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Iodine-mediated aminohalogenation-oxidation to synthesize 2-fluoroalkyl imidazole derivatives

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Abstract

A simple and efficient method of iodine-mediated aminohalogenation-oxidation of fluorinated *N'*-propargyl amidines to synthesize 2-fluoroalkyl imidazole-5-carbaldehydes was developed. This method showed good functional group compatibility and wide substrate scope, as variety of substituted substrates proceeded smoothly to give the corresponding products in moderate to excellent yields. And this method was also suitable to unfluorinated substrates. Fluorinated allyl amidines used as starting materials, aminohalogenated products were obtained as the final products. Studies on the mechanism indicated that the carbonylation proceeded via 5-iodomethyl imidazole intermediate, and the carbonyl oxygen atom was demonstrated that originated from dioxygen.

Keywords Iodine-mediated · Propargyl amidine · Aminohalogenation-oxidation · Imidazole-5-carbaldehyde · 5-iodomethyl imidazole

Introduction

Fluorine was featured by unique chemical properties for the smaller atomic radius and the strongest electronegativity. The selective introduction of a fluorine atom or fluorine-containing group into organic molecules would dramatically modulate their lipophilicity, metabolic stability, bioavailability, and other properties (Groult et al. 2017; Kirsch 2012; Gouverneur et al. 2012). Be provided with new characteristics, fluorinated compounds are omnipresent in pharmaceuticals, agrochemicals, energetic materials, and other high-value chemical products (wang et al. 2014; Meanwell 2011; Purser et al. 2008). Despite great progress in constructing C-F and C-R_f over the past decade (Sather et al. 2016; Yang et al. 2015; Concepción et al. 2015; Liu et al. 2015), exploring a simple and efficient strategy to synthesize compounds with a fluorine atom or fluoroalkyl group at a desirable position in a highly controllable manner is still demanding.

Imidazoles which possess prominent chemical properties and physiological activity are common nitrogen heterocyclic compounds in bioactive molecules (Zhang et al. 2014; Jin et al. 2014). However, the numbers of pharmaceuticals, agrochemicals and other materials comprising fluorinated imidazoles remain limited for only few strategies that dedicate for constructing imidazole with a fluoroalkyl group at C-2 position efficiently (Du et al. 2008). Although some methods of transition metal-catalyzed fluoroalkylation can be applied in synthesis of 2-fluoroalkyl imidazoles (Zhang et al. 2011a; Chu and Qing 2012), the necessities of high cost, harsh conditions, complex system, and big toxicity result them in lacking of practicability and universality. In which of that situation, the use of fluorinated building blocks is a good alternative choice (Deutsch et al. 2016; Nie et al. 2011). Hashmi (Weyrauch et al. 2010), Wu (Li et al. 2013a; Li et al. 2012), Saito (Takahashi et al. 2020; Suzuki et al. 2017; Asari et al. 2016; Saito et al. 2011; Saito et al. 2010), Wan (Hu et al. 2014), Liu (Yi et al. 2018) and Maldvogel (Herszman et al. 2019) have developed efficient means of synthesizing imidazole/oxazole derivatives by halogen-induced electrophilic cyclization of propargyl amidines/

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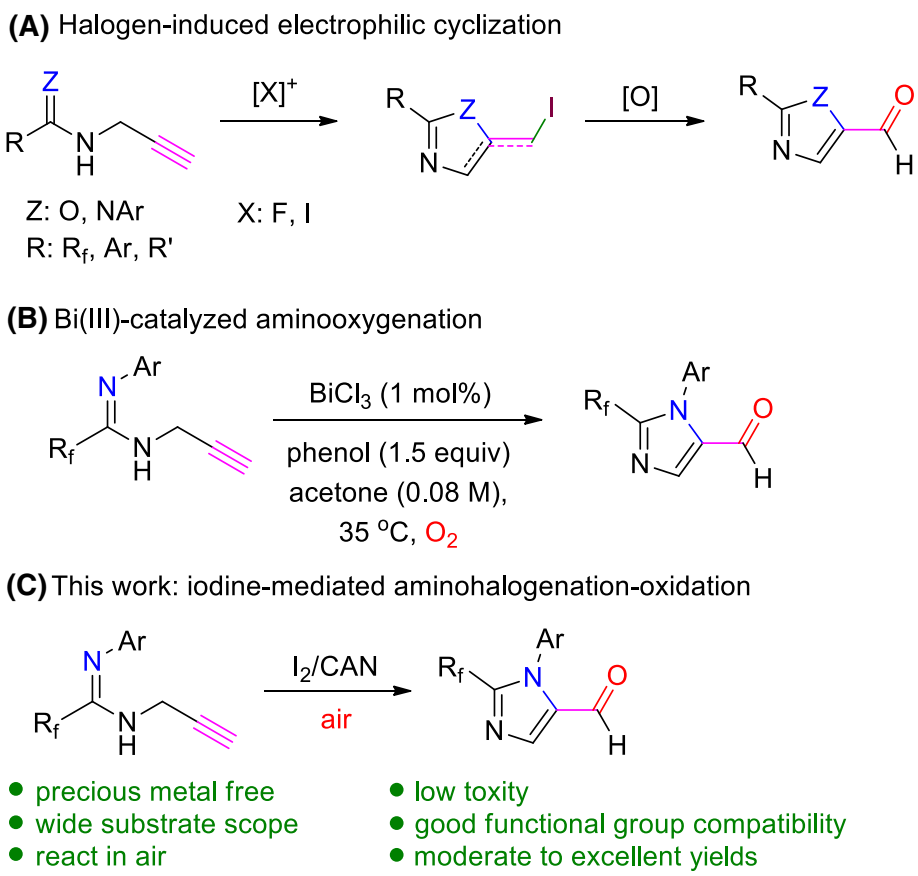
amides, respectively. The resulting halides could be used as intermediate for synthesizing various compounds with imidazole/oxazole motif, which allowed for quickly accessing a large number of diverse imidazole/oxazole derivatives for drug discovery and other industries (Scheme 1a). In 2020, a novel Bi(III)-catalyzed aminooxygenation was reported by us (Li et al. 2020). Under a dioxygen atmosphere, fluorinated propargyl amidines converted to 2-fluoroalkyl imidazole-5-carbaldehydes in one step. In spite of high atomic economy, this reaction was not environmentally friendly for using a large amount of toxic acetone and phenol, in which excess phenol would pollute the products because of the similar polarity. In view of the importance of this compound, we would report a practical method to synthesize 2-fluoroalkyl imidazole-5-carbaldehydes in moderate to excellent yields. Compared with previous works, this one pot-two step reaction had a more simple system, which could proceed smoothly in air. Most notably, the desired products were obtained with higher purity as byproducts and other impurities could be removed easily.

