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Electrosynthesis of fluorinated indole derivatives

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ABSTRACT

Anodic fluorination of various *N*-acetyl-3-substituted indole derivatives was successfully carried out in Et$_4$NF-4HF/MeCN to provide the corresponding *trans*-2,3-difluoro-2,3-dihydroindoles exclusively or selectively. Treatment of difluorinated products with a base provided monofluoroindole derivatives or monofluoroindoline derivative depending on the substituents at the 3-position.

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1. Introduction

Many heterocyclic compounds have unique biological activities. On the other hand, partially fluorinated heterocycles are currently attracting much attention since the introduction of fluorine atom(s) into heterocyclic compounds very often greatly enhances or dramatically changes their biological activities.[1] Indole and its derivatives are often focused in synthetic and semi-synthetic medicines or pharmaceutical intermediates.[2] Recently, fluorination of indole derivatives through chemical method using fluorinating reagents like selectfluor™ has been reported.[3] In these cases, fluorinated oxindole derivatives were obtained as main products in high yields. More than 30 years ago, Hesse and his co-workers reported fluorination of indole derivatives by using CF$_3$OF in Freon at −78 °C to provide CF$_3$O(F) and difluoro adducts at the 2- and 3-positions in moderate yields.[4] However, fluorinating reagent CF$_3$OF is a toxic gas and difficult to handle. Moreover, Freon must be used.

Previously, we found that 3-substituted benzofuran derivatives were anodically fluorinated to provide *cis*-2,3-difluoro adducts mainly together with *cis*-2-fluoro-3-hydroxy adducts in good yields.[5] With these facts in mind, we investigated anodic fluorination of various 3-substituted indole derivatives.

## 2. Results and discussion

2.1. Oxidation potentials of indole derivatives

First, the oxidation peak potentials (E_p^{ox}) of indole (**1a**) and its derivatives (**1b–e** and **2a–f**) were measured by cyclic voltammetry

in 0.1 M Bu$_4$NBF$_4$/MeCN and 0.1 M Et$_4$NF-4HF/MeCN using a platinum disk electrode. All compounds showed irreversible oxidation waves in cyclic voltammograms, and their first oxidation potentials E_p^{ox} are summarized in Table 1.

Table 1
First oxidation potentials (E_p^{ox}) of indole derivatives **1** and **2**
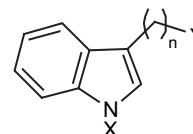
Compound	n	X	Y	E_p^{ox} (V vs SCE)[a]	
				^{n}Bu$_4$NBF$_4$/MeCN	Et$_4$NF-4HF/MeCN
1a	0	H	H	1.26	1.12
1b	0	Ac	H	1.67	1.66
1c	0	Ac	CN	2.17	2.08
1d	0	Ac	Ac	1.99	1.88
1e	0	Ac	COOMe	2.03	1.91
2a	1	H	H	1.15	1.03
2b	1	Ac	H	1.56	1.54
2c	1	Ac	CN	1.81	1.70
2d	1	Ac	Ac	1.64	1.56
2e	1	Ac	COOMe	1.74	1.68
2f	1	Ac	COOBz	1.73	1.65

[a] Substrate concentration: 5 mM. Sweep rate: 100 mV/s. Working electrode: Pt disk ($\phi = 1$ mm).

The oxidation potentials in Et$_4$NF-4HF/MeCN are slightly lower than those in Bu$_4$NBF$_4$/MeCN regardless of substituents on the pyrrole moiety. However, the reason is not clear. Although indole (**1a**) and 3-methylindole (**2a**) are readily oxidizable (E_p^{ox}: 1.12 V and

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1.03 V), their *N*-acetyl derivatives **1b** and **2b** showed much higher oxidation potentials (E_p^{ox}: 1.66 V and 1.54 V). Moreover, the oxidation potentials are significantly affected by the type of the substituent functionality, and are in the following order: CN>COOMe>Ac>H.

Thus, when the electron-withdrawing ability of the substituents at the pyrrole ring increases, the oxidation potential increases. Therefore, the electron-transfer seems to take place from the pyrrole moiety of the indole ring.

## 2.2. Anodic fluorination of indole and its derivatives

First, anodic fluorination of indole (**1a**) was carried out at a constant current in Et₃N-3HF/MeCN; however, only polymeric product was formed and any fluorinated products were not formed (Scheme 1).
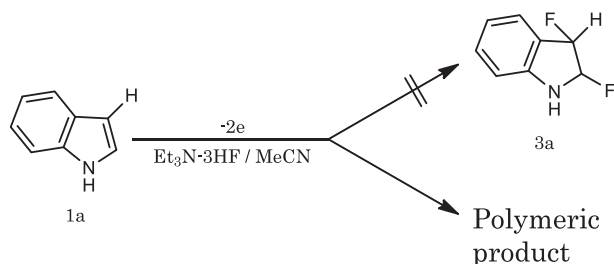
Scheme 1.

