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Copper-mediated oxidative [3+2]-annulation of nitroalkenes and pyridinium ylides: a general access to functionalized indolizines. Efficient synthesis of 1-fluoroindolizines

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A general method for the synthesis of substituted indolizines by copper (II) acetate-promoted oxidative [3+2]-annulation of α-fluoronitroalkenes with *in situ* generated pyridinium ylides was developed. Application of the copper (II) acetate - 2,6-lutidine system opens efficient access to various 1-fluoroindolizines in up to 81% yield. Both electron-rich and electron-deficient nitroalkenes as well as different pyridinium and isoquinolinium salts can be involved in the reaction. Moreover, it was found that copper-mediated annulation is applicable for other α-substituted (alkyl, chloro, ester) nitroalkenes giving rise to the corresponding indolizines. First synthesis of monofluorinated [3,2,2]cyclazines was demonstrated *via* oxidative annulation of 3-unsubstituted fluoroindolizines with diethyl acetylenedicarboxylate.

Introduction

The indolizine fragment is an important structural part of many natural alkaloids as well as important pharmaceuticals (Figure 1).[1] In the recent times, antihypertensive, anticancer, antiinflammatory, antimicrobial, and other biological activities have been explored for substituted indolizines.[2] Among the known methods for their synthesis[3] [3+2]-annulation involving pyridinium salts was widely studied as the simplest and highly straightforward route to multifunctionalized indolizines (Scheme 1). The typical annulation reactions have involved electron-poor alkynes, bearing carbonyl or ester groups, as 2π-components.[4] Also various oxidative annulations with electron-deficient alkenes and different oxidants, were elaborated.[5] However, similar reactions with conjugated nitroalkenes are less explored.[6]

Fluorinated heterocycles are of special interest for drug design.[7] [3+2]-Cycloaddition could be a direct and highly attractive approach to the synthesis of monofluorinated indolizines. However, this approach has never been realized due to low stability of 1-fluoroalkynes.[8] Recently we have demonstrated the application of fluorinated α-nitroalkenes as synthetic equivalents of fluoroalkynes in [3+2]-cycloadditions towards monofluorinated pyrroles and triazoles.[9] Straightforward preparation of 1-fluoroindolizines from fluoronitroalkenes looked especially attractive. Currently fluorinated indolizines are almost unknown.[10] Herein we report the first synthesis of 1-fluoroindolizines as well as convenient route to other substituted indolizines by copper-mediated oxidative [3+2]-annulation of nitroalkenes with pyridinium salts (Scheme 1).

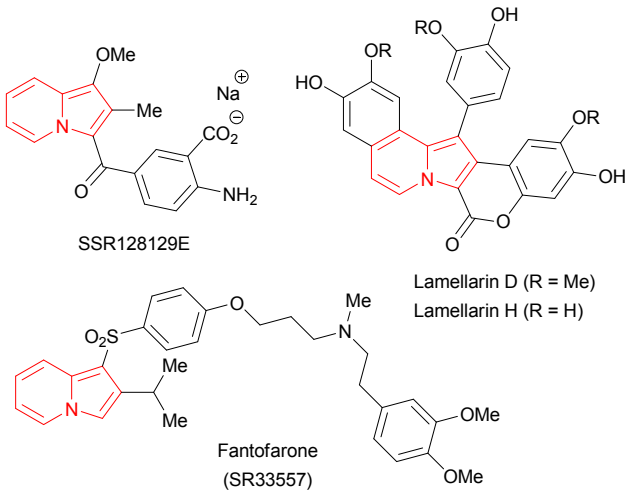

Figure 1. Representative bioactive indolizine derivatives.

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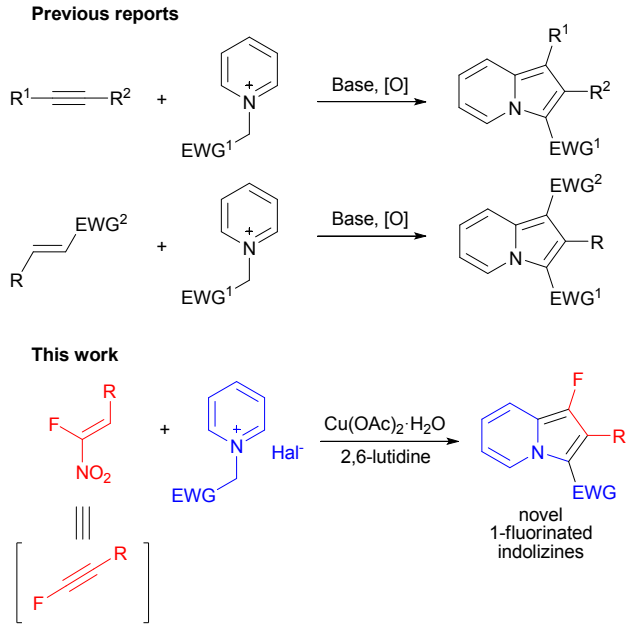
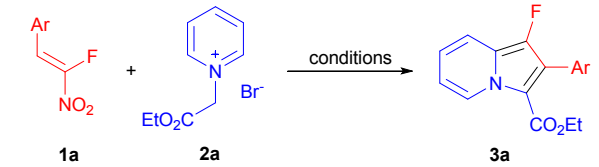


Scheme 1. Approaches to indolizines via [3+2]-annulation.

Table 1 Optimization of the reaction conditions (See ESI for full details)



1a **2a** **3a**

Ar = 4-Cl-C_6H_4-

Entry	Oxidant (equiv.)	Base (equiv.)	Solvent	Yield **3a**[a], %
1	-	Et_3N (1.5)	CH_2Cl_2	trace
2	$Cu(OAc)_2·H_2O$ (1.5)	Et_3N (1.5)	CH_2Cl_2	23
3	$Cu(OAc)_2·H_2O$ (1.5)	DBU (1.5)	CH_2Cl_2	33
4	$Cu(OAc)_2·H_2O$ (1.5)	DIPEA (1.5)	CH_2Cl_2	26
5	$Cu(OAc)_2·H_2O$ (1.5)	Py (5)	CH_2Cl_2	48
6	$Cu(OAc)_2·H_2O$ (1.5)	Py (5)	MeCN	38
7	$Cu(OAc)_2·H_2O$ (1.5)	Py (5)	DMF	17
8	$Cu(OAc)_2·H_2O$ (1.5)	Py (5)	DCE	52
9[b]	$Cu(OAc)_2·H_2O$ (1.5)	Py (5)	DCE	61
10[b]	$Cu(OAc)_2·H_2O$ (1.5)	DMAP (5)	DCE	24
11[b]	$Cu(OAc)_2·H_2O$ (1.5)	2,6-lutidine (5)	DCE	63
12[b,c]	**$Cu(OAc)_2·H_2O$ (1.5)**	**2,6-lutidine (5)**	**DCE**	**69**

[a] Yields were determined by ^{19}F NMR with $PhCF_3$ as internal standard; [b] The reagents were mixed at 0°C, then stirred at r. t.; [c] 1.5 equiv. of **2a**.

Results and discussion

We started our study with the model reaction of fluoronitroalkene **1a** and pyridinium salt **2a** in dichloromethane with triethylamine as a base without external oxidant (entry 1, Table 1). Under these particular conditions complete consumption of starting nitroalkene **1a** was observed. However, only traces of target indolizine **3a** were detected.[11] To our delight, running the reaction in the presence of copper (II) acetate as an oxidant[12] resulted in 23% yield of **3a** (entry 2). Other oxidants were found less efficient. Using strong nitrogen bases (triethylamine, DIPEA, DMAP, DBU) gave only satisfactory yields of indolizine (entries 2-4,10), probably due to polymerization of intermediate anionic species.[13] Finally, after exhaustive optimization studies (See SI for full details of optimization process) it was found that the reaction proceeds most efficiently with 1.5-2 equivalents of pyridinium salt and 1.5 equivalents of copper acetate at rt in 1,2-dichloroethane using 2,6-lutidine as a base. This resulted in formation of target 1-fluoroindolizine **3a** in 69% yield.

With the optimized conditions in hand, the scope of the reaction was investigated. First, the influence of the nature of the pyridinium salts was examined (Scheme 2). To this end various pyridinium salts bearing different electron withdrawing groups were tested. 3-Ethoxycarbonyl- and 3-cyano-substituted fluorinated indolizines **3a**,**b** were prepared in good isolated yields after 8 hours of stirring at rt. Pyridinium salts derived from aliphatic and aromatic haloketones reacted more quickly to form products **3c,d** in 48-51% yields.[14] The sterically more hindered CO_2Bn-substituted pyridinium salt reacted significantly slower, 3 days were required for its complete conversion to form product **3e**. The respective salt containing the more bulky tert-butyloxycarbonyl group was found unreactive.

Next, various C2-C4 substituted pyridinium salts **2** were tested thus leading to substituted C5-C8 indolizines **3f-j**.[15] 2-Picoline derived salt gave the 5-substituted indolizine **3g** in moderate yield. The reaction with 3-picoline derived salt **2h** gave a mixture of isomeric indolizines **3h** in a 3:1 ratio in favor of the 8-substituted isomer. More bulky salt **2j** having the phthalimidomethyl group in the position 3 of the pyridine ring produced the corresponding 6-substituted indolizine **3j** highly regioselectively. On the contrary, selective formation of the 8-isomer (e.g., for **3i**) may be explained by electronic factors.[16] Also it was found that isoquinolinium salts are applicable for the annulation. For example, the corresponding benzoindolizine **3k** was efficiently synthesized under optimal conditions.

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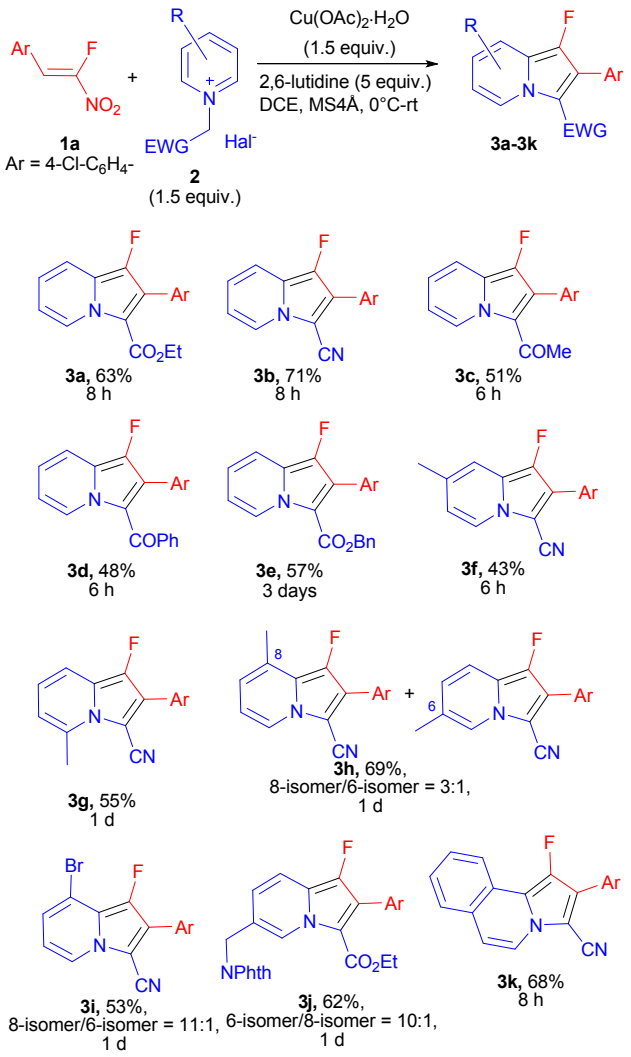
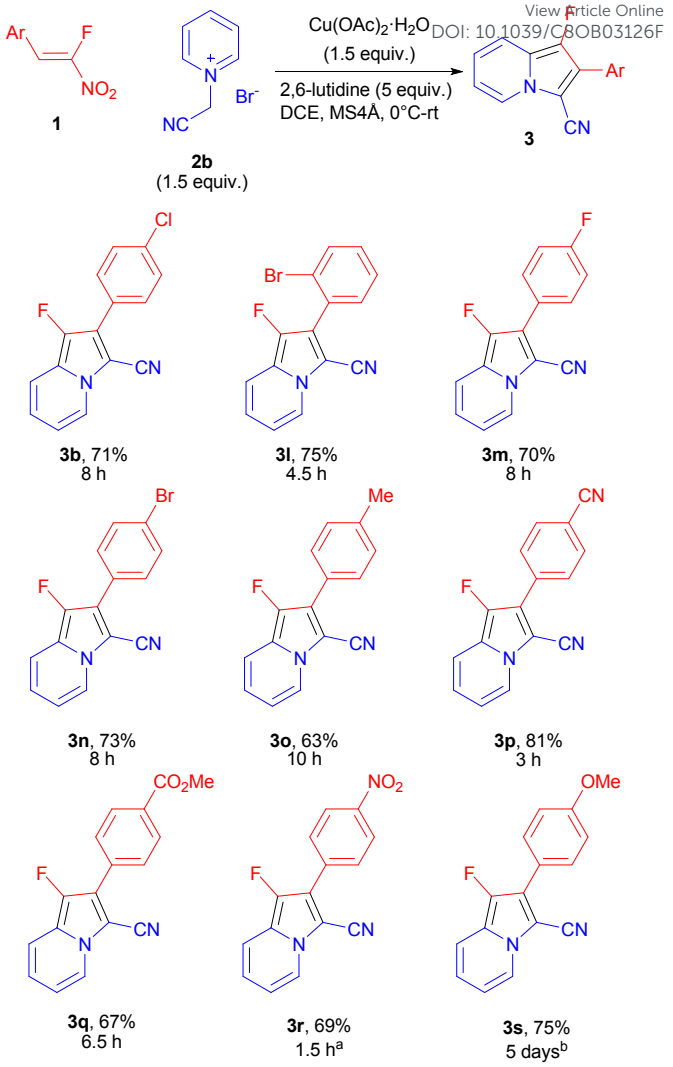


Scheme 2. Synthesis of 1-fluoroindolizines **3** from various pyridinium salts **2**.