Experimental

Materials and instruments

All reagents used in this paper were purchased from commercial sources and purified before used by standard procedures. Unless otherwise specified, all reactions were carried out in a Schlenk tube and magnetic stirred under an ambient circumstance. TLC analysis was performed on silica gel plates, column chromatography over silica gel (mesh 300–400) and petroleum ether/ethyl acetate combination was used as eluent. Melting points were measured on a Melt-Temp apparatus and were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300/400 (300 MHz/400 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300/400 (282 MHz) spectrometer with $CFCl_3$ as internal standard. ^{13}C NMR spectra were taken on a Bruker AM-300/400 (101 MHz) spectrometer with TMS as internal standard. Mass spectra were recorded in Zhejiang University. Elemental analyses were recorded in Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.



Scheme 1 Works on synthesizing 2-fluoroalkyl imidazole derivatives

General procedure for synthesis of 2-fluoroalkyl imidazole-5-carbaldehyde

To a Schlenk tube was added I_2 (101.5 mg, 0.4 mmol, 0.4 equiv), CH_3CN (5.0 mL). With stirring, Ceric ammonium nitrate (CAN) (548.2 mg, 1.0 mmol, 1.0 equiv) and $NaHCO_3$ (126.0 mg, 1.5 mmol, 1.5 equiv) were added in batches. Some minutes later, a solution of *N'*-propargyl amidine (1.0 mmol, 1.0 equiv) in CH_3CN (1.0 mL) was added dropwise. Then the reaction was carried out in dark, and monitored by TLC. To the end, the system was quenched by addition of saturated $Na_2S_2O_3$, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under vacuum, and the residue was further purified by column chromatography to give the desired product.

General procedure for synthesis of 5-iodomethyl-2-trifluoromethyl imidazole

Under Nitrogen, to a solution of I_2 (507.6 mg, 1.5 mmol, 1.5 equiv) in CH_3CN (5.0 mL) was added CAN (1.1 g, 1.5 mmol, 1.5 equiv) and $NaHCO_3$ (168.0 mg, 2.0 mmol, 2.0 equiv). Some minutes later, a solution of *N'*-propargyl amidine (1.0 mmol, 1.0 equiv) in CH_3CN (1.0 mL) was added dropwise. Then the reaction was carried out in dark, and monitored by TLC. To the end, the reaction was quenched by addition of saturated $Na_2S_2O_3$, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum, and the residue was further purified by column chromatography to give the 5-iodomethyl imidazole, kept at 0 ℃, in 64% yield.

General procedure for synthesis of 5-(iodomethyl)-2-(trifluoromethyl)-4,5-dihydro-1H-imidazole

To a schlenk tube was added $NaHCO_3$ (126.0 mg, 1.5 mmol, 1.5 equiv), and a solution of allyl amidine (1.0 mmol) in CH_3CN (4 mL). And the system was placed in an ice-water bath. With stirring, a solution of ICl (178.6 mg, 1.1 mmol, 1.1 equiv) in CH_3CN (1 mL) was added dropwise. Then the system was allowed to warm to room temperature, and monitored by TLC. To the end, the reaction was quenched by addition of saturated $Na_2S_2O_3$, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under vacuum, and the residue was further purified by column chromatography to give the desired product.

Characterization for 2-fluoroalkyl imidazole derivatives

1-Phenyl-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2a)

White solid, m. p.: 60 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.93 (s, 1H), 7.56 (m, 3H), 7.37 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.14 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.7, 140.7 (q, J = 38.6 MHz), 137.7, 134.7, 133.6, 130.6, 129.5, 127.2, 117.7 (q, J = 270.5 MHz). MS (EI), m/e (%): 240 (M^+). Anal. Calcd. for $C_{11}H_7F_3N_2O$: C, 55.01; H, 2.94; N, 11.66; Found: C, 54.77; H, 11.84; N, 2.83.

1-(4-Methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2b)

White solid, m. p.: 116–117 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.91 (s, 1H), 7.28 (d, J = 12.0 MHz, 2H), 7.02 (d, J = 12.0 MHz, 2H), 3.89 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.99 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.0, 161.0, 140.9 (q, J = 39.1 MHz), 137.4, 134.9, 128.3, 125.9, 118.2 (q, J = 266.1 MHz), 114.6, 55.6. MS (EI), m/e (%): 270 (M^+). HRMS (EI), Calcd. for $C_{12}H_9N_2O_2F_3$: 270.0616; Found: 270.0613.

1-(4-Nitrophenyl)-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2c)

White solid, m. p.: 151–154 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.33 (d, J = 8.0 MHz, 2H), 7.90 (s, 1H), 7.47 (d, J = 8.0 MHz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.17 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 148.8, 141.0 (q, J = 39.4 MHz), 139.9, 139.3, 132.4, 128.4, 124.8, 117.9 (q, J = 292.9 MHz). MS (EI), m/e (%): 285.0 (M^+). HRMS (EI), Calcd. for $C_{11}H_6F_3N_3O_3$: 285.0361; Found: 285.0362.

Ethyl 4-(5-formyl-2-(trifluoromethyl)-1H-imidazol-1-yl) benzoate (2d)

White solid, m. p.: 93–95 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.23 (d, J = 8.4 MHz, 2H), 7.95 (s, 1H), 7.43 (d, J = 8.4 MHz, 2H), 4.44 (q, J = 7.2 MHz, 2H), 1.43 (t, J = 7.2 MHz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -59.97 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 165.1, 140.9 (q, J = 39.3 MHz), 138.8, 137.5, 134.5, 132.7, 130.7, 127.2, 117.5, 269.7 (q, J = 269.7 MHz), 61.6, 14.3. MS (EI), m/e (%): 312 (M^+). Anal. Calcd. for $C_{14}H_{11}F_3N_2O_3$: C, 53.85; H, 3.55; N, 8.97; Found: C, 54.04; H, 3.65; N, 8.88.

1-(4-Chlorophenyl)-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2e)

White solid, m. p.: 84 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 7.93 (s, 1H), 7.53 (d, J = 8.7 MHz, 2H), 7.31 (d, J = 8.7 MHz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.03 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.5, 141.0 (q, J = 38.7 MHz), 138.7, 136.8, 134.5, 132.3, 129.8, 128.4, 117.5 (q, J = 270.5 MHz). MS (EI), m/e (%): 274 (M^+). Anal. Calcd. for $C_{11}H_6F_3N_2ClO$: C, 48.11; H, 2.20; N. 10.20; Found: C, 48.00; H, 2.26; N, 10.08.

1-*m*-Tolyl-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2f)

White solid, m. p.: 29–33 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.85 (s, 1H), 7.34 (m, 2H), 7.10 (s, 2H), 2.02 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -60.20 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.9, 140.6 (q, J = 39.0 MHz), 139.9, 137.2, 134.8, 133.4, 131.4, 129.3, 127.6, 124.2, 117.5 (q, J = 269.7 MHz), 21.2. MS (EI), m/e (%): 254 (M^+). Anal. Calcd. for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02; Found: C, 56.57; H, 5.54; N, 11.20.

