacuum. Crude product was purified by flash chromatography (hexane/EtOAc, 15/1) followed by purification by preparative HPLC (22% water in acetonitrile, retention time 10.4 min). Yield: 230 mg (80%). White crystals. Mp: 55−56 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, J = 7.7 Hz, 2H), 7.96 (d, J = 7.7 Hz, 2H), 7.67−7.34 (m, 6H), 3.28 (t, J = 7.6 Hz, 2H), 2.70 (tt, J = 17.6, 7.59 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 197.3, 189.0 (t, J = 31.0 Hz), 136.4, 134.4, 133.3, 131.8, 130.2 (t, J = 3.2 Hz), 128.7, 128.7, 128.0, 119.6 (t, J = 253.1 Hz), 30.9 (t, J = 4.0 Hz), 28.6 (t, J = 23.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.8 (t, J = 17.6 Hz, 2F). Anal. Calcd for $C_{17}H_{14}F_2O_2$ (288.10): C, 70.83; H, 4.90. Found: C, 70.81; H, 4.85.

Preparation of 3-Fluoropyridines 4 (General Procedure). *Silyl Enol Ethers* **2**. For experiments listed in Table 3, enol ethers **2** were obtained according to the literature procedure.[24] For experiments listed in Table 4, the following protocol was used: Sodium iodide (420 mg, 2.8 mmol, 1.4 equiv) was placed in a tube and dried under vacuum using heat gun. After being cooled to room temperature, the tube was filled with argon. Then MeCN (2 mL), ketone (2 mmol, 1 equiv), and triethylamine (304 mg, 3 mmol, 1.5 equiv) were successively added. The mixture was cooled with an ice/water bath, and chlorotrimethylsilane (3.32 mL, 2.6 mmol, 1.3 equiv) was added at 0 °C. The cooling bath was removed, and the mixture was stirred for 12 h at room temperature. Then the volatile components were evaporated under vacuum (a vacuum of about 10−20 Torr was applied with heating in a water bath at about 50 °C). The solid residue was washed with hexane (3 × 15 mL) (the hexane layers were decanted and filtered through a cotton plug). The combined filtrates were concentrated under vacuum using a rotary evaporator, furnishing the crude silyl enol ether, which was used in photoredox reaction without purification.

Reaction of Iodoketones **1** *with Silyl Enol Ethers* **2**. A reaction tube with a stir bar was evacuated and filled with argon. Then, iodoketone **1** (1 mmol, 1 equiv), DMF (2 mL), PPh_3 (65.5 mg, 0.25 mmol, 0.25 equiv), propylene oxide (69.6 mg, 1.2 mmol, 1.2 equiv), *fac*-Ir(ppy)$_3$ (0.2 mg, 0.003 mmol, 0.003 equiv), and silyl enol ether **2** [1.6 mmol of purified enol ether (Table 3); crude enol ether prepared from 2 mmol of ketone (Table 4)] were successively added at room temperature. The reaction vessel was irradiated with a strip of blue LED for 15 h; during irradiation, the mixture was cooled with room temperature water. Then ammonium acetate (462 mg, 6 mmol, 6 equiv) was added, and the mixture was stirred for 3 h at 120 °C and then cooled to room temperature. DMF was evaporated under reduced pressure, and the residue was purified by flash chromatography.

3-Fluoro-2,6-diphenylpyridine (**4a**). Yield: 224 mg (90%). White crystals. Mp: 66−67 °C. R_f: 0.42 (hexane/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.0 Hz, 2H), 8.12 (d, J = 7.2 Hz, 2H), 7.7 (dd, J = 8.6, 3.2 Hz, 1H), 7.62−7.41 (m, 7H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 157.0 (d, J = 260.8 Hz), 152.9 (d, J = 4.6 Hz), 145.0 (d, J = 10.6 Hz), 138.6, 135.7 (d, J = 5.8 Hz), 129.3, 129.0, 129.0, 128.9, 128.8, 128.5, 126.9, 124.9 (d, J = 21.5 Hz), 120.1 (d, J = 4.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −127.1 (d, J = 10.5 Hz, 1F). HRMS (ESI): calcd for $C_{17}H_{13}FN$ (M + H) 250.1027, found 250.1021.