Scheme 3. Synthesis of 1-fluoroindolizines **3** from various fluoronitroalkenes **1**. [a] reaction temperature 0°C. [b] 2.3 equiv. of **2b**.

Next, the scope of α-fluoronitroalkenes **1** was studied, thus revealing generality of the method (Scheme 3). Nitroalkenes **1** bearing both electron-donating and electron-withdrawing substituents can be involved in the cycloaddition to open access to monofluorinated indolizines **3** in good yields. It should be pointed out that significant influence of a substituent in the aryl group on the reactivity of nitroalkene **1** was observed. Electron-neutral substrates, including sterically hindered *ortho*-bromo-substituted nitroalkene, were converted into indolizines **3b,l-o** within 4.5-10 h. Electron-poor *para*-cyano-substituted nitroalkene reacted much faster, and complete conversion to form **3p** was reached after 3h at r.t. The most reactive *para*-nitro-substituted substrate afforded indolizine **3r** after 1.5 hours at 0°C. On the contrary, electron-rich *para*-methoxy-substituted nitroalkene required 5 days and increased amounts of pyridinium salt for complete conversion to **3s**. The structures of all obtained indolizines **3** were unambiguously determined by ^{1}H and ^{13}C NMR spectra as well as by HRMS data. In addition, single crystal X-ray analysis was performed for the indolizine **3s** (Figure 2).[17]

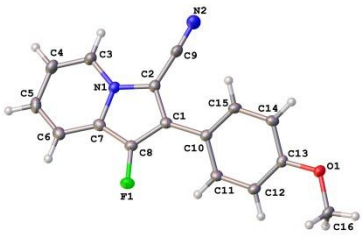
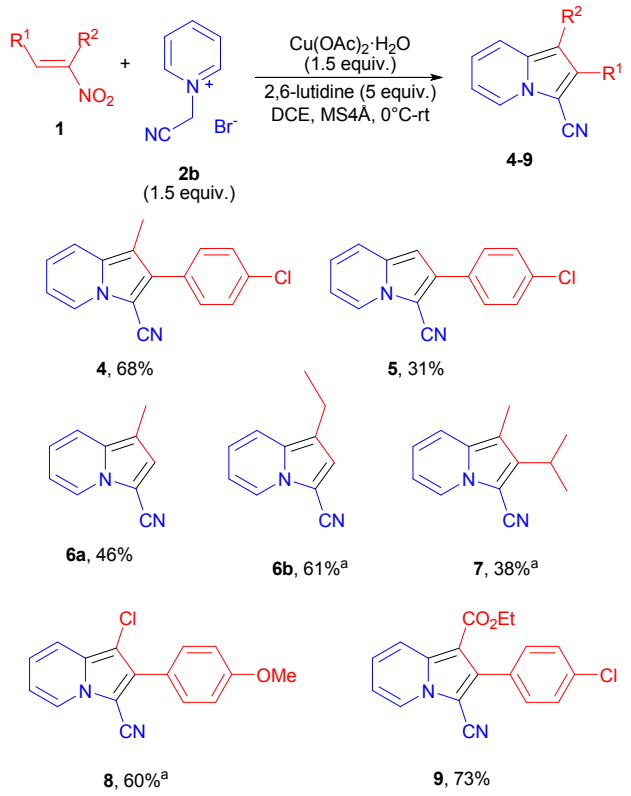


Figure 2. Molecular structure of **3s** in representation of atoms *via* thermal ellipsoids at 50% probability level. Only one symmetry-independent molecule is shown.

Inspired by the efficiency of copper-mediated annulation for the synthesis of fluorinated indolizines and to test the generality of the method, we investigated the reactivity of other α-substituted nitroalkenes in the presented indolizine synthesis. To the best of our knowledge, only few reports were devoted to the synthesis of indolizines from nitroalkenes by oxidative annulation, where silver carbonate[6a,b], or TEMPO[5d] have been used as oxidants. The main advantage of proposed method is utilization of cheap and easily available copper

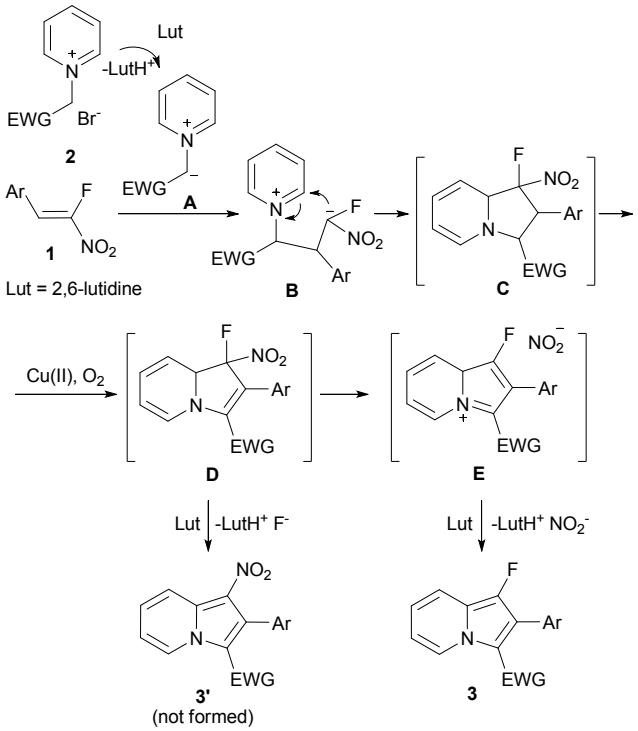
acetate monohydrate. Different nitroalkenes were tested to further extend the scope of copper-mediated annulation (Scheme 4). To our delight, the reaction was found to be very general. For example, α-methylated nitroalkene afforded the corresponding indolizine **4** in good yield. On the contrary, 1-unsubstituted indolizine **5** was obtained in lower yield from α-unsubstituted nitroalkene. Probably, these observations may be explained by the increased stability of three-substituted intermediate **B** (cf. Scheme 5) towards anionic polymerization. Further, the method was also found applicable for aliphatic and even for β-unsubstituted nitroalkenes. Overall, the corresponding indolizines **5-7** were obtained in moderate yield, probably, because of high susceptibility of electron-rich indolizines to further oxidation.[6b,18]

Annulation of α-chloronitroalkenes with pyridinium salts was of particular interest, because of hardly predictable either HNO_2 or HCl elimination.[19] In our case, α-chloronitroalkenes exhibited a reactivity close to their fluorinated analogues and formed 1-chloroindolizine **8** chemoselectively. However, α-bromonitroalkene was unreactive under these conditions, probably because of significant steric hindrance. In the case of electron-poor α-nitrocinnamate the reaction proceeded smoothly providing the corresponding indolizine **9** in good yield. It should be mentioned that the copper-mediated annulation with α-nitrocinnamate established the route to indolizines, while the oxidant-free base-catalyzed reaction with pyridinium salts is known to lead to isoxazoles.[20]



Scheme 4. Synthesis of indolizines **4-9** from different fluoronitroalkenes **1**. [a] 2.0 equiv. of **2b**.

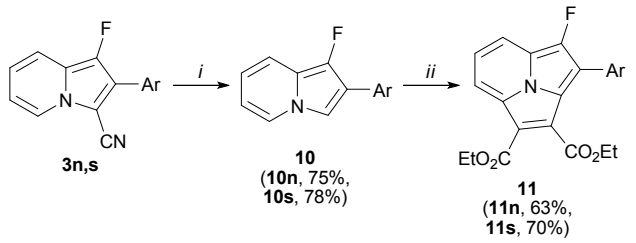
Either concerted or stepwise mechanisms can be considered for the present [3+2]-annulation.[21] The high dependence on the electronic nature of the nitroalkenes makes the stepwise anionic mechanism more likely. However, the concerted scenario cannot be excluded. Following the stepwise mechanism Michael addition of the formed ylide **A** to the nitroalkene **1** results in the formation of the anion **B**,[22] which attacks the alpha-position of pyridinium fragment to form tetrahydroindolizine **C**. Here, coordination of copper to the pyridinium ylide might possess a significant promoting effect on the reaction, similarly to copper-catalyzed cycloadditions with azomethine ylides.[23] Next, dehydrogenation with Cu(II)/atmospheric oxygen affords intermediate dihydroindolizine **D**.[24,25] Finally, aromatization takes place, presumably *via* expulsion of nitrite-anion by nitrogen lone pair and formation of intermediate **E**.[26] In the case of fluorinated substrates this step may be expected to proceed by either elimination of HNO_2 or HF. Gratifyingly, due to a strong C–F bond, HNO_2 elimination is favored resulting in formation of the monofluorinated indolizines **3** (Scheme 5). A similar behavior has been observed previously for the synthesis of monofluorinated triazoles.[9b]



Scheme 5. Proposed mechanism for the synthesis of indolizines **3**.

Next, the reactivity of fluorinated indolizines was studied (Scheme 6). 3-Cyano-substituted derivatives **3n,s** were used as a starting materials for the synthesis of 3-unsubstituted indolizines **10.** Alkaline hydrolysis followed by treatment with concentrated hydrochloric acid gave 3-unsubstituted fluoroindolizines **10** in up to 78% total yield. Importantly, no substitution of fluorine in position 1 was observed to prove stability of 3-fluoroindolizines in alkaline solution. Subsequent heating of **10** with diethyl acetylenedicarboxylate at 90 °C in the presence of catalytic amount (20%) of copper diacetate

under air resulted in the formation of novel fluorinated [3,2,2]cyclazines **11** in up to 70% yield as a result of oxidative [8+2]-cycloaddition (Scheme 8). This new procedure based on similar oxidative system is advantageous in comparison to literature application of Pd/C.[27] No formation of side-products was observed in the synthesis of target cyclazines **11** which are stable under the cyclization conditions.



i: 1. KOH, EtOH, reflux; 2. conc. HCl, 80 °C

ii: $EtO_2CC{\equiv}CCO_2Et$, $Cu(OAc)_2{\cdot}H_2O$ (20 mol.%), PhMe, air, 90 °C, 5-8h

Scheme 6. Synthesis of fluorinated cyclazines **11**.