Then, anodic fluorination of *N*-acetyl derivative **1b** was examined similarly in anodically stable Et₄NF-4HF/MeCN, and *trans*-2,3-difluoro product **3b** was exclusively formed as major product although the yield was low (Table 2, Run 1). Thus, it was found that N-protection of indoles was necessary for the anodic fluorination. But pure fluorinated compound **3b** was not obtained due to its instability during separation with column chromatography resulting in hydrolysis of **3b**.

Table 2
Anodic fluorination of indole derivatives **1b**–**e**
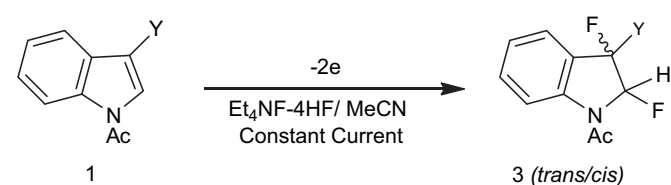
Run	Substrate	Y	Charge passed (F/mol)	Yield of 3%[a] (*trans/cis*)
1	**1b**	H	4	15 (>99/trace)
2	**1c**	CN	3	20 (82:18)
3	**1d**	Ac	2.6	56 (78:22)
4	**1e**	COOMe	2.4	52 (74:26)

[a] Determined by ¹⁹F NMR.

Next, we carried out anodic fluorination of *N*-acetylindole derivatives having various electron-withdrawing groups at the 3-position. 3-Acetyl- and 3-methoxycarbonylindoles **1d** and **1e** underwent anodic fluorination smoothly to provide *trans*-2,3-difluoro products **3d** and **3e** selectively in moderate yields (Runs 3 and 4) while *trans*-2,3-difluoro product **3c** was obtained more selectively in reasonable yield from 3-cyanoindole derivative **1c** (Run 2).

We also carried out anodic fluorination of indole derivatives having various substituted methylene groups **2b**–**f** at the 3-position. The results are summarized in Table 3.

Table 3
Anodic fluorination of indole derivatives **2b**–**f**
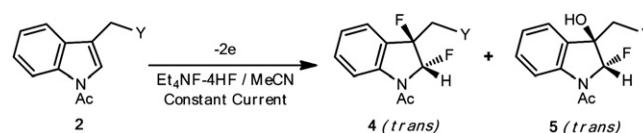
Run	Substrate	Y	Charge passed (F/mol)	Yield of 4[a] (%)	Yield of 5[a] (%)
1	**2b**	H	2.3	33	Trace
2	**2c**	CN	3	18	7[b]
3	**2d**	Ac	2.5	44	Trace
4	**2e**	COOMe	3	68	Trace
5	**2f**	COOBz	3	23	9

[a] Determined by ¹⁹F NMR.
[b] (1-Acetyl-2-fluoro-2,3-hydroindol-3-ylidene)acetonitrile (**6c**) was detected in 2% yield.

Anodic fluorination of 1-acetyl-3-methyl derivative **2b** proceeds similarly to the case of 1-acetylindole (**1b**) and *trans*-2,3-difluoro product **4b** was obtained exclusively in 33% (Run 1). The yield was twice of that of **3b**. In the case of 3-cyanomethyl derivative **2c**, *trans*-2,3-difluoro product **4c** was obtained in low yield and a small amount of *trans*-1-acetyl-2-fluoro-3-hydroxy-2,3-dihydroindole (**5c**) was also formed (Run 2). Moreover, a small amount (2%) of dehydrofluorination product **6c** was also detected by ¹⁹F NMR and HRMS. On the other hand, anodic fluorination of 3-acetyl and 3-(methoxycarbonyl)methyl derivatives **2d** and **2e** provided the corresponding *trans*-2,3-difluoro products in moderate yields (Runs 3 and 4); however, the anodic fluorination of 3-(benzyloxycarbonyl)methyl derivative **2f**, which is similar to compound **2e**, provided *trans*-2,3-difluoro product **4f** in much lower yield (Run 5). In this case, *trans*-(2-fluoro-3-hydroxy-2,3-dihydro)indole derivative **5f** was also formed.