1-(3-Chlorophenyl)-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2g)

White solid, m. p.: 51–54 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.85 (s, 1H), 7.51 (m, 1H), 7.41 (m, 1H), 7.30 (s, 1H), 7.19 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.36 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 140.8 (q, J = 39.4 MHz), 138.6, 135.2, 134.7, 134.5, 130.9, 130.4, 127.4, 125.5, 117.8 (q, J = 272.7 MHz). MS (EI): m/e (%): 274 (M^+). HRMS (EI), Calcd. for $C_{11}H_6F_3ClN_2O$: 274.0121; Found: 274.0122.

2-(Trifluoromethyl)-1-(3-(trifluoromethyl)phenyl)-1H-imidazole-5-carbaldehyde (2h)

White solid, m. p.: 74–77 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.87 (s, 1H), 7.77 (m, 1H), 7.62 (m, 1H), 7.54 (m, 1H), 7.48 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.34 (s), -62.86 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 141.1 (q, J = 39.4 MHz), 139.2, 134.5, 132.2 (q, J = 33.3 MHz), 130.5, 130.2, 127.4 (q, J = 3.0 MHz), 124.3 (q, J = 4.0 MHz), 123.1 (q, J = 273.7 MHz), 122.1, 117.8 (q, J = 268.7 MHz). MS (EI), m/e (%): 308 (M^+). HRMS (EI), Calcd. for $C_{12}H_6F_6N_2O$: 308.0384; Found: 308.0385. Anal. Calcd. for $C_{12}H_6F_6N_2O$: C,46.77; H, 1.96; N, 9.09; Found: C, 46.89; H, 2.01; N, 9.18.

1-(2-Methoxyphenyl)-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2i)

White solid: m. p.: 104–106 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.84 (s, 1H), 7.46 (m, 1H), 7.23 (d, J = 8.0 MHz, 1H), 7.01 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.83 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 154.7, 140.6 (q, J = 39.4 MHz), 137.5, 134.5, 132.1, 128.3, 122.5, 120.7, 118.0 (q, J = 272.7 MHz), 111.9, 55.8. MS (EI), m/e (%): 270 (M^+). HRMS (EI), Calcd. for $C_{12}H_9F_3N_2O_2$: 270.0616; Found: 270.0617.

1-(2-Iodophenyl)-2-(trifluoromethyl)-1H-imidazole-5-carbaldehyde (2j)

White solid, m. p.: 44–46 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.98 (m, 2H), 7.54 (t, J = 7.7 MHz, 1H), 7.41 (d, J = 7.8 MHz, 1H), 7.30 (t, J = 7.5 MHz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.92 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 140.2 (q, J = 39.3 MHz), 139.9, 138.5, 137.2, 133.8, 131.9, 129.3, 128.2, 117.4 (q, J = 270.5 MHz), 97.1. MS (EI), m/e (%): 239 (M^+). Anal. Calcd. For $C_{11}H_6F_3N_2IO$: C, 36.09; H, 1.65; N, 7.65; Found: C, 36.11; H, 1.57; N, 7.86.

2-(Chlorodifluoromethyl)-1-(4-methoxyphenyl)-1H-imidazole-5-carbaldehyde (2k)

White solid, m. p.: 138–140 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51, 7.82, 7.21 (d, J = 8.0 MHz, 2H), 6.94 (d, J = 8.0 MHz, 2H), 3.81 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -48.02 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 160.8, 144.3 (t, J = 31.8 MHz), 137.2, 135.0, 128.7, 126.1, 119.9 (t, J = 289.9 MHz), 114.5, 55.6. MS (EI), m/e (%): 286 (M^+). HRMS (EI), Calcd. for $C_{12}H_9ClF_2N_2O_2$: 286.0321; Found: 286.0320.

2-(Chlorodifluoromethyl)-1-(4-(trifluoromethyl) phenyl)-1H-imidazole-5-carbaldehyde (2l)

White solid, m. p. 122–124 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.87 (s, 1H), 7.74 (d, J = 8.0 MHz, 2H), 7.43 (d, J = 8.0 MHz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -47.90 (s, 2F), -62.81 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 143.5 (t, J = 32.8 MHz), 138.1, 136.3, 133.4, 131.6 (q, J = 33.3 MHz), 127.1, 125.6, 122.3 (q, J = 273.7 MHz), 118.7 (t, J = 289.9 MHz). MS (EI), m/e (%): 324 (M^+). HRMS (EI), Calcd. for $C_{12}H_6ClF_5N_2O$: 324.0089; Found: 324.0091.

2-(Chlorodifluoromethyl)-1-(2-ethylphenyl)-1H-imidazole-5-carbaldehyde (2m)

White solid, m. p.: 77–78 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.88 (s, 1H), 7.47 (m, 1H), 7.39 (m, 1H), 7.28 (m, 1H), 7.19 (m, 1H), 2.19 (m, 2H), 1.06 (t, J = 8.0 MHz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -48.87 (d, J = 16.9 MHz, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 144.0 (t, J = 32.3 MHz), 141.1, 137.7, 134.5, 132.5, 130.9, 127.6, 126.7, 119.9 (t, J = 299.0 MHz), 23.2, 13.5. MS (EI), m/e (%): 284 (M^+). HRMS (EI), Calcd. for $C_{13}H_{11}ClF_2N_2O$: 284.0528; Found: 284.0524.

1-(2-Bromophenyl)-2-(chlorodifluoromethyl)-1H-imidazole-5-carbaldehyde (2n)

Light yellow solid. m. p.: 63–64 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.86 (s, 1H), 7.67 (m, 1H), 7.40 (m, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -49.18 (q). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 143.8 (t, J = 32.3 MHz), 138.5, 133.9, 133.8, 133.5, 131.9, 129.2, 128.3, 122.3, 119.7 (t, J = 289.9 MHz). MS (EI), m/e (%): 334 (M^+). HRMS (EI), Calcd. for $C_{11}H_6ClBrF_2N_2O$: 298.9632 (M-Cl); Found: 298.9628 (M-Cl).

2-(Bromodifluoromethyl)-1-*p*-tolyl-1H-imidazole-5-carbaldehyde (2o)

White solid (decompose in heating). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.90 (s, 1H), 7.35 (d, J = 8.4 MHz, 2H), 7.27 (d, J = 8.4 MHz, 2H), 2.47 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −44.97 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.0, 144.9 (t, J = 29.1 MHz), 140.8, 137.3, 134.7, 131.2, 130.0, 127.2, 111.2 (t, J = 300.4 MHz), 21.3. MS (EI), m/e (%): 314 (M^+). HRMS (EI), Calcd. for $C_{12}H_9N_2OF_2Br$: 313.9866; Found: 313.9861.

2-(Bromodifluoromethyl)-1-(2-(trifluoromethyl) phenyl)-1H-imidazole-5-carbaldehyde (2p)

White solid, m. p.: 69–71 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.96 (s, 1H), 7.87 (m, 1H), 7.75 (m, 2H), 7.51 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -45.53 (s, 2F), -60.70 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 145.6 (t, J = 29.2 MHz), 139.2, 134.7, 132.9, 132.4, 130.9, 129.3, 127.6 (q, J = 5.1 MHz), 122.8 (q, J = 272.0 MHz), 110.7 (t, J = 301.1 MHz). MS (EI), m/e (%): 368 (M^+). Anal. Calcd. for $C_{12}H_6BrF_6N_2O$: C, 39.05; H, 1.66; N, 7.59; Found: C, 39.20; H, 1.66; N, 7.46.