Experimental section

General experimental

All reactions were performed in oven-dried (150 °C) glassware. Most of the chemicals were acquired from commercial sources and used as received. Starting fluoronitroalkenes $XC_6H_4CH{=}C(F)NO_2$ (**1a** (X = p-Cl), **1b** (X = o-Br), **1c** (X = p-F), **1d** (X = p-Br), **1e** (X = p-Me), **1f** (X = p-CN), **1g** (X = p-CO_2Me), **1h** (X = p-NO_2), **1i** (X = p-OMe)) were prepared by radical nitration of corresponding fluorobromostyrenes by $Fe(NO_3)_3$ in 1,4-dioxane (**1a,**[9a] **1d**,[9d] **1e**,[9a] **1i**[9a]) or by $Fe(NO_3)_3$/TEMPO/1,2-DCE system (**1b,c**,**f-h**[9a]). Other starting materials were prepared according to the literature procedures: 1-chloro-4-(2-nitroprop-1-enyl)benzene **1j**,[28] 1-chloro-4-(2-nitrovinyl)-benzene **1k**,[29] 2-nitroprop-1-ene **1l** and 2-nitrobut-1-ene **1m**,[30] 4-methyl-2-nitropent-2-ene **1n**,[31] 1-(2-chloro-2-nitrovinyl)-4-methoxybenzene **1o**,[9c] ethyl 3-(4-chlorophenyl)-2-nitroacrylate **1p**;[32] N-substituted pyridinium salts: **2a** (R=CH_2CO_2Et),[33] **2b** (R=CH_2CN),[5g] **2c** (R=$CH_2C(O)Me$),[34] **2d** (R=$CH_2C(O)Ph$),[35] **2e** (R=CH_2CO_2Bn);[36] N-cyanomethyl pyridinium $XC_5H_4N^+CH_2CN$ salts: **2f** (X = p-Me),[5g] **2g** (X = o-Me),[5g] **2h** (X = m-Me),[6d] **2i** (X = m-Br);[37] N-cyanomethyl isoquinolinium salt **2k**.[38] TLC were performed on silica coated on aluminium with UV254 indicator. Visualization was accomplished with UV. Column chromatography was performed on silica (0.04–0.063 mm, 60 Å). NMR spectra were recorded at Bruker Fourier 300 and Bruker AV-300 instruments at the 300 MHz (^{1}H NMR), 75 MHz (^{13}C NMR), and 282 MHz (^{19}F NMR) frequencies. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad); pseudo t corresponds to not well-resolved doublet of doublets with similar (within 0.3 Hertz) coupling constants. Assignment of hydrogen and carbon atoms of indolizine core was made basing on 2D NMR for selected compounds (**3q**, **5, 10n**) and literature data.[6a] High resolution mass spectra were acquired at Bruker micrOTOF spectrometer using electrospray ionization (ESI).

1-(Ethyloxycarbonylmethyl)-3-(phthalimidomethyl)pyridinium bromide (2j)

The solution of 3-(phthalimidomethyl)-pyridine (80 mg, 0.33 mmol)[39] and ethyl bromoacetate (59 mg, 0.33 mmol) in EtOAc (0.5 ml) was refluxed for 5 h, then cooled to r. t., and formed white precipitate was filtered. Recrystallization of mother liquor followed by filtration afforded additional product. Yield 110 mg (79%). mp = 152-155°C (EtOAc) (decomp.) ^{1}H NMR (DMSO-d_6, 300 MHz): 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 4.21 (q, *J* = 7.0 Hz, 2H, CH_2), 5.05 (s, 2H, -**CH_2**-N_{Phth}), 5.67 (s, 2H, N-**CH_2**-CO_2Et), 7.92 (m, 4H, CH_{Phth}), 8.26 (m, 1H, H5), 8.77 (d, *J* = 7.8 Hz, 1H, H4), 9.06 (d, *J* = 5.7 Hz, 1H, H6), 9.11 (s, 1H, H2). ^{13}C NMR (DMSO-d_6, 300MHz, DEPT-135): 14.4 (CH_3), 38.5 (-**CH_2**-N_{Phth}), 60.8 (CH_2), 62.8 (N-**CH_2**-CO_2Et), 123.9 (CH_{Phth}), 128.0 (CH_{Py}), 132.3 (C_{Phth}), 135.1 (CH_{Phth}), 137.8 (C_{Phth}), 144.8 (CH_{Py}), 145.8 (CH_{Py}), 146.3 (CH_{Py}), 166.6 (C_{Phth}), 168.2 (CO_2Et). HRMS (ESI): m/z calcd. for $[C_{18}H_{17}BrN_2O_4\text{-}Br]^+$: 325.1183, found: 325.1192.

General procedure 1 for the synthesis of indolizines 3-9

Suspension of pyridinium salt **2** (0.3 mmol, 1.5 equiv.) and 4Å molecular sieves (powder, 100 mg) in DCE (2 ml) was cooled to 0°C using ice-cooling bath, then 2,6-lutidine (92 mg, 1 mmol, 5 equiv.) was added. After stirring for 5 min, nitroalkene **1** (0.2 mmol, 1.0 equiv.) was added, followed by addition of $Cu(OAc)_2{\cdot}H_2O$ (60 mg, 0.3 mmol, 1.5 equiv.) The mixture was stirred at 0°C for 15 min, then warmed to r.t and the stirring was continued for 3 h – 5 d. After the reaction was complete (TLC monitoring), the solvent was evaporated under reduced pressure with silica gel, and the crude product was purified by column chromatography (PE/EtOAc, 4:1 – 19:1) to afford indolizines **3-9**.

1-Fluoro-2-(4-chlorophenyl)-3-(ethyloxycarbonyl)-indolizine (3a).

Indolizine **3a** was obtained from α-fluoronitroalkene **1a** (30.2 mg, 0.15 mmol) and pyridinium salt **2a** (1.5 equiv.) following the general procedure 1 (reaction time 8 h). Column chromatography (eluent: 8:1 PE/EtOAc) afforded **3a** (30 mg, 63%) as a yellow oil, which solidifies upon storage in a refrigerator. R_f = 0.56 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.1 Hz, 3H, CH_3), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2), 6.79 (td, *J* = 6.9, 0.9 Hz, 1H, H6), 7.02 (dd, *J* = 8.8, 6.9 Hz, 1H, H7), 7.40 (s, 4H, CH_{Ar}), 7.52 (d, *J* = 8.8 Hz, 1H, H8), 9.48 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 59.8 (CH_2), 106.2 (C3), 113.4 (CH), 114.8 (d, J_{CF} = 3.3 Hz, CH), 120.5 (d, $^2J_{CF}$ = 9.1 Hz, C2), 121.3 (d, J_{CF} = 1.8 Hz, CH), 123.7 (d, $^2J_{CF}$ = 26.0 Hz, C8a), 126.6 (CH), 127.7 (CH_{Ar}), 129.9 (d, $^3J_{CF}$ = 1.6 Hz, C_{Ar}), 132.0 (CH_{Ar}), 133.6 (C-Cl), 140.1 (d, $^1J_{CF}$ = 241.6 Hz, C1-F), 161.6 (d, $^3J_{CF}$ = 2.9 Hz, **C**O_2Et). ^{19}F NMR (282 MHz, $CDCl_3$): δ -175.0 (s). HRMS (ESI): m/z calcd. for $[C_{17}H_{13}ClFNO_2]$: 317.0613, found: 317.0602.

1-Fluoro-2-(4-chlorophenyl)-indolizine-3-carbonitrile (3b).

Indolizine **3b** was obtained from α-fluoronitroalkene **1a** (30.2 mg, 0.15 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 8 h). Column chromatography (eluent: 7:1 PE/EtOAc) afforded **3b** (28.7 mg, 71%) as a white solid. R_f = 0.41 (PE/EtOAc, 3:1) (UV), mp = 144-145°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (td, *J* = 6.9, 1.1

Hz, 1H, H6), 7.01 (dd, *J* = 8.8, 6.9 Hz, 1H, H7), 7.47 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 7.53 (d, *J* = 8.9 Hz, 1H, H8), 7.77 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 8.18 (d, *J* = 7.0 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 88.4 (d, $^3J_{CF}$ = 6.3 Hz, C3), 113.8 (CN), 113.8 (CH), 115.8 (d, J_{CF} = 3.4 Hz, CH), 120.5 (d, $^2J_{CF}$ = 8.9 Hz, C2), 121.7 (d, J_{CF} = 2.0 Hz, CH), 123.9 (d, $^2J_{CF}$ = 26.3 Hz, C8a), 124.4 (CH), 127.4 (d, $^3J_{CF}$ = 3.3 Hz, C_{Ar}), 129.3 (CH_{Ar}), 129.5 (d, $^4J_{CF}$ = 3.3 Hz, CH_{Ar}), 134.7 (C-Cl), 138.1 (d, $^1J_{CF}$ = 244.9 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -171.8 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_8ClFN_2$ + H^+]: 270.0355, found: 270.0347.

1-Fluoro-2-(4-chlorophenyl)-3-acetyl-indolizine (3c).

Indolizine **3c** was obtained from α-fluoronitroalkene **1a** (40.3 mg, 0.2 mmol) and pyridinium salt **2c** (1.5 equiv.) following the general procedure 1 (reaction time 6 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3c** (29.2 mg, 51%) as a yellow oil. R_f = 0.31 (PE/EtOAc, 5:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H, Me), 6.88 (pseudo td, *J* ≈ 7.0, 0.8 Hz, 1H, H6), 7.14 (dd, *J* = 8.8, 6.9 Hz, 1H, H7), 7.38 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 7.47 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 7.55 (d, *J* = 8.8 Hz, 1H, H8), 7.77 (d, *J* = 8.2 Hz, 2H, CH_{Ar}), 9.96 (d, *J* = 7.2 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9 (Me), 114.5 (CH), 114.6 (CH), 116.0 (C3), 121.1 (d, $^2J_{CF}$ = 9.0 Hz, C2), 123.5 (CH), 124.2 (d, $^2J_{CF}$ = 25.7 Hz, C8a), 127.7 (CH), 128.8 (CH_{Ar}), 130.1 (br s, C_{Ar}), 131.7 (CH_{Ar}), 134.7 (C-Cl), 140.7 (d, $^1J_{CF}$ = 242.3 Hz, C1-F), 187.8 (d, $^4J_{CF}$ = 3.1 Hz, C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -173.8 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_{11}ClFNO$ + H^+]: 288.0586, found: 288.0581.

1-Fluoro-2-(4-chlorophenyl)-3-(phenylcarbonyl)-indolizine (3d).

Indolizine **3d** was obtained from α-fluoronitroalkene **1a** (50.4 mg, 0.25 mmol) and pyridinium salt **2d** (1.5 equiv.) following the general procedure 1 (reaction time 6 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3d** (42 mg, 48%) as a yellow solid. R_f = 0.29 (PE/EtOAc, 5:1) (UV), mp = 123-124°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (td, *J* = 7.2, 1.3 Hz, 1H, H6), 7.01 (s, 4H, CH_{Ar}), 7.06 (d, *J* = 7.3 Hz, 2H, CH_{Ph}), 7.13-7.25 (m, 2H), 7.34-7.40 (m, 2H), 7.60 (dt, *J* = 8.9, 1.0 Hz, 1H, H8), 9.79 (dd, *J* = 7.2, 1.0 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.4 (CH), 114.8 (d, J_{CF} = 3.3 Hz, CH), 115.2 (C3), 121.4 (d, $^2J_{CF}$ = 7.8 Hz, C2), 123.5 (CH), 124.9 (d, $^2J_{CF}$ = 26.1 Hz, C8a), 127.2 (CH), 127.6 (CH), 127.8 (CH), 129.2 (d, $^3J_{CF}$ = 2.1 Hz, C_{Ar}), 129.3 (CH), 130.8 (CH), 131.9 (CH), 133.2 (C-Cl), 139.5 (C_{Ar}), 140.3 (d, $^1J_{CF}$ = 243.6 Hz, C1-F), 186.1 (d, $^4J_{CF}$ = 3.0 Hz, C=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -173.3 (s). HRMS (ESI): m/z calcd. for [$C_{21}H_{13}ClFNO$ + H^+]: 350.0742, found: 350.0736.

1-Fluoro-2-(4-chlorophenyl)-3-(benzyloxycarbonyl)-indolizine (3e).

Indolizine **3e** was obtained from α-fluoronitroalkene **1a** (40.3 mg, 0.2 mmol) and pyridinium salt **2e** (2.0 equiv.) following the general procedure 1 (reaction time 3 days). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3e** (43 mg, 57%) as a yellow oil, which solidifies upon storage in a refrigerator. R_f = 0.49 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16 (s, 2H, CH_2), 6.83 (td, *J* = 7.1, 0.9 Hz, 1H, H6), 7.00-7.07 (m, 3H), 7.29 (br s, 7H, CH_{Ar}), 7.54 (d, *J* = 8.9 Hz, 1H, H8), 9.53 (d, *J* = 7.1 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.7 (CH_2), 106.1 (d, $^3J_{CF}$ = 1.7 Hz, C3), 113.5 (CH), 114.9 (d, J_{CF} = 3.4 Hz, CH), 120.7 (d, $^2J_{CF}$ = 9.6 Hz, C2), 121.6 (CH), 124.1 (d, $^2J_{CF}$ = 25.6 Hz, C8a), 126.7 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 129.3 (C_{Ar}), 129.8 (d, $^3J_{CF}$ = 2.0 Hz, C_{Ar}), 131.9 (CH), 133.7 (C-Cl), 135.5 (CH), 140.2 (d, $^1J_{CF}$ = 241.6 Hz, C1-F), 161.4 (d, $^4J_{CF}$ = 2.9 Hz, **C**O_2Bn). ^{19}F NMR (282 MHz, $CDCl_3$): δ -174.1 (s). HRMS (ESI): m/z calcd. for [$C_{22}H_{15}ClFNO_2$ + H^+]: 376.0731, found: 376.0731.