The stereochemistry of fluorinated compound **3e** was confirmed by the X-ray crystal structure analysis, and it was found to be a *trans*-form as shown in Figure 1.
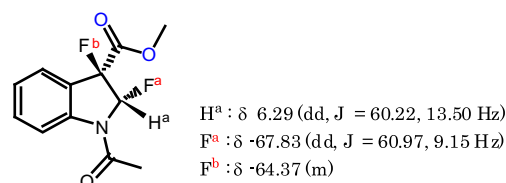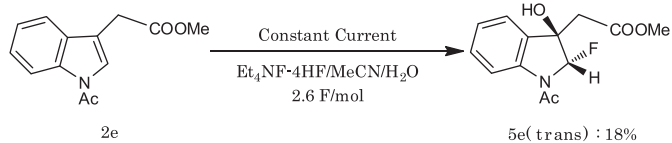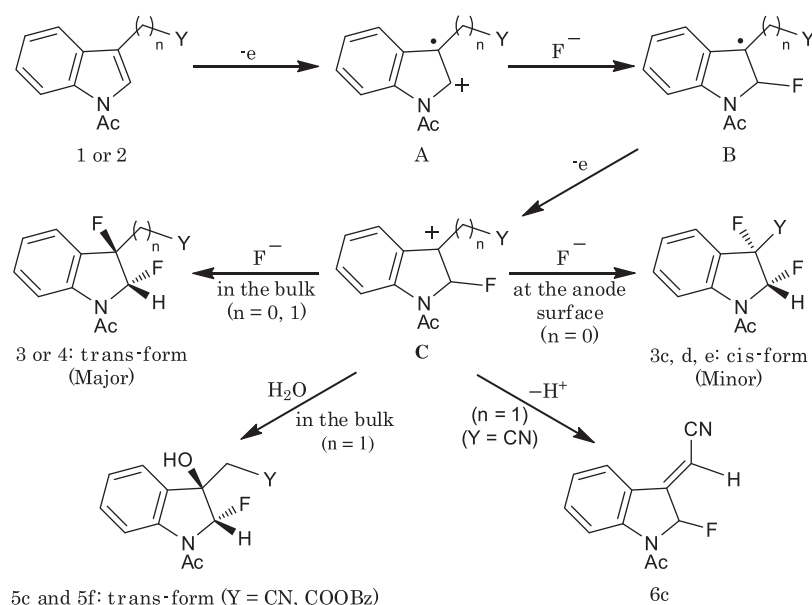
Hᵃ : δ 6.29 (dd, J = 60.22, 13.50 Hz)
Fᵃ : δ -67.83 (dd, J = 60.97, 9.15 Hz)
Fᵇ : δ -64.37 (m)

Figure 1. Configuration of fluorinated compound **3e**.

Based on this result, we can conclude that anodic fluorination of *N*-acetylindole derivatives with or without a methylene substituent at the 3-position provided 2,3-difluoro adducts very selectively; however, anodic fluorination of 3-cyanomethyl and 3-(benzyloxycarbonyl) methyl derivatives **2c** and **2f** also provided minor products, *trans*-2-fluoro-3-hydroxyindole **5c** and **5f**. Purification of **5c** by column chromatography was unsuccessful because of its instability. This finding can be attributed to the air moisture, which suppresses the fluorination process and promotes the attack of hydroxide ions. This speculation was also proved by conducting similar electrolysis of **2e** in the presence of a few drops of water in MeCN. As excepted, the difluorinated **4e** product could not be detected at all but *trans*-2-fluoro-3-hydroxy-2,3-dihydroindole derivative **5e** was obtained solely with 18% yield as shown in Scheme 2.

A possible mechanism of the formation of 2,3-difluoro and 2-fluoro-2,3-dihydroindole derivatives **3**–**5** is illustrated in Scheme 3. The anodic fluorination reaction seems to take place by electron transfer from the pyrrole moiety of the indole to form radical cation

Scheme 2.

1.2 equiv of piperidine in acetonitrile gave pure **6e** in good yield without further purification.[5]