3-Fluoro-6-(4-methoxyphenyl)-2-phenylpyridine (**4b**). Yield: 228 mg (82%). White crystals. Mp: 72−73 °C. R_f: 0.17 (hexane/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, 8.2 Hz, 2H), 8.04 (d, J = 8.8, 2H), 7.62 (dd, J = 8.6, 3.2 Hz, 1H), 7.57−7.42 (m, 4H), 7.01 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.6, 156.7 (d, J = 259.7 Hz), 152.7 (d, J = 4.6 Hz), 144.9 (d, J = 10.6 Hz), 135.9 (d, J = 6.1 Hz), 131.4, 129.3, 129.0 (d, J = 6.2 Hz), 128.5, 128.2, 125.0 (d, J = 21.6 Hz), 119.4 (d, J = 4.0 Hz), 114.2, 55.5. ^{19}F NMR (282 MHz, $CDCl_3$, 1F) δ: −128.3 (d, J = 9.4 Hz). Anal. Calcd for $C_{18}H_{14}FNO$ (279.31): C, 77.40; H, 5.05; N, 5.01. Found: C, 77.40; H, 5.01; N, 5.03.

6-(4-Chlorophenyl)-3-fluoro-2-phenylpyridine (**4c**). Yield: 224 mg (79%). Colorless oil. R_f: 0.25 (hexane/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, J = 7.8 Hz, 2H), 8.06 (d, J = 7.8 Hz, 2H), 7.69 (dd, J = 8.6, 3.2 Hz, 1H), 7.59−7.39 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 157.0 (d, J = 260.9 Hz), 153.0 (d, J = 4.7 Hz), 143.8 (d, J = 10.4 Hz), 138.4, 135.4, 134.2 (d, J = 6.1 Hz), 130.3 (d, J = 6.8 Hz), 129.1, 128.9, 128.7, 126.9, 125.1 (d, J = 21.6 Hz), 120.5 (d, J = 4.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.8 (d, J = 10.8 Hz, 1F). Anal. Calcd for $C_{17}H_{11}ClFN$ (283.73): C, 71.96; H, 3.91; N, 4.94. Found: C, 71.84; H, 3.79; N, 4.87.

3-Fluoro-6-(naphthalen-1-yl)-2-phenylpyridine (**4d**). Yield: 170 mg (57%). White crystals. Mp: 135−136 °C. R_f: 0.18 (hexane/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.23 (d, J = 7.3 Hz, 2H), 8.08−7.87 (m, 3H), 7.80 (dd, J =

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8.6, 3.1 Hz, 1H), 7.65−7.46 (m, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 157.1 (d, J = 260.9 Hz), 152.8 (d, J = 4.6 Hz), 145.2 (d, J = 10.8 Hz), 135.9, 135.8 (d, J = 5.8 Hz), 133.7 (d, J = 7.3 Hz), 129.4, 129.1, 129.1, 128.8, 128.6, 128.5, 127.8, 126.6, 126.4, 126.2, 125.0 (d, J = 21.6 Hz), 124.7, 120.4 (d, J = 4.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ −127.0 (d, J = 10.4 Hz, 1F). HRMS (ESI): calcd for $C_{21}H_{15}FN$ (M + H) 300.1183, found 300.1178.

*3-Fluoro-6-(furan-2-yl)-2-phenylpyridine (**4e**).* Yield: 143 mg (60%). yellow oil. R_f: 0.29 (hexane/EtOAc, 22/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.1 Hz, 2H), 7.65 (dd, J = 8.6, 3.2 Hz, 1H), 7.59−7.39 (m, 5H), 7.13 (d, J = 3.2 Hz, 1H), 6.59−6.51 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 156.4 (d, J = 260.2 Hz), 153.4, 145.6, 143.2, 135.5, 129.4, 129.1, 129.0, 128.5, 124.8 (d, J = 21.9 Hz), 118.5, 112.2, 108.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.2 (d, J = 9.6 Hz). HRMS (ESI): calcd for $C_{15}H_{11}FNO$ (M + H) 240.0819, found 240.0813.

*3-Fluoro-5-methyl-2,6-diphenylpyridine (**4f**).* Crude product was purified by flash chromatography (hexane/EtOAc, 30/1) followed by purification preparative HPLC (11% water in acetonitrile, retention time 12.3 min). Yield 158 mg (60%). White crystals. Mp: 92−93 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, J = 7.8 Hz, 2H), 7.67−7.60 (m, 2H), 7.55−7.38 (m, 7H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 156.5 (d, J = 260.9 Hz), 154.4 (d, J = 4.5 Hz), 142.6 (d, J = 10.3 Hz), 140.1, 135.6 (d, J = 5.8 Hz), 131.8 (d, J = 4.0 Hz), 129.3, 128.9, 128.8 (d, J = 6.0 Hz), 128.5, 128.2, 128.1, 126.3 (d, J = 20.5 Hz), 19.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −128.2 (d, J = 11.2 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{15}FN$ (M + H) 264.1183, found 264.1187.