1-Fluoro-2-(4-chlorophenyl)-7-methyl-indolizine-3-carbonitrile (3f).

Indolizine **3f** was obtained from α-fluoronitroalkene **1a** (60.5 mg, 0.30 mmol) and pyridinium salt **2f** (1.5 equiv.) following the general procedure 1 after stirring at 0°C for 1.5 h, followed by 4 h at r. t. Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3f** (36.5 mg, 43%) as a white solid. R_f = 0.36 (PE/EtOAc, 5:1) (UV), mp = 137-138°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, Me), 6.66 (dd, *J* = 7.1, 1.2 Hz, 1H, H6), 7.29 (br s, H8), 7.46 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.76 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.08 (d, *J* = 7.1 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (Me), 87.5 (d, $^3J_{CF}$ = 6.5 Hz, C3), 114.0 (d, $^3J_{CF}$ = 3.3 Hz, C8-H), 114.3 (d, $^4J_{CF}$ = 2.4 Hz, CN), 116.6 (C6-H), 120.7 (d, $^2J_{CF}$ = 8.9 Hz, C2), 124.0 (C5-H), 124.3 (d, $^2J_{CF}$ = 26.3 Hz, C2), 127.6 (d, $^3J_{CF}$ = 3.3 Hz, C_{Ar}), 129.3 (CH_{Ar}), 129.4 (d, $^4J_{CF}$ = 3.5 Hz, CH_{Ar}), 132.8 (d, $^4J_{CF}$ = 1.9 Hz, C7), 134.6 (C-Cl), 137.2 (d, $^1J_{CF}$ = 243.4 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -172.4 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_{10}ClFN_2^+$]: 284.0511, found: 285.0513.

1-Fluoro-2-(4-chlorophenyl)-5-methyl-indolizine-3-carbonitrile (3g).

Indolizine **3g** was obtained from α-fluoronitroalkene **1a** (60.5 mg, 0.30 mmol) and pyridinium salt **2g** (1.5 equiv.) following the general procedure 1 after stirring at 0°C for 1.5 h, followed by 26 h at r. t.. Column chromatography (eluent: 9:1, then 5:1 PE/EtOAc) afforded **3g** (47 mg, 55%) as a white solid. R_f = 0.51 (PE/EtOAc, 3:1) (UV), mp = 171-172°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, 3H, Me), 6.64 (d, *J* = 6.8 Hz, 1H, H6), 6.95 (dd, *J* = 8.9, 6.8 Hz, 1H, H7), 7.46 (d, *J* = 8.9 Hz, 1H, H8), 7.46 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.70 (d, *J* = 8.5 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 (Me), 87.5 (d, $^3J_{CF}$ = 5.3 Hz, C3), 113.7 (d, $^3J_{CF}$ = 3.1 Hz, C8-H), 114.7 (C6-H), 116.7 (d, $^4J_{CF}$ = 2.0 Hz, CN), 122.2 (d, $^4J_{CF}$ = 1.0 Hz, C7-H), 122.8 (d, $^2J_{CF}$ = 8.8 Hz, C2), 125.1 (d, $^2J_{CF}$ = 26.1 Hz, C8a), 127.3 (d, $^3J_{CF}$ = 3.0 Hz, C_{Ar}), 129.1 (CH_{Ar}), 130.1 (d, $^4J_{CF}$ = 2.3 Hz, CH_{Ar}), 134.7 (C-Cl), 136.3 (C5), 138.3 (d, $^1J_{CF}$ = 244.1 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -171.3 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_{10}ClFN_2$ + H^+]: 285.0589, found: 285.0586.

1-Fluoro-2-(4-chlorophenyl)-8-methyl-indolizine-3-carbonitrile and 1-Fluoro-2-(4-chlorophenyl)-6-methyl-indolizine-3-carbonitrile (3h).

Indolizines **3h** were obtained from α-fluoronitroalkene **1a** (30.3 mg, 0.15 mmol) and pyridinium salt **2h** (1.5 equiv.) following the general procedure 1 (reaction time 17 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3h** (29.5 mg, 69%, regioisomer ratio: 8-Me/6-Me = 3:1) as a slightly yellow solid. R_f = 0.52 (PE/EtOAc, 3:1) (UV). Major isomer (**8-Me**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H, Me), 6.66-6.74 (m, 2H, H6, H7), 7.46 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 8.03 (d, *J* = 7.1 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8 (d, $^4J_{CF}$ = 4.1 Hz, Me), 88.3 (d, $^3J_{CF}$ = 6.2 Hz,

C3), 113.8 (C6-H), 114.0 (d, $^{4}J_{CF}$ = 2.7 Hz, CN), 115.1 (d, $^{3}J_{CF}$ = 3.4 Hz, C8), 120.4 (d, $^{2}J_{CF}$ = 9.9 Hz, C2), 121.5 (d, $^{4}J_{CF}$ = 2.6 Hz, C7-H), 122.2 (C5-H), 124.0 (d, $^{2}J_{CF}$ = 22.0 Hz, C8a), 127.5 (d, $^{3}J_{CF}$ = 3.3 Hz, C_{Ar}), 129.2 (CH_{Ar}), 129.4 (d, $^{4}J_{CF}$ = 3.5 Hz, CH_{Ar}), 134.6 (C-Cl), 139.4 (d, $^{1}J_{CF}$ = 245.6 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -168.1 (s). Minor isomer (**6-Me**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, Me), 6.87 (t, *J* = 9.1 Hz, 1H, H7), 7.44 (d, *J* = 9.1 Hz, 1H, H8), 7.46 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 8.01 (s, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3 (Me), 88.3 (d, $^{3}J_{CF}$ = 6.6 Hz, C3), 113.9 (d, $^{4}J_{CF}$ = 2.1 Hz, CN), 120.4 (d, $^{2}J_{CF}$ = 9.2 Hz, C2), 124.1 (d, $^{2}J_{CF}$ = 23.1 Hz, C8a), 125.1 (d, $^{5}J_{CF}$ = 1.8 Hz, C6), 127.6 (d, $^{3}J_{CF}$ = 3.3 Hz, C_{Ar}), 128.2 (d, $^{4}J_{CF}$ = 4.5 Hz, C8-H), 129.2 (CH_{Ar}), 129.3 (d, $^{4}J_{CF}$ = 3.6 Hz, CH_{Ar}), 134.5 (C-Cl), 138.1 (d, $^{1}J_{CF}$ = 244.4 Hz, C1-F). Other signals are not visible due to overlapping. ^{19}F NMR (282 MHz, $CDCl_3$): δ -171.3 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_{10}ClFN_2$ + H^+]: 285.0589, found: 285.0589.

1-Fluoro-2-(4-chlorophenyl)-8-bromo-indolizine-3-carbonitrile (3i).

Indolizine **3i** was obtained from α-fluoronitroalkene **1a** (20.1 mg, 0.10 mmol) and pyridinium salt **2i** (1.5 equiv.) following the general procedure 1 (reaction time 20 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3i** (18.5 mg, 53%) containing traces of 6-substituted isomer (ratio 11:1) as a white solid. R_f = 0.34 (PE/EtOAc, 5:1) (UV), mp = 211-213 °C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (t, *J* = 7.1 Hz, 1H, H6), 7.20 (d, *J* = 7.1 Hz, 1H, H7), 7.49 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.75 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.17 (d, *J* = 7.1 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 89.7 (d, $^{3}J_{CF}$ = 6.6 Hz, C3), 110.2 (d, $^{3}J_{CF}$ = 4.5 Hz, C8), 113.0 (d, $^{4}J_{CF}$ = 2.1 Hz, CN), 113.5 (CH), 121.6 (d, $^{2}J_{CF}$ = 17.3 Hz, C8a), 121.9 (d, $^{2}J_{CF}$ = 9.2 Hz, C2), 123.4 (CH), 125.3 (d, J_{CF} = 2.0 Hz, CH), 126.8 (d, $^{3}J_{CF}$ = 3.2 Hz, C_{Ar}), 129.4 (CH_{Ar}), 129.6 (d, $^{4}J_{CF}$ = 3.2 Hz, CH_{Ar}), 135.2 (C-Cl), 138.9 (d, $^{1}J_{CF}$ = 250.6 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -164.0 (s). Characteristic signals of the minor (6-substituted) isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.7 Hz, 1H), 8.34 (s, 1H, H5). ^{19}F NMR (282 MHz, $CDCl_3$): δ -169.4 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_7BrClFN_2$ + H^+]: 348.9538, found: 348.9535.

1-Fluoro-2-(4-chlorophenyl)- 3-(ethyloxycarbonyl)-6-(phthalimidomethyl)-indolizine (3j).

Indolizine **3j** was obtained from α-fluoronitroalkene **1a** (40.3 mg, 0.20 mmol) and pyridinium salt **2j** (1.5 equiv.) following the general procedure 1 (reaction time 21 h). Column chromatography (eluent: 3:1 PE/EtOAc) afforded **3j** (59.2 mg, 62%) with traces of 8-substituted isomer (ratio 10:1) as a yellow solid. R_f = 0.26 (PE/EtOAc, 3:1) (UV), mp = 144-145°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, *J* = 7.1 Hz, 3H, CH_3), 4.20 (q, *J* = 7.1 Hz, 2H, CH_2), 4.85 (-**CH_2**-NPhth), 7.10 (d, *J* = 9.2 Hz, 1H, H7), 7.37 (s, 4H, CH_{Ar}), 7.45 (d, *J* = 9.2 Hz, 1H, H8), 7.71 (m, 2H, CH_{Phth}), 7.85 (m, 2H, CH_{Phth}), 9.64 (s, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 39.6 (-**CH_2**-N_{Phth}), 60.0 (CH_2), 106.8 (d, $^{3}J_{CF}$ = 1.3 Hz, C3), 115.1 (d, $^{3}J_{CF}$ = 3.4 Hz, C8-H), 120.1 (C6), 120.9 (d, $^{2}J_{CF}$ = 9.2 Hz, C2), 122.2 (d, $^{4}J_{CF}$ = 2.7 Hz, C7-H), 122.8 (d, $^{2}J_{CF}$ = 26.0 Hz, C8a), 123.5 (CH_{Phth}), 126.5 (C5-H), 127.7 (CH_{Ar}), 129.6 (d, $^{3}J_{CF}$ = 2.0 Hz, C_{Ar}), 131.9 (C_{Phth}), 131.9 (CH_{Ar}), 133.6 (C-Cl), 134.1 (CH_{Phth}), 140.2 (d, $^{1}J_{CF}$ = 242.5 Hz, C1-F), 161.4 (d, $^{3}J_{CF}$ = 2.6 Hz, **C**O_2Et, 168.9 (C_{Phth}). ^{19}F NMR (282 MHz, $CDCl_3$): δ -173.8 (s). HRMS (ESI): m/z calcd. for [$C_{26}H_{18}ClFN_2O_4$]: 477.1012, found: 477.1018. Characteristic signals of the minor (8-substituted) isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.26 (s, 2H, N-**CH_2**-NPhth), 6.67 (m, 1H, H6), 6.94 (d, *J* = 7.6 Hz, 1H, H7), 9.40 (d, *J* = 6.6 Hz, 1H, H5). ^{19}F NMR (282 MHz, $CDCl_3$): δ -169.3 (s).

2-(4-Chlorophenyl)-1-fluoropyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (3k).

Indolizine **3k** was obtained from α-fluoronitroalkene **1a** (40.3 mg, 0.20 mmol) and isoquinolinium salt **2k** (1.5 equiv.) following the general procedure 1 (reaction time 8 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3k** (43.5 mg, 68%) as a white solid. R_f = 0.50 (PE/EtOAc, 3:1) (UV), mp = 189-190°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 7.50-7.71 (m, 3H), 7.79 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 7.96 (dd, *J* = 7.1, 0.9 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 90.6 (d, $^{3}J_{CF}$ = 6.8 Hz, C3), 113.5 (d, $^{4}J_{CF}$ = 2.4 Hz, CN), 114.2 (CH), 120.0 (d, $^{2}J_{CF}$ = 20.6 Hz, C8a), 120.9 (d, $^{2}J_{CF}$ = 10.3 Hz, C2), 121.9 (CH), 123.6 (d, J_{CF} = 4.5 Hz, C_{Ar}), 123.8 (d, J_{CF} = 8.7 Hz, CH), 127.2 (CH), 127.3 (d, $^{3}J_{CF}$ = 4.5 Hz, C_{Ar}), 127.7 (C), 128.2 (CH), 128.8 (CH), 129.3 (CH), 129.4 (CH), 134.7 (C-Cl), 142.0 (d, $^{1}J_{CF}$ = 247.9 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -163.0 (s). HRMS (ESI): m/z calcd. for [$C_{19}H_{10}ClFN_2$ + H^+]: 321.0589, found: 321.0597.