Furthermore, dehydrofluorination of compound **3d** was carried out similarly in MeCN containing piperidine (1.2 equiv). However, the dehydrofluorination did not proceed and a large amount (75%) of the starting material **3d** was recovered (Table 4, Run 1). When **3d** was treated with stronger base like MeONa in MeOH for 1 h, 3-fluoro-1*H*-
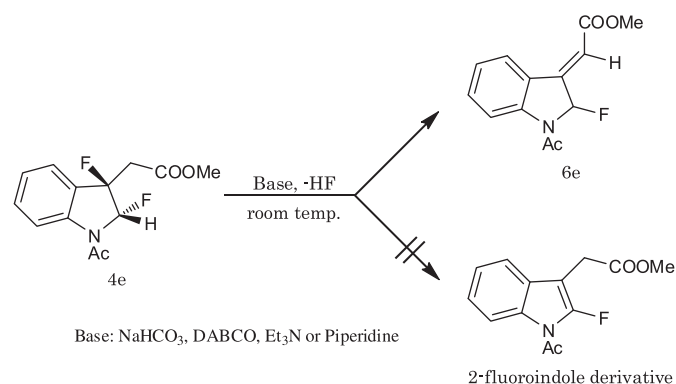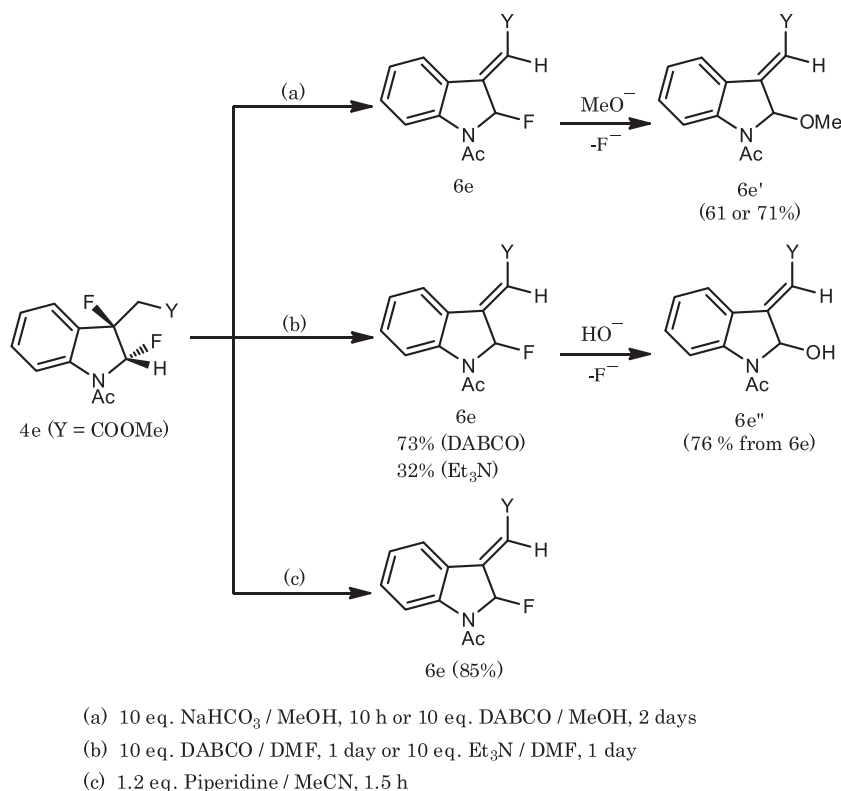

Scheme 3.

A, followed by fluoride ion attack at the 2-position of the indole to give the radical intermediate **B**, which was further oxidized to give the cation **C**. There are three possible pathways to form fluorinated compounds through capturing the cation **C**; (a) a fluoride ion attacks **C** in the bulk of the electrolytic solution to provide *trans*-form of compounds **3** and **4** as major products whether the methylene group is attached to the pyrrole ring or not; (b) A fluoride ion attacks at the spacially restricted anode surface to give *cis*-form of compounds **3c**–**e**; (c) A hydroxide ion attacks **C** in the bulk to provide *trans*-form products **5c** and **5f** from **2c** and **2f**, respectively. It is interesting that a small amount of dehydrofluorination product **6c** was detected by ^{19}F NMR, GC–MS and HRMS, even no base was present in the electrolytic solution. This can be explained as follows. After generation of cationic intermediate **C**, elimination of the α-proton of the strongly electron-withdrawing cyano group takes place prior to the attack of fluoride ion to **C**.

Next, we attempted to convert *trans*-2,3-difluoro-2-3-dihydroindole (**4e**) to the corresponding 2-fluoroindole derivative by the treatment of **4e** with various bases as shown in Scheme 4. However, the expected 2-fluoroindole derivative was not formed at all but methyl (1-acetyl-2-fluoro-2-hydroindole-3-ylindene)1acetate (**6e**) was formed. Treatment of **4e** with a strong base like EtOK in EtOH resulted in hydrolysis to give complicated decomposition products.

Treatment with 10 equiv of sodium hydrogen carbonate (NaHCO₃) or 1,4-diazabicyclo[2.2.2]octane (DABCO)[4] in MeOH resulted in 2-methoxy dehydrofluorination product **6e′**[6] in moderate yield as shown in Scheme 5a. When 10 equiv of DABCO or Et₃N in aprotic polar solvent like *N*,*N*-dimethylformamide (DMF) was used, dehydrofluorination product **6e** was obtained as the almost pure product in 73% and 32%, respectively. Unfortunately, further purification of the crude product through silica gel column chromatography provided 2-hydroxy dehydrofluorination product **6e″**[4,7] as shown in Scheme 5b. However, treatment of **4e** with

Scheme 4.

indole (**8**) was obtained in moderate yield (46%) (Run 2). When dehydrofluorination was carried out using sodium methoxide in DMF instead of methanol, 1-acetyl-3-fluoroindole (**7**) was obtained as a main product beside compound **8** (Run 3). When NaOMe/DMF was used for **3e**, products **7** and **8** were obtained at almost same ratio (Run 4).