*4-(5-Fluoro-6-phenylpyridin-2-yl)benzonitrile (**4g**).* Yield: 186 mg (68%). White crystals. Mp: 118−119 °C. R_f: 0.14 (hexane/EtOAc, 25/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.19 (d, J = 8.2, 2H), 8.10 (d, J = 7.5, 2H), 7.85−7.68 (m, 3H), 7.66−7.44 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 157.6 (d, J = 263.6 Hz), 150.6 (d, J = 5.0 Hz), 145.9 (d, J = 11.5 Hz), 142.6, 135.2 (d, J = 5.5 Hz), 132.7, 129.7, 129.0 (d, J = 6.1 Hz), 128.6, 127.4, 125.3 (d, J = 21.8 Hz), 120.7 (d, J = 4.5 Hz), 118.9, 112.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −124.6 (d, J = 8.2 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{11}FN_2Na$ (M + Na) 297.0798, found 297.0787.

*3-Fluoro-2-phenyl-6-styrylpyridine (**4h**).* Crude product was purified by flash chromatography (hexane/EtOAc, 20/1) followed by purification preparative HPLC (20% water in acetonitrile). Retention time: *E*-isomer, 12.2 min; *Z*-isomer, 10.6 min. *E*-Isomer. Yield: 146 mg (53%). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J = 6.9 Hz, 2H), 7.70−7.23 (m, 11H), 7.17 (dd, J = 16.1, 1.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 156.6 (d, J = 260.9 Hz), 151.6 (d, J = 4.9 Hz), 145.6 (d, J = 11.0 Hz), 136.8, 135.7 (d, J = 5.6 Hz), 132.9, 129.3, 129.1, 129.0, 128.8, 128.5, 128.4, 127.2, 124.6 (d, J = 21.6 Hz), 121.7 (d, J = 4.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.4 (d, J = 8.1 Hz, 1F). HRMS (ESI): calcd for $C_{19}H_{15}FN$ (M + H) 276.1183, found 276.1180. *Z*-Isomer. Yield: 63 mg (23%). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92 (d, J = 7.5, 2H), 7.53−7.40 (m, 3H), 7.40−7.23 (m, 6H), 7.14 (dd, J = 8.5, 3.4 Hz, 1H), 6.90 (d, J = 12.4 Hz, 1H), 6.77 (d, J = 12.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 156.2 (d, J = 261.0 Hz), 152.1 (d, J = 5.1 Hz), 145.4 (d, J = 10.6 Hz), 137.1, 135.5 (d, J = 5.5 Hz), 133.4, 129.7, 129.2, 129.1, 128.9, 128.51, 128.48, 127.7, 124.1 (d, J = 17.1 Hz), 124.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.3 (d, J = 9.5 Hz, 1F). HRMS (ESI): calcd for $C_{19}H_{15}FN$ (M + H) 281.1083, found 276.1186.

*3-Fluoro-2-phenyl-5H-indeno[1,2-b]pyridine (**4i**).* Yield: 154 mg (59%). Pale yellow crystals. Mp: 152−153 °C. R_f: 0.22 (hexane/EtOAc, 20/1). ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 7.4 Hz, 1H), 8.09 (d, J = 7.8 Hz, 2H), 7.52 (m, 7H), 3.90 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.8 (d, J = 256.9 Hz), 156.6 (d, J = 3.7 Hz), 144.0, 140.4, 137.3 (d, J = 5.2 Hz), 136.1 (d, J = 5.1 Hz), 129.1, 129.1, 129.0, 128.5, 127.5, 125.3, 121.1, 121.1, 120.8, 34.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −127.7 (d, J = 9.0 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{13}FN$, (M + H) 262.1027, found 262.1031.

*3-Fluoro-6-(4-iodophenyl)-2-(4-methoxyphenyl)pyridine (**4j**).* The crude product was recrystallized from methanol. Yield: 324 mg (80%). White crystals. Mp: 138−139 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 8.4 Hz, 2H), 7.79 (s, 4H), 7.56 (dd, J = 8.4, 2.9 Hz, 1H), 7.51−7.41 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 160.6, 156.9 (d, J = 260.8 Hz), 151.5 (d, J = 4.7 Hz), 144.9 (d, J = 10.5 Hz), 138.1, 137.9, 130.4 (d, J = 6.7 Hz), 128.6, 128.1 (d, J = 5.9 Hz), 124.9 (d, J = 21.7 Hz), 119.1 (d, J = 4.2 Hz), 113.9, 95.2, 55.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.4 (d, J = 8.4 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{14}FINO$ (M + H) 406.0099, found 406.0100.