2-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-imidazole-5-carbaldehyde (2q)

White Solid, m. p.: 139–142 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57, 7.83, 7.22 (d, J = 12.0 MHz, 2H), 6.94 (d, J = 12.0 MHz, 2H), 6.51 (t, J = 52.0 MHz, 1H), 3.81 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.86 (d, J = 52.64 MHz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 160.7, 144.9 (t, J = 21.0 MHz), 138.5, 134.3, 128.4, 126.0, 114.6, 108.4 (t, J = 238.0 MHz), 55.6. MS (EI), m/e (%): 252 (M^+). HRMS (EI), Calcd. for $C_{12}H_{10}F_2N_2O_2$: 252.0710; Found: 252.0709.

2-(Difluoromethyl)-1-(naphthalen-1-yl)-1H-imidazole-5-carbaldehyde (2r)

White solid, m. p.: 185–188 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.98 (m, 2H), 7.90 (m, 1H), 7.49 (m, 4H), 7.03 (m, 1H), 6.41 (t, J = 12.0 MHz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.81 (qd, J_1 = 39.5 MHz, J_2 = 67.7 MHz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 144.4 (q, J = 27.3 MHz), 137.3, 133.8, 132.9, 130.0, 129.0, 127.5, 127.3, 126.3, 124.8, 124.0, 120.1, 107.1 (t, J = 239.4 MHz). MS (EI), m/e (%): 272 (M^+). HRMS (EI), Calcd. for $C_{15}H_{10}F_2N_2O$: 272.0761; Found: 272.0759.

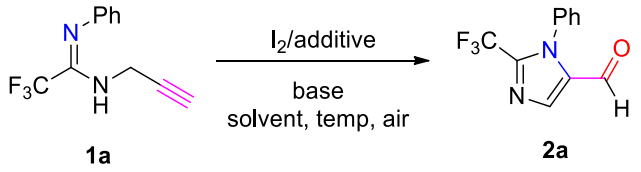
1-(4-Methoxyphenyl)-2-(perfluoroethyl)-1H-imidazole-5-carbaldehyde (2s)

White solid, m. p.: 74–75 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.87 (s, 1H), 7.20 (d, J = 12.0 MHz, 2H), 6.94 (d, J = 8.0 MHz, 2H), 3.81 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -82.30 (t, J = 5.6 MHz, 3F), -108.29 (s, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 160.9, 139.6 (t, J = 54.5 MHz), 137.5, 135.2, 128.4, 126.1, 118.1 (qt, J_1 = 287.9 MHz, J_2 = 70.7 MHz), 114.5, 109.1 (tq, J_1 = 255.5 MHz, J_2 = 39.4 MHz), 55.6. MS (EI), m/e (%): 272 (M^+). HRMS (EI), Calcd. for $C_{13}H_9F_5N_2O_2$: 320.0584; Found: 320.0586. Anal. Calcd. for $C_{13}H_9F_5N_2O_2$: C,48.76; H, 2.83; N, 8.75; Found: C, 48.89; H, 2.89; N, 8.87.

5-Iodo-1-(4-methoxyphenyl)-6-phenyl-2-(trifluoromethyl)-1,4-dihydropyrimidine (2t)

Light yellow solid (decompose at rt). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (m, 3H), 7.00 (m, 2H), 6.91 (d, J = 8.7 MHz, 2H), 6.61 (d, J = 8.7 MHz), 4.85 (s, 2H), 3.69 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -65.53 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 145.5 (q, J = 33.5 MHz), 143.3, 136.6, 131.7, 131.1, 130.0, 128.6, 128.1, 117.7 (q, J = 277.1 MHz), 113.7, 73.6, 57.6, 55.3. MS (ESI): 459.3 ($M+H^+$). HRMS (ESI), Calcd. for $C_{18}H_{15}F_3IN_2O$: 459.0181; Found: 459.0187.

Table 1 Optimization for iodine-mediated aminohalogenation-oxidation[a]



1a **2a**

Entry	Iodine (equiv)	Additive (equiv)	Solvent	Base[b]	Yield (%)[c]
1	NIS (1.0)	–	CH_3CN	K_2CO_3	56
2	ICl (1.0)	–	CH_3CN	K_2CO_3	49
3	I_2 (1.0)	–	CH_3CN	K_2CO_3	12
4	I_2 (1.0)	O_2	CH_3CN	K_2CO_3	9
5	I_2 (1.0)	$AgNO_3$ (1.0)	CH_3CN	K_2CO_3	82(14)[d,e]
6	I_2 (1.0)	CAN (1.0)	CH_3CN	K_2CO_3	87
7	I_2 (0.5)	CAN (1.0)	CH_3CN	K_2CO_3	82
8	I_2 (0.4)	CAN (1.0)	CH_3CN	K_2CO_3	77(8)
9	I_2 (0.3)	CAN (1.0)	CH_3CN	K_2CO_3	45(33)
10	**I_2 (0.4)**	**CAN (1.0)**	**CH_3CN**	**$NaHCO_3$**	**87**
11	I_2 (0.4)	CAN (1.0)	CH_3CN	NaOAc	78
12	I_2 (0.4)	CAN (1.0)	acetone	$NaHCO_3$	/
13	I_2 (0.4)	CAN (1.0)	THF	$NaHCO_3$	54
14	I_2 (0.4)	CAN (1.0)	CH_2Cl_2	$NaHCO_3$	0(24)
15	I_2 (0.4)	CAN (1.0)	DMF	$NaHCO_3$	66(11)
16	I_2 (0.4)	CAN (1.0)	CH_3CN	$NaHCO_3$	27[f]

[a]Reaction conditions: **1a** (1.0 mmol), solvent (6.0 mL), air, 6 h, rt

[b]Base: 1.5 equiv

[c]Isolated yield

[d]Number in parentheses represents the yield of 5-methyl imidazole

[e]**2a** was obtained in 80% at 50 ℃

[f]50 ℃

Ethyl 5-formyl-1-phenyl-1H-imidazole-2-carboxylate (2u)

White solid, m. p.: 102–104 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.98 (s, 1H), 7.54 (m, 3H), 7.32 (m, 2H), 4.29 (q, J = 7.2 MHz, 2H), 1.26 (t, J = 7.2 MHz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.3, 157.7, 141.1, 138.1, 135.5, 135.0, 129.9, 129.3, 127.0, 62.2, 13.9. MS (EI), m/e (%): 244 (M^+). Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47; Found: C, 63.88; H, 5.19; N, 11.32.