On the basis of these results, we propose a mechanism of defluorination reaction as shown in Scheme 6. A methoxide ion attacks the carbonyl group at the 3-position of the indoline ring, followed by elimination of a fluoride ion to form product **7**. In addition, other methoxide ion attacks the acetyl group on nitrogen atom, followed by the elimination of methanolysis of the amide moiety to provide product **8**.[4,8]

In summary, it was found that the introduction of a substituent at the 3-position of 1-acetylindol changed its behavior in anodic fluorination and significantly increased the yields of fluorinated products. *trans*-2,3-Difluoroindoles were mainly formed. Moreover,

(a) 10 eq. NaHCO$_3$ / MeOH, 10 h or 10 eq. DABCO / MeOH, 2 days
(b) 10 eq. DABCO / DMF, 1 day or 10 eq. Et$_3$N / DMF, 1 day
(c) 1.2 eq. Piperidine / MeCN, 1.5 h

Scheme 5.

Table 4
Dehydrofluorination of difluoroproducts **3d** and **3e**
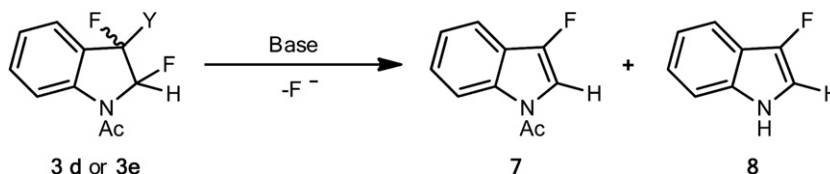
| Run	Compound	Y	Base	Solvent	Time (h)	Yield[a] (%)		Overall yield (%)
						7	**8**	
1	**3d**	Ac	Piperidine	MeCN	13.5	0	0	0[b]
2	**3d**	Ac	NaOMe	MeOH	1	0	46	46
3	**3d**	Ac	NaOMe	DMF	5	49	9	58
4	**3e**	COOMe	NaOMe	DMF	5	14	17	31

[a] Determined by ^{19}F NMR.
[b] Starting material was recovered in 75% yield.

defluorination of 2,3-difluoro products was achieved by using various bases to provide the corresponding 2-fluoroindole derivatives.

3. Experimental section

3.1. General

^{1}H, ^{19}F NMR spectra were obtained on a JEOL JNM EX-270 (270.05 MHz) in a deuteriochloroform (CDCl$_3$) solution using tetramethylsilane as an internal standard. ^{19}F spectra were given in δ parts per million with mono-fluorobenzene (C$_6$H$_5$F, δ −36.5 ppm) as external standard. Cyclic voltammetry was measured using ALS CH instruments Electrochemical Analyzer Model 600C. Mass spectra were obtained by EI method with Shimadzu GCMS-QP5050A. High-resolution mass spectra were obtained on JEOL MStation JMS-700 mass spectrometer operating at the ionization energy of 70 eV. Preparation electrolysis experiments were achieved using Metronix

3d (Y = Me)
3e (Y = OMe)
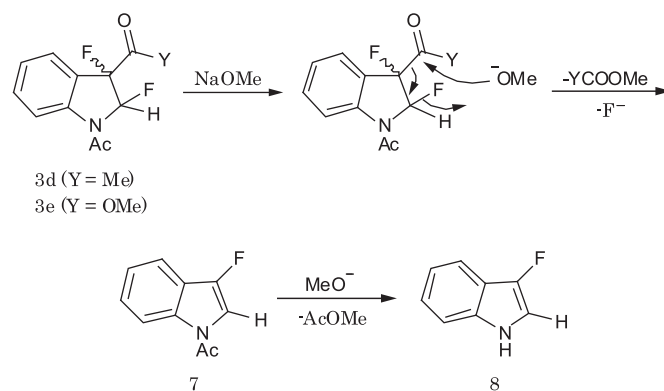
Scheme 6.

Corp. constant current power supply model 5944 monitored with a Hokuto Denko Coulomb/Amperehour Meter HF-201.

3.2. General synthesis of *N*-acetylindole derivatives 1c−e and 2b−f

The compounds **1c−e** and **2b−e** were prepared according to the reported procedures.[9] To indole derivatives (1 mmol) in DMF (10 ml) was dropwised acetic anhydride (5 mmol, 5.00 equiv) followed by addition of K_2CO_3 (5 mmol, 5.00 equiv). After stirring for 2−3 h under reflux, the reaction mixture was cooled to room temperature and quenched by saturated aqueous $NaHCO_3$, reasonably. Then AcOEt solvent was poured into the solution and the aqueous phase was extracted with organic solvent three times after shaking the mixture solution sufficiently. The combined organic phases were washed with water and brine, and dried with Na_2SO_4. The filtrate was concentrated through evaporation even in vacuo and the residue was purified by chromatography on silica gel eluting hexanes/AcOEt (10/1) to afford the respected *N*-acetylindole compounds. The compound **2f** was prepared similarly.