*5-Fluoro-6-(4-methoxyphenyl)-2,3′-bipyridine (**4k**).* Yield: 234 mg (84%). White crystals. Mp: 85−86 °C. R_f: 0.18 (hexane/EtOAc, 3/2). ^1H NMR (300 MHz, $CDCl_3$) δ: 9.24 (br s, 1H), 8.62 (br d, J = 4.4 Hz, 1H), 8.34 (dt, J = 8.0, 1.9 Hz, 1H), 8.09 (dd, J = 8.9, 1.3 Hz, 2H), 7.61 (dd, J = 8.5, 3.2 Hz, 1H), 7.49 (dd, J = 10.8, 8.5 Hz, 1H), 7.37 (dd, J = 7.9, 4.8 Hz, 1H), 7.05−6.98 (m, 2H), 3.85 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 160.7, 157.1 (d, J = 261.3 Hz), 150.0 (d, J = 4.8 Hz), 149.8, 148.2, 145.3 (d, J = 10.6 Hz), 134.2, 134.2 (d, J = 7.0 Hz), 130.3 (d, J = 6.8 Hz), 127.8 (d, J = 5.9 Hz), 125.0 (d, J = 21.8 Hz), 123.6, 119.4 (d, J = 4.3 Hz), 113.9, 55.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −125.8 (d, J = 10.8 Hz, 1F). HRMS (ESI): calcd for $C_{17}H_{14}FN_2O$ (M + H) 281.1085, found 281.1084.

*2-(4-Chlorophenyl)-3-fluoro-6-(thiophene-2-yl)pyridine (**4l**).* Yield: 164 mg (57%). Pale yellow oil. R_f: 0.21 (hexane/EtOAc, 25/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.1 (d, J = 8.5, 2H), 7.60−7.34 (m, 6H), 7.11 (t, J = 4.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 156.4 (d, J = 260.7 Hz), 148.6 (d, J = 4.8 Hz), 144.1, 143.4 (d, J = 10.7 Hz), 135.5, 133.6 (d, J = 6.0 Hz), 130.2 (d, J = 7.0 Hz), 128.7, 128.1, 127.8, 125.2 (d, J = 22.2 Hz), 124.6 (d, J = 1.0 Hz), 118.8 (d, J = 4.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.1 (d, J = 10.3 Hz, 1F). HRMS (ESI): calcd for $C_{15}H_{10}ClFNS$ (M + H) 290.0201, found 290.0196.

*6-tert-Butyl-2-(4-chlorophenyl)-3-fluoropyridine (**4m**).* Yield: 160 mg (61%). White crystals. Mp: 60−61 °C. R_f: 0.16 (hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.06 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.41−7.25 (m, 2H), 1.41 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 164.9 (d), 156.0 (d, J = 258.6 Hz), 142.1 (d, J = 9.2 Hz), 135.1, 134.7 (d, J = 6.3 Hz), 130.2 (d, J = 7.0 Hz), 128.7, 124.4 (d, J = 21.0 Hz), 119.4 (d, J = 3.8 Hz), 37.6, 30.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −129.3 (d, J = 10.4 Hz, 1F). HRMS (ESI): calcd for $C_{15}H_{16}ClFN$ (M + H) 264.0950, found 264.0950.

*Methyl 4-(5-Fluoro-4-methyl-6-phenylpyridin-2-yl)benzoate (**4n**).* Yield: 244 mg (76%). White crystals. Mp: 136−137 °C. R_f: 0.23 (hexane/EtOAc, 11/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.16−8.14 (m, 4H), 8.13−8.09 (m, 2H), 7.58 (d, J = 4.8 Hz, 1H), 7.55−7.41 (m, 3H), 3.95 (s, 3H), 2.42 (d, J = 1.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 167.0, 156.6 (d, J = 259.9 Hz), 150.9 (d, J = 5.7 Hz), 145.0 (d, J = 12.2 Hz), 142.9, 135.6 (d, J = 7.11 Hz), 135.8 (d, J = 4.90 Hz), 130.2, 130.1, 129.3, 129.1 (d, J = 6.1 Hz), 128.5, 126.8, 122.6 (d, J = 2.0 Hz), 52.3, 14.9 (d, J = 4.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −131.8 (s, 1F). HRMS (ESI): calcd for $C_{20}H_{17}FNO_2$ (M + H) 322.1238, found 322.1230.