Imidazo[1,2-a]pyridine-3-carbaldehyde (2v)

White solid, m. p.: 113–115 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 9.51 (d, J = 7.0 MHz, 1H), 8.33 (s, 1H), 7.82 (d, J = 8.0 MHz, 1H), 7.57 (t, J = 7.0 MHz, 1H), 7.15 (t, J = 7.0 MHz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 149.2, 146.7, 130.1, 128.6, 117.7, 115.4. MS (EI), m/e (%): 146 (M^+). HRMS (EI), Calcd. for $C_8H_6N_2O$: 146.0680; Found: 146.0682.

2-Phenyloxazole-5-carbaldehyde (2w)

White solid, m. p.: 70–72 ℃. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.18 (d, J = 7.3 MHz, 2H), 7.96 (s, 1H), 7.52 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 165.6, 149.7, 139.2, 132.4, 129.2, 127.8, 126.0. MS (EI), m/e (%): 173 (M^+). HRMS (EI): Calcd For $C_{10}H_7NO_2$: 173.0477; Found 173.0476.

5-(Iodomethyl)-1-(4-methoxyphenyl)-2-(trifluoromethyl)-1 H-imidazole (6b)

White solid (decompose at rt). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J = 9.0 MHz, 2H), 7.29 (s, 1H), 7.04 (d, J = 9.0 MHz, 2H), 4.17 (s, 2H), 3.91 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -65.57 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2, 138.5, 137.3 (q, J = 38.6 MHz), 132.1, 129.0, 124.9, 118.5 (q, J = 269.1 MHz), 114.8, 55.7. MS (ESI): 383.2 ($M + H^+$). HRMS (ESI), Calcd. For $C_{12}H_{11}N_2OF_3I^+$: 382.98672; Found: 382.9868 ± 0.002.

5-(Iodomethyl)-1-phenyl-2-(trifluoromethyl)-4,5-dihydro-1H-imidazole (4a)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (m, 2H), 6.77 (m, 1H), 6.63 (m, 2H), 3.70 (m, 1H), 3.42 (m, 2H), 3.30 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -75.71 (s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0 (q, J = 44.4 MHz), 145.3, 129.7, 119.7, 115.5 (q, J = 292.9 MHz), 114.6. MS (EI), m/e (%): 354 (M^+). HRMS (EI), Calcd. For $C_{11}H_{10}N_2F_3I$: 353.9841; Found: 353.9840.

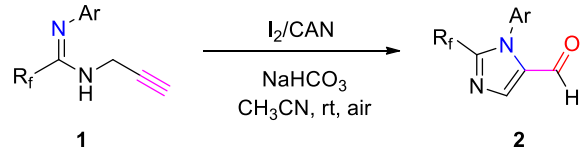
1-(4-chlorophenyl)-2-(trifluoromethyl)-1H-imidazole (5e)

Light yellow semisolid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 12.0 MHz, 2H), 7.32 (d, J = 12.0 MHz, 2H), 7.25 (s, 1H), 7.15 (s, 1H). ^{19}F NMR (565 MHz, $CDCl_3$) δ -59.56 (s). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.14 (q, J = 39.26 MHz), 135.87, 134.69, 129.71, 129.01, 127.43, 125.01, 118.58 (q, J = 276.3 MHz). MS (EI), m/e (%): 246 (M^+). HRMS (EI) Calcd for $C_{10}H_6ClF_3N_2$: 246.0172, Found: 246.0170.

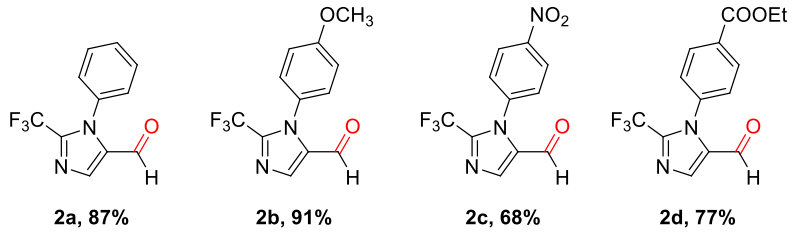
Results and discussion

In our initial studies, *N*-phenyl *N'*-propargyl 2-trifluoromethyl amidine **1a** was chosen as the model reaction to explore the optimal conditions. Be treated with NIS in CH_3CN at room temperature under air atmosphere, **1a** converted to **2a** in a moderate yield of 56% (Table 1, entry 1). A lower yield

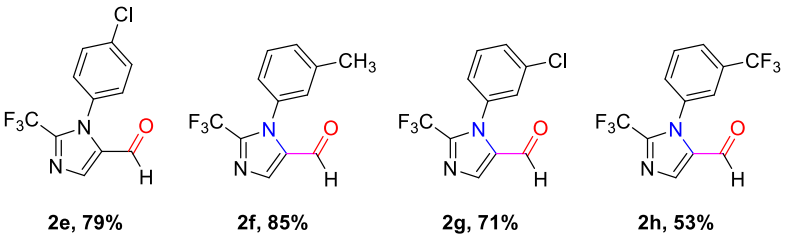
Table 2 Scope of iodine-mediated aminohalogenation-oxidation of 1[a, b]



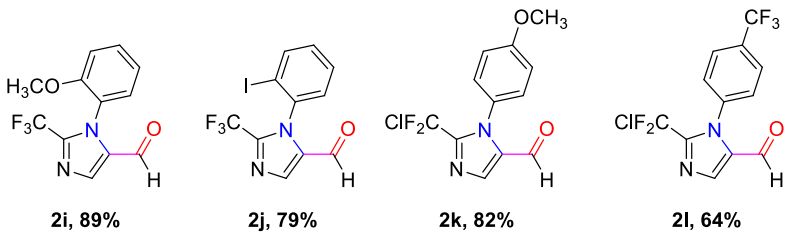
1 2



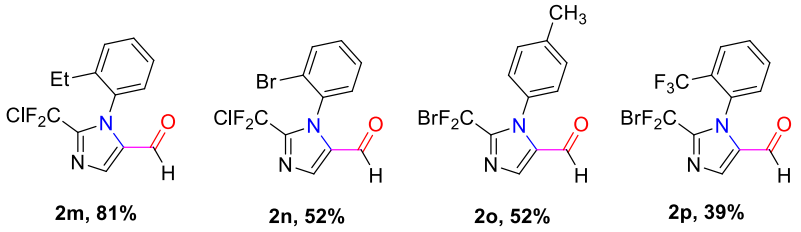
2a, 87% **2b, 91%** **2c, 68%** **2d, 77%**



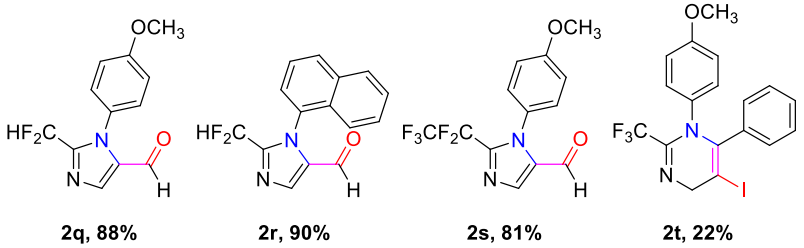
2e, 79% **2f, 85%** **2g, 71%** **2h, 53%**