3.2.1. Benzyl (1-acetyl-3-indolyl)acetate (2f).
Pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.59 (s, Ac−3H), 3.78 (d, 2H, J=1.08 Hz), 5.18 (s, 2H), 7.24−7.51 (m, Ar−9H), 8.43 (d, 1H, J=8.10 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 24.03 (CH$_3$), 31.07 (CH$_2$), 66.94 (OCH$_2$), 114.78, 116.61, 118.75, 123.54, 123.69, 125.40, 128.32, 128.51 (CH), 128.28, 129.90, 135.47, 135.58 (C), 168.29, 170.47 (C=O); HRMS (EI): m/z calcd for C$_{19}$H$_{17}$NO$_3$, 307.1208; found, 307.1211.

3.3. Anodic fluorination of *N*-acetylindole derivatives 1b−e and 2b−f

Electrolysis was performed with platinum electrodes (1×1 cm^2) in a 0.3 M solution of the supporting electrolyte, which was fluoride salt in acetonitrile (4 ml) containing *N*-acetylindole derivatives **1b−e** and **2b−f** (0.2 mmol). The electrolysis was carried out in an undivided cell at room temperature. Constant-current (6 mA/cm^2) was applied until the starting materials thoroughly disappeared that was judged by TLC. The products were further purified by silica gel column chromatography using hexane/ethyl acetate as an eluent. In the cases compounds **1b−e**, difluorinated products either *trans*-form or *cis*-form were collected and then further separated by HPLC. On the other hand, *trans*-form difluorinated products were collected on head followed by 2-fluoro-3-hydroxyindole derivatives when started from compounds **2b−f**. All collections were then evaporated under reduced pressure.

3.3.1. 1-Acetyl-2,3-difluoro-2,3-dihydroindole (3b) trans-form.
^{19}F NMR (254 MHz, CDCl$_3$) δ −69.21 (dt, 1F, J=59.19, 11.18 Hz), −95.41 (dt, 1F, J=53.60, 11.18 Hz); MS (m/z) 197 (M$^+$). Purification was failed due to its instability.

3.3.2. (1-Acetyl-2,3-difluoro-2,3-dihydro-3-cyano)indole (3c) cis and trans mixture.
^{19}F NMR (254 MHz, CDCl$_3$) δ −55.92 (s,1F), −62.55 (d, 1F, J=59.19 Hz), −71.48 (m, 1F), −88.41 (m, 1F); MS (m/z) 222(M$^+$); HRMS (EI): m/z calcd for C$_{11}$H$_8$F$_2$N$_2$O, 222.0605; found, 222.0594.

3.3.3. (1,3-Diacetyl-2,3-difluoro-2,3-dihydro)indole (3d) cis and trans mixture.
^{19}F NMR (254 MHz, CDCl$_3$) δ −65.15 (m, 1F), −67.90 (dd, 1F, J=60.97, 7.37 Hz), −77.23 (dd, 1F, J=64.78, 14.73 Hz), −96.74 (d, 1F, J=16.77 Hz); MS (m/z) 239(M$^+$), 197, 177; HRMS (EI): m/z calcd for C$_{12}$H$_{11}$F$_2$NO$_2$, 239.0758; found, 239.0747.

3.3.4. Methyl (1-acetyl-2,3-difluoro-2,3-dihydro-3-indolyl)carboxylate (3e) trans-form.
White solid: mp 117−118 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.42 (s, Ac−3H), 3.92 (s, OMe−3H), 6.29 (dd, 1H, J=60.22,

13.50 Hz), 7.23 (dt, Ar−1H, J=7.56, 1.08 Hz), 7.51 (m, Ar−2H), 8.23 (d, Ar−1H, J=8.64 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −64.37 (m, 1F), −67.83 (dd, 1F, J=60.97, 9.15 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 23.27 (CH$_3$), 53.64 (CH$_3$), 99.43 (d, J=44.75 Hz), 102.61 (d, J=44.07 Hz) (C−F), 117.24, 124.95, 126.37, 132.78 (CH), 124.90, 132.83 (C), 164.90 (dd, J=29.02, 2.24 Hz), 168.46 (d, J=2.78 Hz) (C=O); MS (m/z) 255 (M$^+$), 213, 193, 175; HRMS (ESI-TOF): m/z [M+Na$^+$] calcd for C$_{12}$H$_{11}$F$_2$NO$_3$Na, 278.0605; found, 278.0596.