*3-Fluoro-4-methyl-2-phenyl-5,6-dihydrobenzo[h]quinolone (**4o**).* Yield: 162 mg (56%). White crystals. Mp: 106−107 °C. R_f: 0.31 (hexane/EtOAc, 20/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.46 (d, J = 7.3 Hz, 1H), 8.14 (d, J = 7.0 Hz, 2H), 7.62−7.19 (m, 6H), 2.91−3.06 (m, 4H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ:155.9 (d, J = 257.9 Hz), 147.4 (d, J = 5.1 Hz), 142.4 (d, J = 12.8 Hz), 137.2, 136.4 (d, J = 5.8 Hz), 134.7, 132.3 (d, J = 15.9 Hz), 131.7, 129.04, 128.95, 128.8, 128.4, 127.6, 127.2, 125.5, 27.8, 24.4, 10.9 (d, J = 6.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −130.9 (s, 1F). HRMS (ESI): calcd for $C_{20}H_{17}FN$ (M + H) 290.1340, found 290.1347.

*2-(2,4-Dimethylphenyl)-3-fluoro-6-(4-fluorophenyl)pyridine (**4p**).* Crude product was purified by flash chromatography (hexane/EtOAc, 30/1) followed by purification preparative HPLC (5% water in acetonitrile, retention time 9.2 min). Yield: 204 mg (69%). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09−7.96 (m, 2H), 7.67 (dd, J = 8.6, 3.5 Hz, 1H), 7.53 (t, J = 8.8 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.20−7.09 (m, 4H), 2.42 (s, 3H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 163.5 (d, J = 248.2 Hz), 156.4 (d, J = 257.0 Hz), 151.9 (d, J = 4.7 Hz), 147.8 (d, J = 15.3 Hz), 138.9, 136.7, 134.8 (d, J

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= 3.2 Hz), 132.4 (d, J = 4.0 Hz), 131.4, 130.1 (d, J = 1.9 Hz), 128.8 (d, J = 8.3 Hz), 126.6, 124.2 (d, J = 21.1 Hz), 119.9 (d, J = 3.8 Hz), 115.7 (d, J = 21.6 Hz), 21.7, 19.9 (d, J = 2.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −119.4 (m, 1F), −131.2 (d, J = 7.7 Hz, 1F). HRMS (ESI): calcd for $C_{19}H_{15}F_2NNa$ (M + Na) 318.1065, found 318.1066.

*6-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-(2,4-dimethylphenyl)-3-fluoropyridine (**4q**).* Yield: 255 mg (76%). White crystals. Mp: 116−117 °C. R_f: 0.13 (hexane/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67−7.57 (m, 2H), 7.56−7.43 (m, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.17 (s, 1H) 7.14 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 4.34−4,29 (m, 4H), 2.41 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 156.1 (d, J = 256.2 Hz), 152.3 (d, J = 4.7 Hz), 147.5 (d, J = 15.0 Hz), 144.5, 143.8, 138.7, 136.7, 132.6 (d, J = 4.0 Hz), 132.4, 131.3, 130.1, 126.5, 124.1 (d, J = 21.1 Hz), 120.2, 119.5 (d, J = 3.7 Hz), 117.5, 116.0, 64.6, 64.4, 21.4, 19.94 (d, J = 2.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −126.8 (d, J = 7.3 Hz, 1F). HRMS (ESI): calcd for $C_{21}H_{19}FNO_2$ (M + H) 336.1394, found 336.1384.

*6-(2,4-Dimethylphenyl)-3-fluoro-2-(naphthalen-2-yl)pyridine (**4r**).* Yield: 203 mg (62%). White crystals. Mp: 111−112 °C. R_f: 0.31 (hexane/EtOAc, 25/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.05−7.88 (m, 3H), 7.64−7.50 (m, 3H), 7.46 (d, J = 7.6 Hz, 1H), 7.40 (dd, J = 8.4, 3.2 Hz, 1H), 7.24−7.12 (m, 2H), 2.54 (s, 3H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 156.7 (d, J = 260.3 Hz), 155.9 (d, J = 5.0 Hz), 144.6 (d, J = 10.0 Hz), 138.3, 136.9, 136.0, 133.7, 133.3, 133.1 (d, J = 5.8 Hz), 131.8, 129.8, 129.0, 128.9, 128.0, 127.7, 126.8 (d, J = 2.5 Hz), 126.2, 126.3, 124.7, 124.4, 123.9 (d, J = 3.9 Hz), 21.7, 20.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −127.2 (s, 1F). HRMS (ESI): calcd for $C_{23}H_{18}FNNa$ (M + Na) 350.1315, found 350.1318.