1-Fluoro-2-(2-bromophenyl)-indolizine-3-carbonitrile (3l).

Indolizine **3l** was obtained from α-fluoronitroalkene **1b** (38.3 mg, 0.156 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 4.5 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3l** (36.5 mg, 75%) as a white solid. R_f = 0.28 (PE/EtOAc, 5:1) (UV), mp = 137-138°C (PhMe). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (pseudo t, *J* ≈ 7.0 Hz, 1H, H6), 7.03 (dd, *J* = 8.9, 6.9 Hz, 1H, H7), 7.32 (dddd, *J* = 7.9, 7.5, 2.8, 1.6 Hz, 1H, CH_{Ar}), 7.40-7.48 (m, 2H, CH_{Ar}), 7.57 (d, *J* = 8.9 Hz, 1H, H8), 7.74 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.20 (d, *J* = 7.1 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 90.4 (d, $^{3}J_{CF}$ = 6.1 Hz, C3), 113.0 (d, $^{4}J_{CF}$ = 2.3 Hz, CN), 113.8 (CH), 116.1 (d, J_{CF} = 3.4 Hz, CH), 121.4 (d, J_{CF} = 2.1 Hz, CH), 121.8 (d, $^{2}J_{CF}$ = 12.0 Hz, C2), 123.2 (d, $^{2}J_{CF}$ = 26.0 Hz, C8a), 124.0 (C-Br), 124.5 (CH), 127.5 (CH), 129.9 (d, $^{3}J_{CF}$ = 2.5 Hz, C_{Ar}), 130.5 (CH), 132.3 (CH), 133.3 (CH), 138.0 (d, $^{1}J_{CF}$ = 245.1 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -166.3 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_8BrFN_2$ + H^+]: 314.9928, found: 314.9930.

1-Fluoro-2-(4-fluorophenyl)-indolizine-3-carbonitrile (3m).

Indolizine **3m** was obtained from α-fluoronitroalkene **1c** (46.2 mg, 0.25 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 8 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3m** (44.5 mg, 70%) as a white solid. R_f = 0.29 (PE/EtOAc, 5:1) (UV), mp = 127-128°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (pseudo td, *J* ≈ 6.9, 0.7 Hz, 1H, H6), 7.01 (dd, *J* = 8.8, 7.0 Hz, 1H, H7), 7.19 (t, *J* = 8.7 Hz, CH_{Ar}), 7.52 (d, *J* = 8.8 Hz, 1H, H8), 7.80 (dd, *J* = 8.7, 5.4 Hz, 2H, CH_{Ar}), 8.17 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 88.4 (d, $^{3}J_{CF}$ = 5.4 Hz, C3), 113.7 (CH), 114.0 (d, $^{4}J_{CF}$ = 2.1 Hz, CN), 115.7 (d, J_{CF} = 3.3 Hz, CH), 116.1 (d, $^{2}J_{CF}$ = 21.7 Hz, CH_{Ar}), 120.7 (d, $^{2}J_{CF}$ = 9.1 Hz, C2), 121.7 (d, J_{CF} = 1.6 Hz, CH), 123.9 (d, $^{2}J_{CF}$ = 26.6 Hz, C8a), 124.4 (CH), 125.0 (t, ^{3}J,$^{4}J_{CF}$ = 3.2 Hz, C_{Ar}),128.7 (d, $^{4}J_{CF}$ = 3.6 Hz, CH_{Ar}), 130.1 (dd, J_{CF} = 8.3, 3.2 Hz, CH_{Ar}), 138.0 (d, $^{1}J_{CF}$ = 244.3 Hz, C1-F), 162.8 (d, $^{1}J_{CF}$ = 249.1 Hz,

C_{Ar}-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -112.0 (m, 1F, C_{Ar}-F), -171.9 (s, 1F, F-1). HRMS (ESI): m/z calcd. for [$C_{15}H_8F_2N_2$ + H^+]: 255.0728, found: 255.0719.

1-Fluoro-2-(4-bromophenyl)-indolizine-3-carbonitrile (3n).

Indolizine **3n** was obtained from α-fluoronitroalkene **1d** (123 mg, 0.5 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 8 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **3n** (115 mg, 73%) as a white solid. R_f = 0.33 (PE/EtOAc, 5:1) (UV), mp = 178-180°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (td, *J* = 6.8, 1.0 Hz, 1H, H6), 7.01 (dd, *J* = 9.0, 6.8 Hz, 1H, H7), 7.52 (d, *J* = 9.0 Hz, 1H, H8), 7.61 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.69 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.17 (d, *J* = 6.8 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 88.3 (d, $^3J_{CF}$ = 6.2 Hz, C3), 113.8 (CN), 113.8 (CH), 115.8 (d, J_{CF} = 3.3 Hz, CH), 120.5 (d, $^2J_{CF}$ = 8.7 Hz, C2), 121.8 (d, J_{CF} = 1.6 Hz, CH), 122.9 (C-Br), 123.9 (d, $^2J_{CF}$ = 26.5 Hz, C8a), 124.4 (CH), 127.8 (d, $^3J_{CF}$ = 3.3 Hz, C_{Ar}), 129.7 (d, $^4J_{CF}$ = 3.3 Hz, CH_{Ar}), 132.2 (CH_{Ar}), 138.1 (d, $^1J_{CF}$ = 245.0 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -171.1 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_8BrFN_2$ + H^+]: 314.9928, found: 314.9926.

1-Fluoro-2-(4-methylphenyl)-indolizine-3-carbonitrile (3o).

Indolizine **3o** was obtained from α-fluoronitroalkene **1e** (46.2 mg, 0.255 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 10 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3o** (40.5 mg, 63%) as a white solid. R_f = 0.34 (PE/EtOAc, 5:1) (UV), mp = 157-158°C (PhMe). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, Me), 6.78 (t, *J* = 6.8 Hz, 1H, H6), 6.98 (dd, *J* = 8.8, 6.8 Hz, 1H, H7), 7.31 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 7.50 (d, *J* = 8.8 Hz, 1H, H8), 7.73 (d, *J* = 7.9 Hz, 2H, CH_{Ar}), 8.17 (d, *J* = 6.8 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3 (Me), 88.4 (d, $^3J_{CF}$ = 6.2 Hz, C3), 113.4 (CH), 114.2 (d, $^4J_{CF}$ = 2.2 Hz, CN), 115.6 (d, J_{CF} = 3.2 Hz, CH), 121.4 (d, J_{CF} = 1.6 Hz, CH), 121.8 (d, $^2J_{CF}$ = 9.2 Hz, C2), 123.9 (d, $^2J_{CF}$ = 26.5 Hz, C8a), 124.4 (CH), 125.9 (d, $^3J_{CF}$ = 3.2 Hz, C_{Ar}), 128.1 (d, $^4J_{CF}$ = 3.1 Hz, CH_{Ar}), 129.7 (CH_{Ar}), 138.1 (d, $^1J_{CF}$ = 244.0 Hz, C1-F), 138.7 (**C**-Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ -171.7 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_{11}FN_2$ + H^+]: 251.0979, found: 251.0979

1-Fluoro-2-(4-cyanophenyl)-indolizine-3-carbonitrile (3p).

Indolizine **3p** was obtained from α-fluoronitroalkene **1f** (23.4 mg, 0.122 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 3 h). Column chromatography (eluent: 4:1 PE/EtOAc) afforded **3p** (26 mg, 81%) as a slightly yellow solid. R_f = 0.21 (PE/EtOAc, 5:1) (UV), mp = 195-196°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (pseudo t, *J* ≈ 6.9 Hz, 1H, H6), 7.06 (dd, *J* = 8.8, 6.9 Hz, 1H, H7), 7.57 (d, *J* = 8.8 Hz, 1H, H8), 7.78 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 7.95 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 8.21 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 88.6 (C3), 97.2 (**C**$_{Ar}$-CN), 112.2 (CN), 113.4 (d, $^4J_{CF}$ = 2.5 Hz, CN), 114.5 (CH), 116.1 (d, J_{CF} = 3.5 Hz, CH), 119.4 (d, $^2J_{CF}$ = 8.4 Hz, C2), 122.1 (d, J_{CF} = 2.0 Hz, CH), 124.0 (d, $^2J_{CF}$ = 25.9 Hz, C8a), 124.5 (CH), 128.7 (d, $^4J_{CF}$ = 3.6 Hz, CH_{Ar}), 132.7 (CH_{Ar}), 133.6 (d, $^3J_{CF}$ = 3.4 Hz, C_{Ar}), 138.4 (d, $^1J_{CF}$ = 246.8 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -169.9 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_8FN_3$ + H^+]: 262.0775, found: 262.0775.

1-Fluoro-2-(4-(methyloxycarbonyl)phenyl)-indolizine-3-carbonitrile (3q).

Indolizine **3q** was obtained from α-fluoronitroalkene **1g** (45.0 mg, 0.2 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 6.5 h). Column chromatography (eluent: 4:1 PE/EtOAc) afforded **3q** (39.5 mg, 67%) as a white solid. R_f = 0.20 (PE/EtOAc, 5:1) (UV), mp = 176-177°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, COSY): δ 3.95 (s, 3H, CO_2Me), 6.83 (pseudo t, *J* ≈ 7.0 Hz, 1H, H6), 7.02 (dd, *J* = 9.0, 6.8 Hz, 1H, H7), 7.54 (d, *J* = 9.0 Hz, 1H, H8), 7.90 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 8.15 (d, *J* = 8.3 Hz, 2H, CH_{Ar}), 8.19 (d, *J* = 7.1 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$, HSQC, HMBC): δ 52.2 (Me), 88.6 (C3), 113.8 (d, $^4J_{CF}$ = 1.7 Hz, CN), 114.1 (CH), 115.9 (d, J_{CF} = 3.2 Hz, CH), 120.4 (d, $^2J_{CF}$ = 8.7 Hz, C2), 121.8 (d, J_{CF} = 1.5 Hz, CH), 123.9 (d, $^2J_{CF}$ = 26.1 Hz, C8a), 124.4 (CH), 128.1 (d, $^4J_{CF}$ = 3.4 Hz, CH_{Ar}), 130.0 (**C**-CO_2Me), 130.2 (CH_{Ar}), 133.4 (d, $^3J_{CF}$ = 3.4 Hz, C_{Ar}), 138.4 (d, $^1J_{CF}$ = 246.0 Hz, C1-F), 166.5 (**C**O_2Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ -170.3 (s). HRMS (ESI): m/z calcd. for [$C_{17}H_{11}FN_2O_2$ + H^+]: 295.0977, found: 295.0986.

1-Fluoro-2-(4-nitrophenyl)-indolizine-3-carbonitrile (3r).

Indolizine **3r** was obtained from α-fluoronitroalkene **1h** (56 mg, 0.264 mmol) and pyridinium salt **2b** (1.5 equiv.) after stirring at 0°C for 1.5 h. Column chromatography (eluent: 4:1 PE/EtOAc) afforded **3r** (55 mg, 69%) as a bright yellow solid. R_f = 0.31 (PE/EtOAc, 3:1) (UV), mp = 178-178.5°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (pseudo t, *J* ≈ 6.9 Hz, 1H, H6), 7.07 (dd, *J* = 8.9, 7.0 Hz, 1H, H7), 7.59 (d, *J* = 8.9 Hz, 1H, H8), 8.01 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 8.23 (d, *J* = 6.8 Hz, 1H, H5), 8.35 (d, *J* = 8.3 Hz, 2H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 88.7 (d, $^3J_{CF}$ = 6.3 Hz, C3), 113.4 (d, $^4J_{CF}$ = 2.2 Hz, CN), 114.6 (CH), 116.1 (d, J_{CF} = 3.4 Hz, CH), 119.0 (d, $^2J_{CF}$ = 8.5 Hz, C2), 122.2 (d, J_{CF} = 2.1 Hz, CH), 124.0 (d, $^2J_{CF}$ = 26.7 Hz, C8a), 124.3 (CH_{Ar}), 124.5 (CH), 128.9 (d, $^4J_{CF}$ = 3.7 Hz, CH_{Ar}), 135.5 (d, $^3J_{CF}$ = 3.4 Hz, C_{Ar}), 138.4 (d, $^1J_{CF}$ = 247.0 Hz, C1-F), 147.5 (C-NO_2). ^{19}F NMR (282 MHz, $CDCl_3$): δ -169.6 (s). HRMS (ESI): m/z calcd. for [$C_{15}H_8FN_3O_2$ + H^+]: 304.0493, found: 304.0502.