3.3.5. Methyl (1-acetyl-2,3-difluoro-2,3-dihydro-3-indolyl)carboxylate (3e) cis-form.
Colorless oil; ^{1}H NMR (270 MHZ, CDCl$_3$) δ 2.45 (s, Ac−3H), 3.84 (s, OMe−3H), 6.44 (d, 1H, J=63.19 Hz), 7.19 (tt, Ar−1H, J=7.56, 0.81 Hz), 7.47 (m, Ar−2H), 8.18 (d, Ar−1H, J=6.48 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −74.68 (dd, 1F, J=62.75, 16.51 Hz), −95.43 (d, 1F, J=14.73 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 26.54 (d, CH$_3$, J=434.53 Hz), 53.71 (CH$_3$), 95.05 (d, J=16.75 Hz), 98.40 (d, J=15.59 Hz) (C−F), 117.18, 125.01, 125.04, 132.53 (CH), 124.60, 132.56 (C), 166.73 (dd, J=31.26, 5.56 Hz), 168.71 (d, J=3.32 Hz) (C=O); MS (m/z) 255(M$^+$), 213, 193; HRMS (ESI-TOF): m/z [M+Na$^+$] calcd for C$_{12}$H$_{11}$F$_2$NO$_3$Na, 278.0605; found, 278.0599.

3.3.6. (1-Acetyl-2,3-difluoro-2,3-dihydro-3-methyl)indole (4b) trans-form.
Colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 1.87 (dd, 3H, J=21.60, 4.86 Hz), 2.42 (s, Ac−3H), 6.10 (dd, 1H, J=61.84, 13.50 Hz), 7.19 (tt, Ar−1H, J=7.56, 0.81 Hz), 7.45 (m, Ar−2H), 8.20 (d, Ar−1H, J=7.29 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −53.17 (dt, 1F, J=20.32, 35.31 Hz), −68.76 (dd, 1F, J=62.75, 11.18 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 17.42 (dd, CH$_3$, J=27.05, 7.25 Hz), 23.27 (CH$_3$), 100.64 (d, J=44.61 Hz), 103.81 (d, J=45.77 Hz) (C−F), 117.20, 123.72 (d, J=1.15 Hz), 124.65 (d, J=3.32 Hz), 131.98 (d, J=3.93 Hz) (CH), 125.74, 129.42 (C), 168.89 (d, J=2.78 Hz) (C=O); MS (m/z) 211(M$^+$), 191, 169, 154, 148, 130; HRMS (EI): m/z calcd for C$_{11}$H$_{11}$F$_2$NO, 211.0809; found, 211.0789.

3.3.7. (1-Acetyl-2,3-difluoro-2,3-dihydro-3-indolyl)acetonitrile (4c) trans-form.
Colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.45 (s, Ac−3H), 3.25 (m, 2H), 6.32 (dd, 1H, J=61.03, 12.42 Hz), 7.24 (tt, Ar−1H, J=7.56, 0.81 Hz), 7.53 (m, Ar−2H), 8.22 (br, Ar−1H); ^{19}F NMR (254 MHz, CDCl$_3$) δ −59.79 (m, 1F), −68.76 (dd, 1F, J=60.97, 12.96 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 20.26 (d, CH$_2$, J=9.49 Hz), 23.64 (CH$_3$), 98.30 (d, J=41.29 Hz), 100.77 (d, J=42.92 Hz) (C−F), 118.62 (CN), 114.41, 116.54 (C), 123.96, 126.24, 132.23, 134.54 (CH), 168.53 (d, J=2.85 Hz) (C=O); MS (m/z) 236 (M$^+$), 194, 154, 127; HRMS (EI): m/z calcd for C$_{12}$H$_{10}$F$_2$N$_2$O, 236.0761; found, 236.0741.

3.3.8. 1-(1-Acetyl-2,3-difluoro-2,3-dihydro-3-indolyl)-2-propanone (4d) trans-form.
Pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.31 (s, 3H), 2.44 (s, 3H), 3.11 (ddd, 1H, J=18.36, 35.65, 4.32 Hz), 3.66 (ddd, 1H, J=18.36, 9.18, 4.86 Hz), 6.66 (dd, 1H, J=58.60, 11.07 Hz), 7.19 (tt, Ar−1H, J=7.56, 0.81 Hz), 7.44 (m, Ar−2H), 8.23 (d, Ar−1H, J=8.37 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −64.57 (m, 1F), −67.71 (dd, 1F, J=59.07, 16.51 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 26.55 (d, CH$_3$, J=436.23 Hz), 30.70 (CH$_3$), 44.33 (dd, CH$_2$, J=25.43, 3.80 Hz), 99.32 (d, J=44.07 Hz), 102.49 (d, J=42.99 Hz) (C−F), 117.47, 123.66, 124.59 (d, J=3.86 Hz), 132.45 (d, J=4.47 Hz) (CH), 126.50, 142.79 (C), 169.00 (d, J=2.85 Hz), 202.06 (d, J=0.61 Hz) (C=O); MS (m/z) 253(M$^+$), 233, 211, 191, 172, 148, 130; HRMS (EI): m/z calcd for C$_{13}$H$_{13}$F$_2$NO$_2$, 253.0914; found, 253.0896.