*6-(2-Bromophenyl)-3-fluoro-2-(naphthalen-2-yl)pyridine (**4s**).* Yield 332 mg (88%). White crystals. Mp 109−110 °C. R_f: 0.44 (hexane/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.58 (s, 1H), 8.25 (dt, J = 8.7, 1.7 Hz, 1H), 8.01−7.91 (m, 2H), 7.93−7.85 (m, 1H), 7.72 (dd, J = 8.0, 0.9 Hz, 1H), 7.66 (dd, J = 7.6, 1.6 Hz, 1H), 7.61 (s, 1H), 7.59 (d, J = 0.6 Hz, 1H), 7.57−7.48 (m, 2H), 7.44 (td, J = 7.5, 1.0 Hz, 1H), 7.30 (dd, J = 7.8, 1.6 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 157.1 (d, J = 261.6 Hz), 154.0 (d, J = 8.0 Hz), 145.1 (d, J = 10.8 Hz), 140.5, 133.7, 133.5, 133.3, 132.7 (d, J = 5.4 Hz), 131.7, 129.9, 129.0, 128.9, 128.1, 127.7 (d, J = 4.38 Hz), 126.9, 126.2, 126.3, 124.6 (d, J = 3.6 Hz), 124.3, 124.0, 122.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −125.7. (t, J = 6.4 Hz, t, 1F). HRMS (ESI): calcd for $C_{21}H_{14}BrFN$ (M + H) 378.0288, 380.0269, found 378.0279, 380.0262.

*16-Fluoro-14-pyridin-2-yl-13-azabicyclo[10.3.1]hexadeca-1-(16),12,14-triene (**4t**).* Yield: 287 mg (92%) White crystals. Mp: 53−54 °C. R_f: 0.23 (hexane/EtOAc, 8/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.62 (d, J = 4.3 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 5.4 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H), 7.23 (s, 1H), 3.12−2.74 (m, 4H), 2.00−1.76 (m, 4H), 1.39−1.23 (m, 4H), 1.18−1.02 (m, 4H), 0.96−0.70 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 158.0 (d, J = 253.4 Hz), 156.2, 151.2 (d, J = 5.4 Hz), 149.9 (d, J = 18.1 Hz), 149.1, 138.8 (d, J = 15.9 Hz), 136.95, 123.3, 121. Four (d, J = 2.7 Hz), 121.2, 31.5 (d, J = 2.1 Hz), 28.6 (d, J = 1.4 Hz), 27.3, 27.2 (d, J = 1.1 Hz), 27.1, 26.8 (d, J = 1.4 Hz), 26.6, 26.5, 26.4, 26.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −131.8 (s, 1F). HRMS (ESI): calcd for $C_{20}H_{25}FN_2Na$ (M + Na) 335.1894, found 335.1881.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02467.

NMR spectra for all compounds, CV curves for studied compounds, and Stern−Volmer plot for fluorescence quenching studies (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265−2319. (b) Kishbaugh, T. L. S. *Curr. Top. Med. Chem.* **2016**, *16*, 3274−3302. (c) Wu, Y.-J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2012; Vol. *24*, pp 1−53.

(2) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315−8359. (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886.

(3) (a) Dolbier, W. R. In *Pyridines: from Lab to Production*; Scriven, E. F. V., Ed.; Academic Press: Oxford, 2013; pp 497−516. (b) Shestopalov, A. M.; Rodinovskaya, L. A.; Mortikov, V. Y.; Fedorov, A. E. In *Fluorine in Heterocyclic Chemistry*; Nenajdenko, V., Ed.; Springer: Cham, 2014; Vol. *2*, pp 1−58.

(4) (a) Schlosser, M.; Rausis, T. *Helv. Chim. Acta* **2005**, *88*, 1240−1249. (b) Schlosser, M.; Rausis, T.; Bobbio, C. *Org. Lett.* **2005**, *7*, 127−129. (c) Schlosser, M.; Ruzziconi, R. *Synthesis* **2010**, *2010*, 2111−2123.