1-Fluoro-2-(4-methoxyphenyl)-indolizine-3-carbonitrile (3s).

Indolizine **3s** was obtained from α-fluoronitroalkene **1i** (39.4 mg, 0.2 mmol) and pyridinium salt **2b** (2.3 equiv.) following the general procedure 1 (reaction time 5 days). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **3s** (40 mg, 75%) as a yellow solid. R_f = 0.26 (PE/EtOAc, 5:1) (UV), mp = 131-133°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, OMe), 6.77 (td, *J* = 6.8, 0.9 Hz, 1H, H6), 6.98 (dd, *J* = 8.9, 6.8 Hz, 1H, H7), 7.03 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.50 (d, *J* = 8.9 Hz, 1H, H8), 7.78 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 8.16 (d, *J* = 6.8 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3 (OMe), 88.2 (d, $^3J_{CF}$ = 6.3 Hz, C3), 113.3 (CH), 114.4 (d, $^4J_{CF}$ = 2.3 Hz, CN), 114.5 (CH_{Ar}), 115.6 (d, J_{CF} = 3.4 Hz, CH), 121.3 (d, $^3J_{CF}$ = 3.2 Hz, C_{Ar}), 121.5 (d, J_{CF} = 1.6 Hz, CH), 121.6 (d, $^2J_{CF}$ = 9.3 Hz, C2), 123.9 (d, $^2J_{CF}$ = 26.1 Hz, C8a), 124.4 (CH), 129.6 (d, $^4J_{CF}$ = 3.2 Hz, CH_{Ar}), 138.0 (d, $^1J_{CF}$ = 243.4 Hz, C1-F), 159.9 (**C**-OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -172.1 (s). HRMS (ESI): m/z calcd. for [$C_{16}H_{11}FN_2O$ + H^+]: 267.0928, found: 267.0929. CCDC 1883657 contains the supplementary crystallographic information for **3s**.

1-Methyl-2-(4-chlorophenyl)-indolizine-3-carbonitrile (4).

Indolizine **4** was obtained from nitroalkene **1j** (39.5 mg, 0.2 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 22 h). Column chromatography

(eluent: 9:1 PE/EtOAc) afforded **4** (36.3 mg, 68%) as white solid. R_f = 0.34 (PE/EtOAc, 5:1) (UV). NMR matches previously reported data.[6a] mp = 157-158°C ($CHCl_3$) (lit.[6a] 156-159).

2-(4-Chlorophenyl)-indolizine-3-carbonitrile (5).

Indolizine **5** was obtained from α-unsubstituted nitroalkene **1k** (36.7 mg, 0.2 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 5 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **5** (15.5 mg, 31%) as a white solid. R_f = 0.29 (PE/EtOAc, 5:1) (UV), mp = 116-118°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (s, 1H, H1), 6.84 (td, *J* = 6.9, 1.0 Hz, 1H, H6), 7.04 (dd, *J* = 8.7, 6.9 Hz, 1H, H7), 7.43 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 7.49 (d, *J* = 8.9 Hz, 1H, H8), 7.73 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 8.27 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$, HSQC, HMBC): δ 92.6 (C3), 99.7 (C1-H), 113.4 (C6-H), 114.5 (CN), 119.3 (C8-H), 122.7 (C7-H), 125.3 (C5-H), 128.6 (CH_{Ar}), 129.2 (CH_{Ar}), 131.0 (C), 134.4 (C8a), 136.2 (C), 136.7 (C). HRMS (ESI): m/z calcd. for [$C_{15}H_9ClN_2$+ H^+]: 253.0527, found: 253.0528.

1-Methyl-indolizine-3-carbonitrile (6a).

Indolizine **6a** was obtained from nitroalkene **1l** (26 mg, 0.3 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 5 h). Column chromatography (eluent: 9:1 PE/EtOAc) afforded **6a** (21.5 mg, 46%) as a pink solid. R_f = 0.37 (PE/EtOAc, 5:1) (UV), mp = 76-77°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, Me), 6.76 (pseudo t, *J* ≈ 6.8 Hz, 1H, H6), 6.94 (dd, *J* = 8.9, 6.8 Hz, 1H, H7), 7.09 (s, 1H, H2), 7.42 (d, *J* = 8.9 Hz, 1H, H8), 8.18 (d, *J* = 7.0 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.3 (Me), 93.4 (C3), 110.4 (C1), 112.7 (CH), 114.4 (CN), 117.7 (CH), 120.5 (CH), 123.3 (CH), 125.2 (CH), 134.5 (C8a). HRMS (ESI): m/z calcd. for [$C_{10}H_8N_2$ + H^+]: 157.0760, found: 157.0765.

1-Ethyl-indolizine-3-carbonitrile (6b).

Indolizine **6b** was obtained from nitroalkene **1m** (30.3 mg, 0.3 mmol) and pyridinium salt **2b** (2.0 equiv.) following the general procedure 1 (reaction time 18 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **6b** (31 mg, 61%) as a reddish oil, which solidifies upon storage in a refrigerator. R_f = 0.32 (PE/EtOAc, 5:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.6 Hz, CH_3), 2.76 (q, *J* = 7.6 Hz, CH_2), 6.75 (pseudo t, *J* ≈ 6.8 Hz, 1H, H6), 6.93 (dd, *J* = 8.9, 6.8 Hz, 1H, H7), 7.12 (s, 1H, H2), 7.44 (d, *J* = 8.9 Hz, 1H, H8), 8.18 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8 (CH_3), 18.4 (CH_2), 93.7 (C3), 112.8 (CH), 114.4 (CN), 117.5 (C1), 117.7 (CH), 120.5 (CH), 120.8 (CH), 125.2 (CH), 133.8 (C8a). HRMS (ESI): m/z calcd. for [$C_{11}H_{10}N_2$ + H^+]: 171.0917, found: 171.0910.

1-Methyl-2-isopropyl-indolizine-3-carbonitrile (7).

Indolizine **7** was obtained from nitroalkene **1n** (39 mg, 0.3 mmol) and pyridinium salt **2b** (2.0 equiv.) following the general procedure 1 (reaction time 3 days). Column chromatography (eluent: 19:1 PE/EtOAc) afforded **7** (22.5 mg, 38%) as a colorless oil, which solidifies upon storage in a refrigerator. R_f = 0.49 (PE/EtOAc, 5:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (d, *J* = 7.1 Hz, 6H, -CH(C**H$_3$**)$_2$), 2.26 (s, 3H, Me), 3.23 (sept, *J* = 7.1 Hz, 1H, -C**H**$(CH_3)_2$) 6.69 (pseudo t, *J* ≈ 6.8 Hz, 1H, H6), 6.91 (dd, *J* = 8.9, 6.7 Hz, 1H, H7), 7.35 (d, *J* = 8.9 Hz, 1H, H8), 8.14 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.5 (Me), 22.6 (CH(**C**$H_3)_2$), 26.3 (**C**$H(CH_3)_2$), 92.0 (C3), 107.3 (C1), 112.0 (CH), 115.2 (CN), 117.0 (CH), 120.7 (CH), 125.0 (CH), 134.6 (C8a), 143.1 (C2). HRMS (ESI): m/z calcd. for [$C_{13}H_{14}N_2$ + H^+]: 199.1230, found: 199.1236.

1-Chloro-2-(4-methoxyphenyl)-indolizine-3-carbonitrile (8).

Indolizine **8** was obtained from α-chloronitroalkene **1o** (21.5 mg, 0.1 mmol) and pyridinium salt **2b** (2.0 equiv.) following the general procedure 1 (reaction time 3 days). Column chromatography (eluent: 12:1 PE/EtOAc) afforded **8** (17 mg, 60%) as a white solid. R_f = 0.31 (PE/EtOAc, 5:1) (UV), mp = 143-145°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H, OMe), 6.88 (pseudo t, *J* ≈ 6.8 Hz, 1H, H6), 7.03 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.12 (dd, *J* = 8.9, 6.7 Hz, 1H, H7), 7.58 (d, *J* = 8.9 Hz, 1H, H8), 7.70 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 8.26 (d, *J* = 6.9 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4 (OMe), 93.0 (C3), 101.0 (C1-Cl), 113.8 (CH), 114.3 (br s, CN), 114.4 (CH_{Ar}), 117.2 (CH), 122.2 (C), 123.0 (CH), 125.3 (CH), 130.5 (CH_{Ar}), 133.4 (C), 134.0 (C), 160.1 (**C**-OMe). HRMS (ESI): m/z calcd. for [$C_{16}H_{11}ClN_2O$ + H^+]: 283.0638, found: 283.0633.

1-(Ethyloxycarbonyl)-2-(4-chlorophenyl)-indolizine-3-carbonitrile (9).

Indolizine **9** was obtained from α-(ethoxycarbonyl)nitroalkene **1p** (25.6 mg, 0.1 mmol) and pyridinium salt **2b** (1.5 equiv.) following the general procedure 1 (reaction time 18 h). Column chromatography (eluent: 5:1 PE/EtOAc) afforded **9** (23.8 mg, 73%) as white solid. R_f = 0.18 (PE/EtOAc, 5:1) (UV), mp = 127-129°C ($CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.1 Hz, 3H, CH_3), 4.25 (q, *J* = 7.1 Hz, 2H, CH_2), 7.07 (t, *J* = 6.9 Hz, 1H, H6), 7.38 (dd, *J* = 8.6, 6.9 Hz, 1H, H7), 7.43 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 7.48 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 8.32-8.42 (m, 2H, H5, H8). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 60.1 (CH_2), 97.3 (C3), 103.7 (C1), 112.6 (CN), 115.2 (CH), 120.8 (CH), 125.5 (CH), 126.5 (CH), 128.2 (CH), 130.0 (C_{Ar}), 131.3 (CH), 134.8 (C-Cl), 138.5 (C), 139.9 (C), 163.3 (**C**O_2Et). HRMS (ESI): m/z calcd. for [$C_{18}H_{13}ClN_2O_2$ + H^+]: 325.0738, found: 325.0738.

1-Fluoro-2-(4-bromophenyl)-indolizine (10n).

To the solution of cyano-substituted indolizine **3n** (62 mg, 0.2 mmol) in EtOH/H_2O (10:1) (2 ml) finely powdered KOH (0.72 g) was added, and the mixture was refluxed for 5 hours. After the starting **3n** was consumed (TLC monitoring), the mixture was evaporated to complete dryness, and 5 ml of saturated HCl solution was carefully added. The mixture was heated at 80°C for 4 hours, then cooled to room temperature and poured into 10% aqueous KOH solution. The product was extracted with CH_2Cl_2 (4×30 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. Column chromatography (eluent: 9:1 PE/EtOAc) afforded **10n** (43 mg, 75%) as a brown oil, which solidifies upon storage in a refrigerator. R_f = 0.42 (PE/EtOAc, 5:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$, COSY): δ 6.39 (ddd, *J* = 7.0, 6.5, 1.1 Hz, 1H, H6), 6.58 (dd, *J* = 9.1, 6.5 Hz, 1H, H7), 7.24 (d, $^4J_{HF}$ = 4.9 Hz, H3), 7.34 (d, *J* = 9.1 Hz, 1H, H8), 7.52 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.57 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.68 (d, *J* = 7.0 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$, HSQC, HMBC): δ 104.7 (d, $^3J_{CF}$ = 2.8 Hz, C3-H), 110.8 (C6-H), 114.3 (d, $^2J_{CF}$ = 8.6 Hz, C2), 115.4 (d, J_{CF} = 3.8 Hz, C8-H), 116.1 (d, J_{CF} = 2.6 Hz, C7-H), 119.1 (d, $^2J_{CF}$ = 26.8 Hz, C8a), 120.6 (C-Br), 124.1 (C5-H), 128.4 (d, $^4J_{CF}$ = 3.7 Hz, CH_{Ar}), 131.3 (d, $^3J_{CF}$ = 3.3 Hz, C_{Ar}), 131.8

(CH_{Ar}), 139.0 (d, $^{1}J_{CF}$ = 241.7 Hz, C1-F). ^{19}F NMR (282 MHz, $CDCl_3$): δ -175.0 (s). HRMS (ESI): m/z calcd. for [$C_{14}H_9BrFN$ + H^+]: 289.9975, found: 289.9973.

1-Fluoro-2-(4-methoxyphenyl)-indolizine (10s).