2i, 89% **2j, 79%** **2k, 82%** **2l, 64%**



2m, 81% **2n, 52%** **2o, 52%** **2p, 39%**



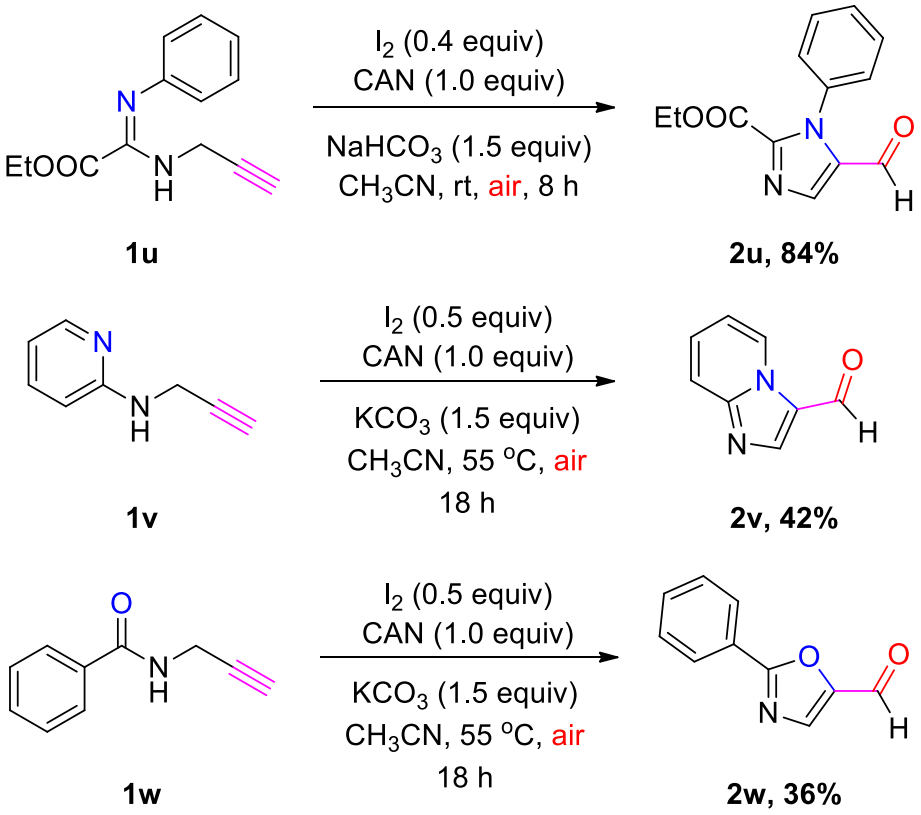
2q, 88% **2r, 90%** **2s, 81%** **2t, 22%**

[a]Reaction conditions: *N*'-propargyl amidines **1** (1.0 mmol), iodine (0.4 equiv), CAN (1.0 equiv), $NaHCO_3$ (1.5 eauiv.), CH_3CN (6.0 mL), air, 6.0 h, rt

[b]Isolated yield

of 49% was obtained when ICl was used (Table 1, entry 2). It was speculated that high oxidative activity of NIS and ICl resulted in the decomposition of **1a** and low yield of **2a**. I_2, a low activity iodinated regent, decreased the yield of **2a** to 12% (Table 1, entry 3). The addition of 1.0 equiv. $AgNO_3$ into the reaction promoted the yield of **2a** to 82% but with concurrent formation of 5-methyl imidazole in 14% yield (Table 1, entry 5) (Zhang et al. 2011b). Excitedly, the yield of **2a**, the sole product, was highlighted to 87% by addition of 1.0 equiv. CAN (Table 1, entry 6) (Likhar et al. 2009).

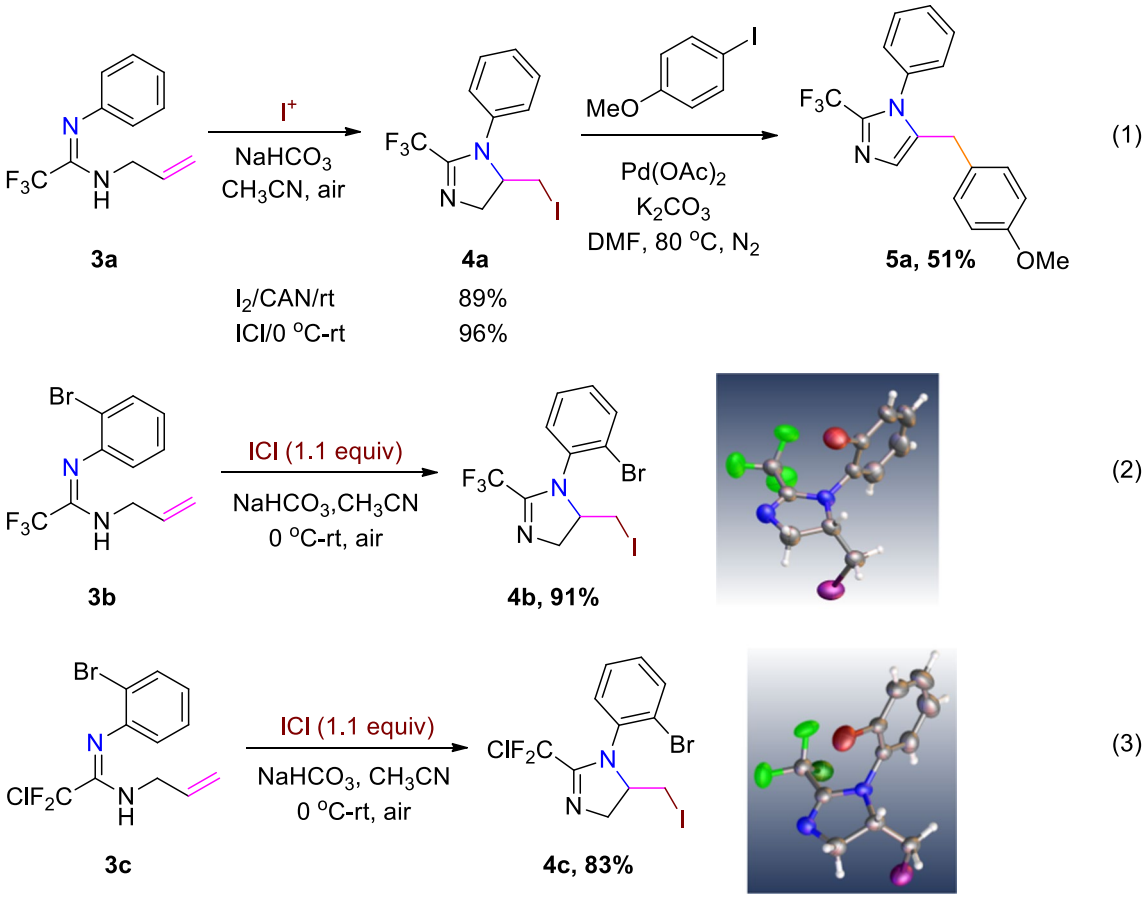
Scheme 2 Reactions of unfluorinated substrates



Further studies showed that an identical yield of 87% was obtained when the loading of I_2 was decreased to 0.4 equiv. in the presence of $NaHCO_3$, which were taken as the optimal reaction conditions (Table 1, entry 10). Other solvents, such as acetone, THF, CH_2Cl_2, and DMF, disfavored the formation of **2a** (Table 1, entries 12–15). Higher temperature would short reaction time, but resulted in a lower yield (Table 1, entry 16).