(5) (a) David, T. K.; Prashanth, N. K.; Rajendraswami, M.; Pallalu, D.; Castelhano, A. L.; Kates, M. J.; Blobaum, A. L.; Jones, C. K.; Emmitte, K. A.; Conn, P. J.; Lindsley, C. W. *Tetrahedron Lett.* **2017**, *58*, 3554−3558. (b) Wilsily, A.; Mennen, S. M.; Cosbie, A.; Milne, J. E. *Org. Process Res. Dev.* **2017**, *21*, 1286−1293. (c) 3-Fluoropyridine subunit is present in a series of fluoroquinolone antibiotics; see: Anon, J.; Tillotson, G. *Antibiotiques* **2008**, *10*, 199−208.

(6) (a) Fukuhara, T.; Yoneda, N.; Suzuki, A. *J. Fluorine Chem.* **1988**, *38*, 435−438. (b) Döbele, M.; Vanderheiden, S.; Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5986−5988. (c) Timperley, C. M.; Banks, R. E.; Young, I. M.; Haszeldine, R. N. *J. Fluorine Chem.* **2011**, *132*, 541−547.

(7) (a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860−2863. (b) Dubbaka, S. R.; Narreddula, V. R.; Gadde, S.; Mathew, T. *Tetrahedron* **2014**, *70*, 9676−9681. (c) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2215−2218. (d) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219−2222.

(8) (a) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482−11484. (b) Neumann, C. N.; Hooker, J. M.; Ritter, T. *Nature* **2016**, *534*, 369−373. (c) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 1452−1455.

(9) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 5602−5605.

(10) (a) Rotstein, B. H.; Stephenson, N. A.; Vasdev, N.; Liang, S. H. *Nat. Commun.* **2014**, *5*, 4365. (b) Petersen, I. N.; Kristensen, J. L.; Herth, M. M. *Eur. J. Org. Chem.* **2017**, *2017*, 453−458. (c) Chun, J.-H.; Pike, V. W. *Chem. Commun.* **2012**, *48*, 9921−9923.

(11) (a) Allen, L. J.; Muhuhi, J. M.; Bland, D. C.; Merzel, R.; Sanford, M. S. *J. Org. Chem.* **2014**, *79*, 5827−5833. (b) Schimler, S. D.; Ryan, S. J.; Bland, D. C.; Anderson, J. E.; Sanford, M. S. *J. Org. Chem.* **2015**, *80*, 12137−12145. (c) Ryan, S. J.; Schimler, S. D.; Bland, D. C.; Sanford, M. S. *Org. Lett.* **2015**, *17*, 1866−1869.

(12) (a) Pews, R. G.; Lysenko, Z. *J. Org. Chem.* **1985**, *50*, 5115−5119. (b) Dolbier, W. R.; Xu, Y.-L. *J. Fluorine Chem.* **2003**, *123*, 71−73. (c) Chen, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2015**, *17*,