Indolizine **10s** was obtained from **3s** (26.6 mg, 0.1 mmol) as described above. Column chromatography (eluent: 9:1 PE/EtOAc) afforded **10s** (20.5 mg, 84%) as a colorless oil, which solidifies upon storage in a refrigerator. R_f = 0.28 (PE/EtOAc, 5:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, OMe), 6.36 (pseudo t, *J* ≈ 6.9 Hz, 1H, H6), 6.56 (dd, *J* = 9.0, 6.8 Hz, 1H, H7), 6.97 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.21 (d, $^{4}J_{HF}$ = 3.9 Hz, H3), 7.34 (d, *J* = 9.0 Hz, 1H, H8), 7.64 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.69 (d, *J* = 7.0 Hz, 1H, H5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3 (OMe), 104.4 (br s, C3-H), 110.3 (CH), 114.2 (d, $^{2}J_{CF}$ = 8.4 Hz, C2), 114.3 (CH_{Ar}), 115.3 (d, J_{CF} = 3.9 Hz, CH), 115.6 (d, J_{CF} = 2.4 Hz, CH), 119.1 (d, $^{2}J_{CF}$ = 26.7 Hz, C8a), 124.1 (CH), 124.9 (br s, C_{Ar}), 128.1 (d, $^{4}J_{CF}$ = 3.3 Hz, CH_{Ar}), 139.0 (d, $^{1}J_{CF}$ = 241.9 Hz, C1-F), 158.6 (C-OMe). ^{19}F NMR (282 MHz, $CDCl_3$): δ -175.4 (br s). HRMS (ESI): m/z calcd. for [$C_{15}H_{12}FNO$ + H^+]: 242.0976, found: 242.0974.

Synthesis of cyclazines (11).

To the solution of indolizines **10** (0.1 mmol) in dry toluene (1 ml), diethyl acetylenedicarboxylate (22 mg, 0.13 mmol, 1.3 equiv.) and $Cu(OAc)_2 \cdot H_2O$ (4 mg, 0.02 mmol, 0.2 equiv.) were added. The mixture was heated at 90°C under open air. After the reaction was complete (TLC monitoring, 5-8 h), the solvent was evaporated under reduced pressure after addition of silica gel and the crude products were purified by column chromatography (PE/EtOAc, 5:1) to afford cyclazines **11**.

Diethyl 3-(4-bromophenyl)-4-fluoro-pyrrolo[2,1,5-cd]indolizine-1,2-dicarboxylate (11n).

[3,2,2]cyclazine **11n** was obtained from indolizine **10n** (18.5 mg, 0.064 mmol) as a bright yellow oil, which solidifies upon storage in a refrigerator (18.4 mg, 63 %). R_f = 0.23 (PE/EtOAc, 5:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H, CH_3), 1.47 (t, *J* = 7.1 Hz, 3H, CH_3), 4.44 (q, *J* = 7.1 Hz, 3H, CH_2), 4.47 (q, *J* = 7.1 Hz, 3H, CH_2), 7.65 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.72 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.92 (t, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 8.48 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.4 (CH_3), 60.6 (CH_2), 62.3 (CH_2), 110.7 (d, $^{4}J_{CF}$ = 1.8 Hz, C), 112.2 (d, J_{CF} = 3.6 Hz, CH), 117.0 (d, $^{4}J_{CF}$ = 3.8 Hz, C), 117.4 (d, $^{2}J_{CF}$ = 10.1 Hz, C), 117.8 (d, J_{CF} = 1.7 Hz, CH), 121.9 (d, $^{2}J_{CF}$ = 29.9 Hz, C), 122.9 (C-Br), 124.6 (d, J_{CF} = 1.7 Hz, C), 126.3 (d, $^{3}J_{CF}$ = 5.5 Hz, C), 128.2 (C), 129.0 ($^{3}J_{CF}$ = 3.9 Hz, C_{Ar}), 130.8 (d, $^{5}J_{CF}$ = 3.7 Hz, CH_{Ar}), 132.1 (CH_{Ar}), 147.0 (d, $^{1}J_{CF}$ = 263.9 Hz, C-F), 163.3 (**C**O_2Et), 165.7 (**C**O_2Et). ^{19}F NMR (282 MHz, $CDCl_3$): δ -151.4 (s). HRMS (ESI): m/z calcd. for [$C_{22}H_{17}BrFNO_4$ + H^+]: 458.0398, found: 458.0391.

Diethyl 4-fluoro-3-(4-methoxyphenyl)-pyrrolo[2,1,5-cd]indolizine-1,2-dicarboxylate (11s).

[3,2,2]cyclazine **11s** was obtained from indolizine **10s** (9.6 mg, 0.036 mmol) as a bright yellow oil, which solidifies upon storage in a refrigerator (10.3 mg, 70 %). R_f = 0.28 (PE/EtOAc, 3:1) (UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 1.47 (t, *J* = 7.1 Hz, 3H, CH_3), 4.45 (q, *J* = 7.1 Hz, 3H, CH_2), 4.47 (q, *J* = 7.1 Hz, 3H, CH_2), 7.05 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.79 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.89 (t, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 8.44 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.5 (CH_3), 55.4 (OMe), 60.5 (CH_2), 62.1 (CH_2), 111.4 (d, J_{CF} = 3.6 Hz, CH), 110.2 (d, $^{4}J_{CF}$ = 1.9 Hz, C), 114.4 (CH_{Ar}), 117.0 (d, J_{CF} = 1.7 Hz, CH), 117.4 (d, $^{4}J_{CF}$ = 4.3 Hz, C), 118.6 (d, $^{2}J_{CF}$ = 10.1 Hz, C), 122.4 (d, $^{2}J_{CF}$ = 30.1 Hz, C), 122.6 (d, $^{3}J_{CF}$ = 3.9 Hz, C_{Ar}), 124.5 (d, J_{CF} = 1.7 Hz, CH), 126.3 (d, $^{3}J_{CF}$ = 5.5 Hz, C), 128.2 (C), 130.6 (d, $^{5}J_{CF}$ = 3.7 Hz, CH_{Ar}), 146.6 (d, $^{1}J_{CF}$ = 261.6 Hz, C-F), 160.0 (**C**-OMe), 163.5 (**C**O_2Et), 166.0 (**C**O_2Et). ^{19}F NMR (282 MHz, $CDCl_3$): δ -153.1 (s). HRMS (ESI): m/z calcd. for [$C_{23}H_{20}FNO_5$ + K^+]: 448.0957, found: 448.0933.

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Conclusions

In conclusion, a mild and efficient method for the synthesis of various indolizines was developed using the copper diacetate/lutidine system. A mechanism involving [3+2]-annulation-oxidation was proposed. A broad scope of the reaction was demonstrated to open access to various 1-fluorinated indolizines. The general nature of the approach was demonstrated to synthesize chloro-, alkyl, and ester-substituted indolizines. A two-step synthesis of monofluorinated [3,2,2]cyclazines from 1-fluoroindolizines was demonstrated as a useful follow-up reaction.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) G. S. Singh and E. E. Mmatli, *Eur. J. Med. Chem.*, 2011, **46**, 5237; (b) V. Sharma and V. Kumar, *Med. Chem. Res.*, 2014, **23**, 3593; (c) T. Fukuda, F. Ishibashi and M. Iwao, *Heterocycles*, 2011, **83**, 491; (d) E. Kim, Y. Lee, S. Lee and S. B. Park, *Acc. Chem. Res.*, 2015, **48**, 538.

2 (a) P. Chatelain, J. Gubin, A. S. Manning and J. Sissman, *Cardiov. Drug. Rev.*, 1991, **9**, 123; (b) S. P. Glasser, S. N. Singh and D. P. Humen, *J. Clin. Pharmacol.*, 1997, **37**, 53; (c) C. Herbert, U. Schieborr, K. Saxena, J. Juraszek, F. De Smet, C. Alcouffe, M. Bianciotto, G. Saladino, D. Sibrac, D. Kudlinzki, S. Sreeramulu, A. Brown, P. Rigon, J.-P. Herault, G. Lassalle, T. L. Blundell, F. Rousseau, A. Gils, J. Schymkowitz, P. Tompa, J.-M Herbert, P. Carmeliet, F. L. Gervasio, H. Schwalbe and F. Bono, *Cancer Cell*, 2013, **23**, 489; (d) P. Chen, A. Chaikuad, P. Bamborough, M. Bantscheff, C. Bountra, C.-w. Chung, O. Fedorov, P. Grandi, D. Jung, R. Lesniak, M. Lindon, S. Muller, M. Philpott, R. Prinjha, C. Rogers, C. Selenski, C. Tallant, T. Werner, T. M. Wilson, S. Knapp and D. H. Drewry, *J. Med. Chem.*, 2016, **59**, 1410; (e) I.-M. Moise, A. Ghinet, D. Belei, J.

Dubois, A. Farce and E. Bicu, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 3730. (f) S. Hagishita, M. Yamada, K. Shirahase, T. Okada, Y. Murakami, Y. Ito, T. Matsuura, M. Wada, T. Kato, M. Ueno, Y. Chikazawa, K. Yamada, T. Ono, I. Teshirogi and M. Ohtani, *J. Med. Chem.*, 1996, **39**, 3636.

3 Reviews: (a) T. Uchida and K. Matsumoto, *Synthesis*, 1976, 209; (b) B. Sadowski, J. Klajn and D. T. Gryko, *Org. Biomol. Chem.*, 2016, **14**, 7804; (c) C. R. de Souza, A. C. Goncalves, M. F. Z. J. Amaral, A. A. Dos Santos and G. C. Clososki, *Targets in Heterocyclic Systems*, 2016, **20**, 365; (d) E. V. Babaev, *Chem. Heterocycl. Compd.*, 2016, **52**, 666 [*Khim. Get. Soed.*, 2016, **52**, 666]; (e) A. G. Mikhailovskii and V. S. Shklyaev, *Chem. Heterocycl. Compd.*, **1997**, *33*, 243-265 [*Khim. Get. Soed.* **1997**, *33*, 291-317]. Selected seminal publications: (f) S. R. Pathipati, A. van der Werf and N. Selander, *Org. Lett.*, 2018, **20**, 3691; (g) C. Zhu, P. Zhao, Y. Qiao, K. Xiao, C. Song and J. Chang, *J. Org. Chem.*, 2017, **82**, 7045; (h) V. Helan, A. V. Gulevich and V. Gevorgyan, *Chem. Sci.*, 2015, **6**, 1928; (i) J. Barluenga, G. Lonzi, L. Riesgo, L. A. Lopez, and M. Tomas, *J. Am. Chem. Soc.*, 2010, **132**, 13200; (j) D. Chernyak, C. Skontos and V. Gevorgyan, *Org. Lett.*, 2010, **12**, 3242.

4 Selected seminal publications: a) D. He, Y. Xu, J. Han, H. Deng, M. Shao, J. Chen, H. Zhang and W. Cao, *Tetrahedron*, 2017, **73**, 938; b) B. Shen, B. Li and B. Wang, *Org. Lett.*, 2016, **18**, 2816; (c) A. Hazra, S. Mondal, A. Maity, S. Naskar, P. Saha, R. Paira, K. B. Sahu, P. Paira, S. Ghosh, C. Sinha, A. Samanta, S. Banerjee and N. B. Mondal, *Eur. J. Med. Chem.*, 2011, **46**, 2132; (d) J. Brioche, C. Meyer and J. Cossy, *Org. Lett.*, 2015, **17**, 2800; (e) A. V. Rotaru, I. D. Druta, T. Oeser and T. J. J. Muller, *Helv. Chim. Acta*, 2005, **88**, 1798; (f) L. Zhang, F. Liang, L. Sun, Y. Hu, H. Hu, *Synthesis*, **2000**, 1733-1737.

5 Selected seminal publications: (a) J. Hu, H. Hu, Y. Liu, X. Wang, Y. Kan and C. Wang, *Eur. J. Org. Chem.*, 2017, 257; (b) H. Hu, J. Feng, Y. Zhu, N. Gu, Y. Kan, *RSC Adv.*, 2012, **2**, 8637; (c) Y. Liu, H. Hu, J. Zhou, W. Wang, Y. He and C. Wang, *Org. Biomol. Chem.*, 2017, **15**, 5016; (d) F. Shi, Y. Zhang, Z. Lu, X. Zhu, W. Kan, X. Wang and H. Hu, *Synthesis*, 2016, **48**, 413; (e) F. Li, J. Chen, Y. Hou, Y. Li, X.-Y. Wu and X. Tong, *Org. Lett.*, 2015, **17**, 5376; (f) C. Wang, H. Hu, J. Xu and W. Kan, *RSC Adv.*, 2015, **5**, 41255; (g) B. Wang, X. Zhang, J. Li, X. Jiang, Y. Hu and H. Hu, *J. Chem. Soc. Perkin Trans 1*, **1999**, 1571.