Then, the generality of this transformation was investigated under the optimal reaction conditions. As shown in Table 2, this reaction showed good functional group compatibility, as *N'*-propargyl amidines with broad spectrum of functional groups converted to the corresponding products smoothly in moderate to excellent yields. Generally, trifluoromethylated substrates containing electron-donating groups gave the desired products in good to excellent yields (**2b**, **2f**, and **2i**). Electron-withdrawing groups would lead to lower yields (**2c**, **2d**, and **2h**). Compared with electronic effect, steric hindrance had little influence on the proceeding of this transformation (**2b** and **2i**, **2e** and **2g**). The effect of other fluoroalkyl groups was also examined. -CF_2X group often resulted in low yields. Of which, -$BrCF_2$ would drastically decrease the yield due to the substrates' instability (**2k**–**2p**). While, the reactions of substrates containing a –CF_2H group proceeded without any difficult to give the desired product in good yields (**2q**–**2r**). **2s** was obtained in 81% for–CF_2CF_3 with higher electron-withdrawing ability. 5-Iodo-1, 4-dihydropyrimidine **2t**, without further oxidation, was afforded in 22% yield when substrate with a phenyl on the terminal alkyne was used.

To our delight, this method was suitable for unfluorinated substrates. 2-(Ethoxycarbonyl) propargyl aminde **1u** produced **2u** in a good yield of 84% under the standard reaction conditions. K_2CO_3 used as base, substrate **1v** proceeded by a similar process to give **2v** in 42% yield at 55 ℃ with a longer time. Under the same conditions, **2w** was obtained in 36% yield, in which oxygen atom acted as nucleophilic regent to attack the activated triple-bonds. Based on the reaction conditions, fluorinated substrates were more suitable to the reaction. It was considered that this result was caused by three factors: first, the solubility of substrates was increased by introduction a fluoroalkyl group, which could initiate the reaction by closing to the iodinated regent in a shorter time (Lipinski et al. 2001); second, 2-fluoroalkyl imidazole ring, as a strong electron-withdrawing group, enhanced the polarity of C-I in iodinated intermediate and promoted its dissociation into free radical with high stability; third, the increased acidity of hydrogen atom on methylene by the fluoroalkyl group speeded up the rearrangement of peroxy-radical intermediate.

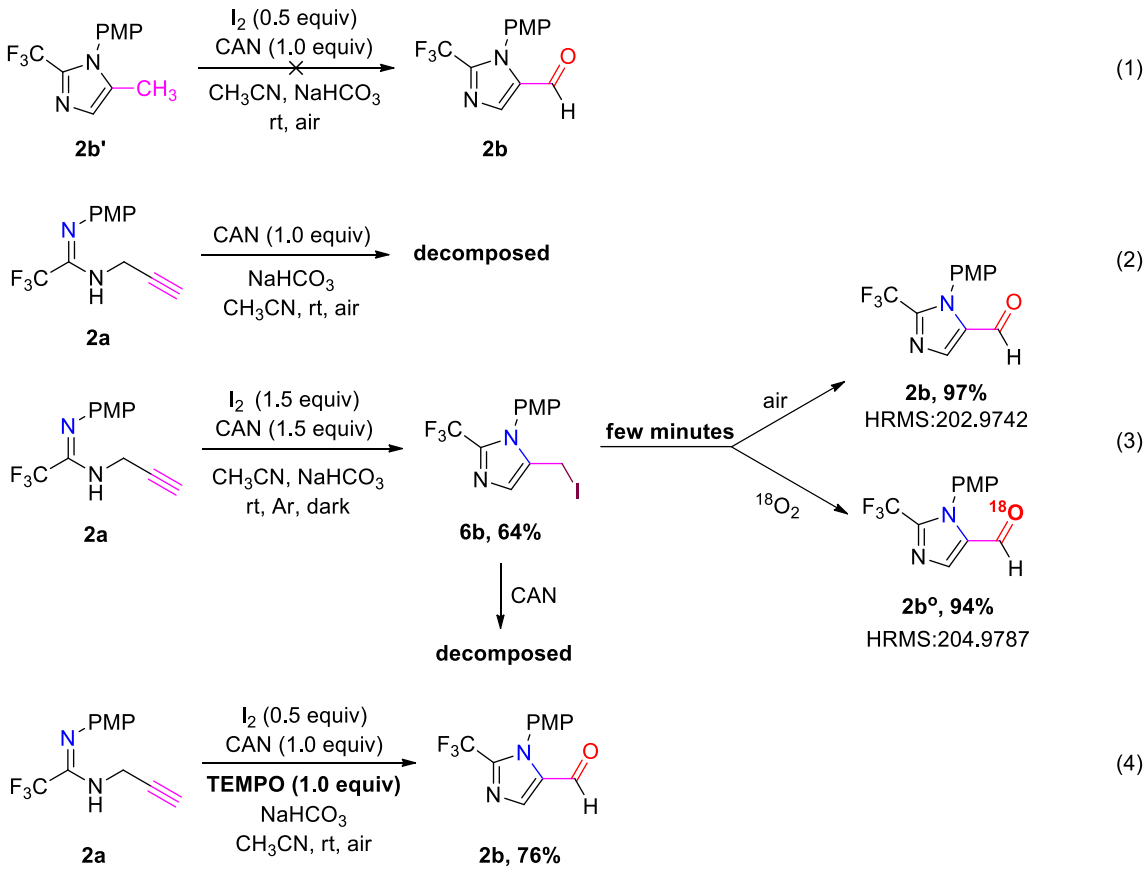


Scheme 3 Reactions of allyl amidines with ICl

We have applied this method to exam the reactions of allyl amidines. Under the standard reaction conditions, **3a** converted to 5-iodomethyl 4, 5-dihydro imidazole **4a** as the final product in a good yield of 89%. And an excellent yield of 96% was obtained when ICl was used as iodinated regent (Scheme 3–1). **4a**, a stable intermediate in air, could add flexibility to further elaborate the 2-fluoroalkyl imidazole compounds (Li et al. 2013b; Chen et al. 2020). Allyl amidines with other functional groups also worked very well to give the corresponding products in good to excellent yields (**4b** and **4c**) (Scheme 2 and 3).