DOI: 10.1021/acs.joc.7b02467
J. Org. Chem. XXXX, XXX, XXX−XXX

2567−2569. (d) Chen, Z.; Zhu, J.; Xie, H.; Li, S.; Wu, Y.; Gong, Y. *Org. Biomol. Chem.* **2011**, *9*, 5682−5691.
(13) (a) Fedorov, O. V.; Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2015**, *80*, 5870−5876. For relevant difluorohomologation reactions, see: (b) Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2015**, *17*, 760−763. (c) Fedorov, O. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2016**, *81*, 9455−9460.
(14) For applications of α,α-difluoro-β-bromoketones (bromo analogues of iodoketones **1**) in the synthesis of heterocycles, see: (a) Fedorov, O. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2017**, *82*, 3270−3275. (b) Fedorov, O. V.; Levin, V. V.; Volodin, A. D.; Struchkova, M. I.; Korlyukov, A. A.; Dilman, A. D. *Tetrahedron Lett.* **2016**, *57*, 3639−3642.
(15) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322−5363. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898−6926. (c) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617−1622. (d) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176.
(16) For reviews on the application of perfluorinated halides in photoredox processes, see: (a) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. *Acc. Chem. Res.* **2016**, *49*, 2284−2294. (b) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937−1945. (c) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. *Org. Biomol. Chem.* **2015**, *13*, 11153−11183. (d) Dagousset, G.; Carboni, A.; Masson, G.; Magnier, E. In *Modern Synthesis Processes and Reactivity of Fluorinated Compounds*; Leroux, F. R., Tressaud, A., Eds.; Elsevier: Amsterdam, 2017; pp 389−426.
(17) For recent light-mediated reactions from our group, see: (a) Panferova, L. I.; Tsymbal, A. V.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2016**, *18*, 996−999. (b) Panferova, L. I.; Smirnov, V. O.; Levin, V. V.; Kokorekin, V. A.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2017**, *82*, 745−753. (c) Panferova, L. I.; Struchkova, M. I.; Dilman, A. D. *Synthesis* **2017**, *49*, 4124−4132. (d) Supranovich, V. I.; Levin, V. V.; Struchkova, M. I.; Korlyukov, A. A.; Dilman, A. D. *Org. Lett.* **2017**, *19*, 3215−3218. (e) Chernov, G. N.; Levin, V. V.; Kokorekin, V. A.; Struchkova, M. I.; Dilman, A. D. *Adv. Synth. Catal.* **2017**, *359*, 3063−3067.
(18) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119−6122.
(19) For nonphotoredox fluoroalkylation of silyl enol ethers, see: (a) Ge, W.-Z.; Wu, Y.-M.; Huang, W.-Y. *Chin. J. Chem.* **1991**, *9*, 527−535. (b) Sato, K.; Higashinagata, M.; Yuki, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *J. Fluorine Chem.* **2008**, *129*, 51−55. (c) Sato, K.; Yamazoe, S.; Akashi, Y.; Hamano, T.; Miyamoto, A.; Sugiyama, S.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *J. Fluorine Chem.* **2010**, *131*, 86−90. (d) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542−1553. (e) Katayev, D.; Vaclavik, J.; Bruning, F.; Commare, B.; Togni, A. *Chem. Commun.* **2016**, *52*, 4049−4052.
(20) Photoredox reactions of CF_3CH_2I have been reported. Mechanistically, these processes may involve prior reductive quenching of the photocatalyst by base, thereby leading to a stronger reducing species; see: (a) Li, L.; Huang, M.; Liu, C.; Xiao, J.-C.; Chen, Q.-Y.; Guo, Y.; Zhao, Z.-G. *Org. Lett.* **2015**, *17*, 4714−4717. (b) Roh, G.; Iqbal, N.; Cho, E. J. *Chin. J. Chem.* **2016**, *34*, 459−464. (c) Zhu, M.; Han, X.; Fu, W.; Wang, Z.; Ji, B.; Hao, X.-Q.; Song, M.-P.; Xu, C. *J. Org. Chem.* **2016**, *81*, 7282−7287.
(21) For the interaction of silylating agents with epoxides, see: Kricheldorf, H. R.; Mörber, G.; Regel, W. *Synthesis* **1981**, *1981*, 383−384.
(22) Enol acetates were notably less reactive compared to silyl enol ethers. For example, photoredox reaction isopropenyl acetate with iodoketone **1a** under the optimized conditions gave only 45% conversion according to ^{19}F NMR control.
(23) Monitoring of the reaction progress by ^{19}F NMR and GC−MS suggests that consumption of starting diketone proceeds faster compared to the formation of the final pyridine product. This means that the elimination of water or hydrogen fluorinde is the rate limiting step.
(24) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075−2088.
(25) Yasui, S.; Tsujimoto, M.; Shioji, K.; Ohno, A. *Chem. Ber.* **1997**, *130*, 1699−1707.
(26) Kelly, C. B.; Patel, N. R.; Primer, D. N.; Jouffroy, M.; Tellis, J. C.; Molander, G. A. *Nat. Protoc.* **2017**, *12*, 472−492.
(27) For visible-light-mediated reactions of halogen-bonded complexes, see: (a) Sun, X.; Wang, W.; Li, Y.; Ma, J.; Yu, S. *Org. Lett.* **2016**, *18*, 4638−4641. (b) Wang, Y.; Wang, J.; Li, G.-X.; He, G.; Chen, G. *Org. Lett.* **2017**, *19*, 1442−1445.
(28) In fact, CF_3CH_2I can couple with silyl enol ethers under our photoredox conditions, though the reaction is slower than that of iodoketones **1**. Thus, only 81% conversion was noted for the coupling of CF_3CH_2I with enol ether **2a** (^{19}F NMR control). In the literature, the photoredox reaction of CF_3CH_2I with silyl enol ethers was described, though a combination of an iridium catalyst with Hunig's base was used to effect the reductive quenching of excited photocatalyst generating a stronger reducing species; see: Huang, M.; Li, L.; Zhao, Z.-G.; Chen, Q.-Y.; Guo, Y. *Synthesis* **2015**, *47*, 3891−3900.

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