6 Oxidative annulations: (a) M. Kucukdisli and T. Opatz, *Eur. J. Org. Chem.*, 2012, 4555; (b) M. Kucukdisli, *New Synthetic Strategies towards Indolizines and Pyrroles*, Dissertation zur Erlangung des Grades Doktor der Naturwissenschaften, Johannes Gutenberg-Universitat: Mainz, 2015. (c) S. Muthusaravanan, S. Perumal, P. Yogeeswari and D. Sriram, *Tetrahedron Lett.*, 2010, **51**, 6439; Non-oxidative annulations: (d) Y. Tominaga, Y. Shiroshita and A. Hosomi, *J. Heterocyclic Chem.*, 1988, **25**, 1745; (e) Y. Tominaga, Y. Ichihara and A. Hosomi, *Heterocycles*, 1988, **27**, 2345; (f) Y. Tominaga, Y. Shiroshita, T. Kurokawa, H. Gotou, Y. Matsuda, A. Hosomi, *J. Heterocyclic Chem.* 1989, **26**, 477; (g) E. Boultadakis, B. Chun, M. J. R. Elsgood and G. M. Weaver, *Synlett*, 2002, 1547.

7 (a) *Fluorine in Heterocyclic Chemistry*, *Vols. 1-2*, Ed. V. G. Nenajdenko, Springer International Publishing: Switzerland, 2014; (b) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Ed. V. A. Petrov, John Wiley & Sons, Inc.: Hoboken, New Jersey, 2009; (c) *Fluorinated Heterocycles*, Eds. A. A. Gakh and K. L. Kirk, ACS Symposium Series 1003; American Chemical Society: Washington, DC, 2009; (d) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (e) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (f) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422.

8 (a) H. G. Viehe, R. Merenyi, J. F. M. Oth and P. Valange, *Angew. Chem., Int. Ed.*, 1964, **3**, 746 [*Angew. Chem.* 1964, **76**, 888]; (b) Z.-K. Yao and Z.-X. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 10864; (c) S. Fabig, G. Haberhauer and R. Gleiter, *J. Am. Chem. Soc.* 2015, **137**, 1833; (d) L. M. Hall, D. P. Tew, N. E. Pridmore, A. C. Whitwood, J. M. Lynam and J. M. Slattery, *Angew. Chem. Int. Ed.*, 2017, **56**, 7551 [*Angew. Chem.*, 2017, **129**, 7659]; (e) I. V. Alabugin and M. Manoharan, *J. Comput. Chem.*, *2007*, **28**, 373.

9 (a) V. A. Motornov, V. M. Muzalevskiy, A. A. Tabolin, R. A. Novikov, Yu. V. Nelyubina, V. G. Nenajdenko, S. L. Ioffe, *J. Org. Chem.*, 2017, **82**, 5274; (b) V. A. Motornov, A. A. Tabolin, R. A. Novikov, Yu. V. Nelyubina, S. L. Ioffe, I. S. Smolyar and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2017, 6851; Other relevant publications on fluoronitroalkenes, see: (c) V. A. Motornov, A. A. Tabolin, R. A. Novikov, Yu. V. Nelyubina, V. G. Nenajdenko and S. L. Ioffe, *Org. Chem. Front*, 2018, **5**, 2588; (d) A. S. Aldoshin, A. A. Tabolin, S. L. Ioffe and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2018, 3816; (e) S. Opekar, R. Pohl, P. Beran, L. Rulisek and P. Beier, *Chem. Eur. J.*, 2014, **20**, 1453.

10 a) E. V. Babaev, *Fluorinated indolizines*, in *Fluorine in Heterocyclic Chemistry*, *Vol. 1.*, Ed. V. G. Nenajdenko, Springer International Publishing: Switzerland, 2014, pp. 157-180. b) About occasional examples of 1,2-difluoroindolizines, see: K. Wu and Q.-Y. Chen, *Synthesis*, 2003, 35.

11 No formation of any intermediate products, like Michael adducts or tetrahydroindolizines was observed, if oxidant-free conditions (Entry 1, Table 1) were applied.

12 About application of copper (II) in the indolizine synthesis, see: (a) Ref.[5a,b]. For similar processes employing Cu(II)/base systems, see: (b) M. Sandeep, P. S. Dushyant, B. Sravani and K. R. Reddy, *Eur. J. Org. Chem.*, 2018, 3036; (c) Y. Yu, Y. Liu, A. Liu, H. Xie, H. Li and W. Wang, *Org. Biomol. Chem.*, 2016, **14**, 7455; (d) D. C. Mohan, C. Ravi, S. N. Rao and S. Adimurthy, *Org. Biomol. Chem.*, 2015, **13**, 3556; (e) J.-l. Liu, Y. Liang, H.-s. Wang and Y.-m. Pan, *Synlett*, 2015, **26**, 2024; (f) S. Ding, Y. Yan and N. Jiao, *Chem. Commun.*, 2013, **49**, 4250.

13 V. Barbier, F. Couty and O. R. P. David, *Eur. J. Org. Chem.*, 2015, **17**, 3679.

14 Even in the cases of the moderate yields of indolizines **3-9** no significant amounts of any side products were isolated/detected in reaction mixtures. Presumably some oligomerization is the main side reaction occurred.

15 Pyridinium salts possessing strong electron-donating (4-Me_2N, 2-OMe) or electron-withdrawing (4-CN, 3-CO_2Me) groups failed to give indolizines **3**. Decomposition (presumably oligomerization) of starting nitroalkene **1a** was observed during the reaction conditions.

16 About examples and possible explanations of 2-site selectivity in 3-substituted pyridinium salts, see: (a) R. J. Sundberg, G. Hamilton and C. Trindle, *J. Org. Chem.*, 1986, **51**, 3672; (b) N. E. Dontsova and A. M. Shestopalov, *Russ. Chem. Bull.*, 2017, **66**, 1030 [*Izv. Akad. Nauk, Ser. Khim.*, 2017, 1030]; (c) I. S. Poddybnyi, *Chem. Heterocycl. Compd.*, 1995, **31**, 682 [*Khim. Get. Soed.* 1995, 774]; (d) T. Sakamoto, S.-i. Kaneda, S. Nishimura and H. Yamanaka, *Chem. Pharm. Bull.*, 1985, **33**, 565; (e) R. Yamaguchi, M. Moriyasu, M. Yoshioka and M. Kawanisi, *J. Org. Chem.*, 1988, **53**, 3507.

17 The crystallographic information for compound **3s** was deposited in the Cambridge Crystallographic Data Centre (CCDC 1883657).

18 About oxidation of indolizines with molecular oxygen, see: Y. Li, H.-Y. Hu, J.-P. Ye, H.-K. Fun, H.-W. Hu and J.-H. Xu, *J. Org. Chem.*, 2004, **69**, 2332.

19 In the similar [3+2]-annulations involving α-bromonitroalkenes, HBr elimination was predominantly observed: (a) E. A. Sheremet, R. I. Tomanov, E. V. Trukhin and V. M. Berestovitskaya, *Russ. J. Org. Chem.*, 2004, **40**, 594 [*Zh. Org. Khim.*, 2004, **40**, 620]; (b) X. Deng, J. T. Liang and N. S. Mani, *Eur. J. Org. Chem.*, 2014, 410; (c) A. Baranski, *Pol. J. Chem.*, 1982, **56**, 1585; (d) W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.*, 1951, **73**, 4664; (e) R. Muruganantham, S. M. Mobin and I. N. N. Namboothiri, *Org. Lett.*, 2007, ***9,*** 1125; (f) J.-W. Xie, Z. Wang, W.-J. Yang, L.-C. Kong and D.-C. Xu, *Org. Biomol. Chem.*, 2009, **7**, 4352.
20 K.-P. Chen, Y.-J. Chen and C.-P. Chuang, *Eur. J. Org. Chem.*, 2010, 5292.
21 (a) O. Tsuge, S. Kanemasa and S. Takenaka, *Bull. Chem. Soc. Jpn*, 1985, **58**, 3320; (b) A. M. Shestopalov, K. S. Chunikhin and L. A. Rodinovskaya, *Chem. Heterocyclic Compd.* 2002, **38**, 310 [*Khim. Get. Soed.*, 2002, 346]; (c) S. B. Nosachev, K. A. Del'netskaya, N. A. Solov'ev and A. G. Tyrkov, *Russ. J. Org. Chem.* 2010, **46**, 1427 [*Zh. Org. Khim.* 2010, **46**, 1422].
22 Also, Cu(II) is known to promote Michael addition to the nitroalkenes. See, T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2009, **38**, 1039.
23 (a) L. M. Stanley, M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887; (b) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou and Y.-D. Wu, *Angew. Chem. Int. Ed.*, 2006, **45**, 1979 [*Angew. Chem.*, 2006, **118**, 2013]; (c) W. Gao, X. Zhang and M. Raghunath, *Org. Lett.*, 2005, **7**, 4241; (d) Y. Oderaotoshi, W. Cheng, S. Fujitomi, Y. Kasano, S. Minakata, and M. Komatsu, *Org. Lett.*, 2003, **5**, 5043.
24 On the role of air in the reoxidation of Cu(I), see: a) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234; Cu(I) or Cu(II)/lutidine systems also found the application in oxidative cross-couplings: (b) T. Yasukawa, H. Miyamura and S. Kobayashi, *Org. Biomol. Chem.*, 2011, **9**, 6208; (c) J. C. Antilla and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 2077.
25 The transformation **C→D** may involve radical steps. However, presence of TEMPO or BHT significantly reduced the yield of target indolizines **3**, although it did not suppress its formation completely (see Table in the ESI).
26 Alternative mechanism for the transformation **C→3** may involve elimination of HNO_2 followed by oxidative aromatization. However, usually elimination of nitrous acid is performed under treatment with strong bases (e.g., DBU), that is not the case for presented protocol. This makes this alternative mechanism less likely. For relevant cases of HNO_2 elimination, see: a) N. Ono, *The nitro group in organic synthesis*, Wiley-VCH, 2001, pp. 214-230; b) Ref.[6a]; c) B. A. Vara and J. N. Johnston, *J. Am. Chem. Soc.*, 2016, **138**, 13794-13797.
27 For reports on [8+2]-cycloadditions leading to cyclazines, see, e.g.: (a) Y. Matsuda, *Yakugaku Zasshi*, 2001, **121**, 971; (b) W. Flitsch and U. Kramer, *Adv. Heterocycl. Chem*., 1978, **22**, 321; (c) A. Galbraith, T. Small, R. A. Barnes and V. Boekelheide, *J. Am. Chem. Soc.,* 1961, **83**, 453; (d) H. Hu, G. Li, W. Hu, Y. Liu, X. Wang, Y. Kan and M. Ji, *Org. Lett.* 2015, **17**, 1114; (e) E. V. Babaev, I. A. Shadrin and V. B. Rybakov, *Chem. Heterocycl. Compd.*, 2018, **54**, 339 [*Khim. Get. Soed.*, 2018, 339].
28 E. M. Schultz, W. A. Bolhofer, A. Augenblick, J. B. Bicking, C. N. Habecker, J. K. Horner, S. F. Kwong, A. M. Pietruszkiewicz, *J. Med. Chem.*, 1967, **10**, 717.
29 V. Ashokkumar and A. Siva, *Org. Biomol. Chem.*, 2015, **13**, 10216.
30 D. H. Lloyd and D. E. Nichols, *J. Org. Chem.*, 1986, **51**, 4294.
31 F. Manoni, U. Farid, C. Trujillo and S. J. Connon, *Org. Biomol. Chem.*, 2017, **15**, 1463.
32 J. Liu, L. Gong and E. Meggers, *Tetrahedron Lett.*, 2015, **56**, 4653.
33 A. V. Malkov, D. Pernazza, M. Bell, M. Bella, A. Masssa, F. Teply, P. Megnani and P. Kocovsky, *J. Org. Chem.*, 2003, **68**, 4727.
34 P. P. N. Rao, M. Amini, H. Li, A. G. Habeeb and E. E. Knaus, *J. Med. Chem.*, 2003, **46**, 4872.
35 M. Ghandi and A. H. Jamea, *Tetrahedron Lett.*, 2011, **52**, 4005.
36 R. E. Banks, W. T. Flowers and S. N. Khaffaf, *J. Fluor. Chem.*, 1991, **53**, 127.
37 J. Day, M. Uroos, R. A. Castledine, W. Lewis, B. McKeever-Abbas and J. Dowden, *Org. Biomol. Chem.*, 2013, **11**, 6502.
38 Q. Han, Y. Jiang, C. Jin, S. Cheng, X. Wang, X. Wang and B. Wang, *Polym. Chem.*, 2014, **5**, 5900.
39 X. Wu, G. Ding, L. Yang, W. Lu, W. Li, Z. Zhang and X. Xie, *Org. Lett.*, 2018, **20**, 5610.

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