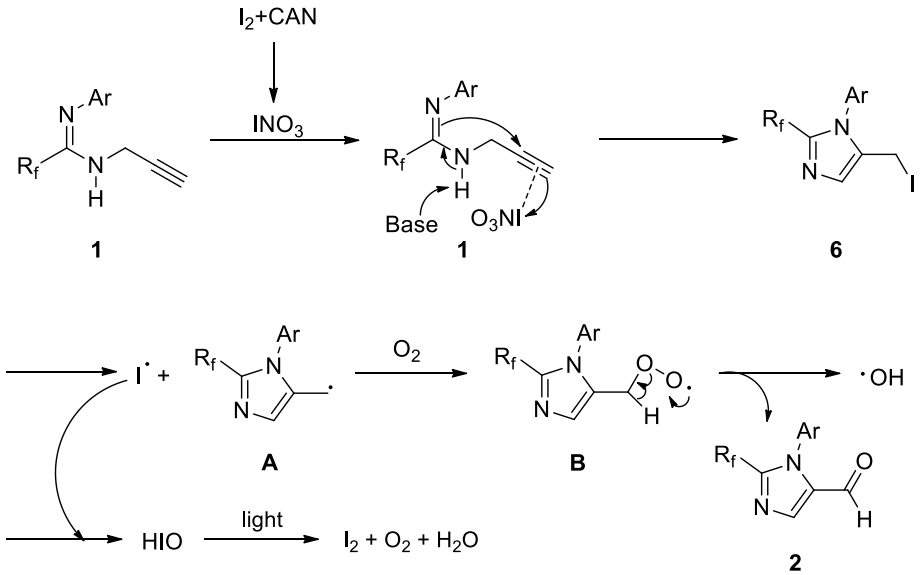
Studies were then carried out to propose a possible mechanism for this transformation. 5-methyl imidazole **2b'**, detected in the reaction system, would not convert to the carbonylated product under the standard reaction conditions (Scheme 4–1). I_2 played a critical role in obtaining the desired product as none was obtained without I_2 (Scheme 4–2). When the reaction proceeded under an argon atmosphere, 5-iodomethyl imidazole **6b** was obtained in 64% yield. Compared to 5-iodomethyl 4,5-dihydro imidazole **4a**, **6b** was very unstable to air and would convert to imidazole-5-carbaldehyde in few minutes at room temperature. A reaction performed under ^{18}O atmosphere resulted in 95% of **2b°** with ^{18}O incorporated, which demonstrated that the oxygen atom on carbonyl group derived from dioxygen (Scheme 4–3). More mechanistic studies showed that the addition of TEMPO into the reaction would not decrease significantly the efficiency of the reaction, and no TEMPO-R adduct was detected by GC–MS and LC–MS analysis (Scheme 4–4) (Wang et al. 2011; Mohan et al. 2013).

Based on above results, a plausible mechanism was proposed in Scheme 5. Substrate **1** reacted with I_2 activated by CAN (Horicuchi et al. 2005) to give the key intermediate of 5-iodomethyl imidazole **6**. The carbon-iodine bond in **6** homolytic cleaved to radical intermediate **A** and iodine radical. In the presence of dioxygen, a radical transfer occurred on **A** to afford peroxy-intermediate **B**. **B** yielded the desired product **2** by releasing a hydroxyl radical (Peng et al. 2015). Iodine broke away from the reaction in the form of I_2 which could be detected by KI-starch test paper.

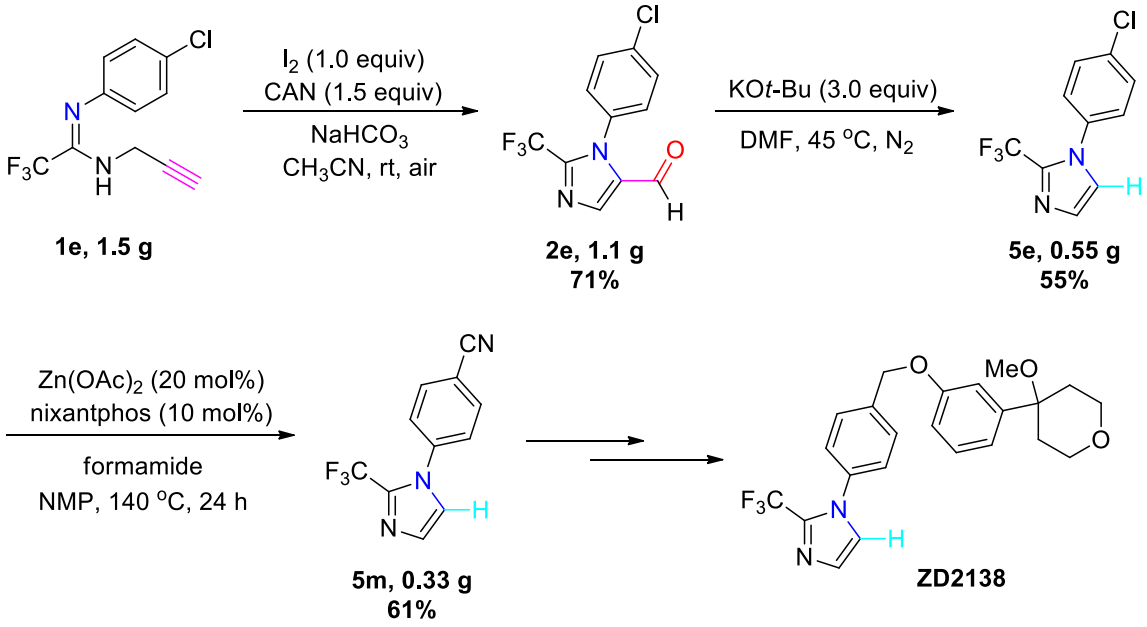


Scheme 4 Investigations on the reaction mechanism

Scheme 5 A plausible mechanism



A decarbonylation occurred on *N*-(*p*-Cl)phenyl 2-trifluoroalkyl imidazole-5-carbaldehyde **2e** in the presence of KO*t*-Bu to afford **5e**. By Zn-catalyzed cyanation (Zhao et al. 2020), **5e** converted to **5m** which is an important intermediate for imidazole derivative of potent 5-lipoxygense inhibitor **ZD2138** (Mano et al. 2003). The synthetic utility of the reaction described in this paper was demonstrated by synthesizing



Scheme 6 A concise routes to synthesize imidazole derivative of **ZD2138**

5m in three steps on gram scale and more environmental friendliness (Scheme 6).

Conclusions

In summary, a simple and efficient method to synthesize 2-fluoroalkyl imidazole derivatives was developed. In the presence of iodinated regent, fluorinated *N'*-propargyl amidines converted to 2-fluoroalkyl imidazole-5-carbaldehydes in moderate to excellent yields by an aminohalogenation-oxidation process. When *N'*-allyl amidines used as substrates, 4,5-dihydro-5-iodomethyl imidazoles were obtained as the final products. These transformations showed an extensive substrate scope and good functional group compatibility. Mechanistic investigations indicated that 5-iodomethyl imidazole, the key intermediate of imidazole-5-carbaldehyde, converted to the desired product by a radical pathway, and the oxygen atom on carbonyl group derived from dioxygen.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interest.

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