3.3.9. Methyl (1-acetyl-2,3-difluoro-2,3-dihydro-3-indolyl)acetate (4e) trans-form.
Pale yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.45 (s, Ac−3H), 3.07 (ddd, 1H, J=17.55, 36.19, 4.32 Hz), 3.51 (ddd, 1H, J=17.28, 8.91, 4.59 Hz), 3.81 (s, OMe−3H), 6.59 (dd, 1H, J=58.87, 10.80 Hz), 7.20 (tt, Ar−1H, J=7.56, 0.81 Hz), 7.46 (m, Ar−2H), 8.23 (d, Ar−1H, J=7.83 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −63.70 (m, 1F), −67.59 (dd, 1F, J=59.19, 16.77 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 23.45 (CH$_3$), 27.17 (d, CH$_3$, J=413.92 Hz), 51.95 (d, CH$_2$, J=30.10 Hz), 101.80 (d, J=45.70 Hz), 104.30 (d, J=44.61 Hz) (C−F), 123.98, 126.28, 131.88

(d, *J*=6.44, 3.86 Hz), 134.19 (CH), 125.40, 143.40 (C), 169.07 (d, *J*=2.78 Hz), 169.40 (d, *J*=3.39 Hz) (C=O); MS (*m/z*) 269(M$^+$), 249, 227, 207, 189, 148, 130; HRMS (ESI-TOF): *m/z* [M+Na$^+$] calcd for $C_{13}H_{13}F_2NO_3Na$, 292.0761; found, 292.0756.

3.3.10. Benzyl (1-acetyl-2,3-difluoro-2,3-dihydro-3-indolyl)acetate (4f) trans-form.

Colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.41 (s, Ac−3H), 3.12 (ddd, 1H, *J*=17.28, 35.92, 4.32 Hz), 3.55 (ddd, *J*=17.55, 8.91, 4.59 Hz), 5.24 (dd, 2H, *J*=17.28, 12.42 Hz), 6.56 (dd, 1H, *J*=58.87, 11.07 Hz), 7.18 (tt, Ar−1H, *J*=7.56, 0.81 Hz), 7.38 (m, Ar−6H), 7.47 (m, Ar−1H), 8.22 (d, Ar−1H, *J*=8.10 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −63.45 (m, 1F), −67.46 (dd, 1F, *J*=59.19, 14.73 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 26.52 (d, CH$_3$, *J*=440.70 Hz), 36.42 (dd, CH$_2$, *J*=26.24, 4.47 Hz), 67.18 (CH$_2$), 99.39 (d, *J*=43.53 Hz), 102.56 (d, *J*=42.99 Hz) (C−F), 124.70 (d, *J*=3.32 Hz), 128.23, 128.46, 128.60, 132.60 (d, *J*=3.93 Hz), 135.12 (CH), 117.48 (d, *J*=2.85 Hz), 123.76 (d, *J*=1.70 Hz), 143 (C), 167.91, 168.89 (d, *J*=2.78 Hz) (C=O); MS (*m/z*) 220(M$^+$−OBz, −F), 205; HRMS (EI): *m/z* calcd for $C_{19}H_{17}F_2NO_3$, 345.1176; found, 345.1162.

3.3.11. 1-Acetyl-2-fluoro-3-hydroxy-2,3-dihydroindole (5c) trans-form.

^{19}F NMR (254 MHz, CDCl$_3$) δ −65.13 (d, *J*=62.75 Hz); MS (*m/z*) 236 (M$^+$+2H), 194, 154. Pure adduct could not be obtained because of its instability.

3.3.12. Benzyl (2-fluoro-3-hydroxy-2,3-dihydro-3-indolyl)acetate (5f) trans-form.

Yellow oil; ^{19}F NMR (254 MHz, CDCl$_3$) δ −61.83 (dt, *J*=62.75, 5.59 Hz); MS (*m/z*) 234 (M$^+$+H, −CH$_2$Ph, −OH); HRMS (ESI-TOF): *m/z* [M+Na$^+$] calcd for $C_{19}H_{18}FNO_4Na$, 366.1118; found, 366.1102.

3.3.13. (1-Acetyl-2-fluoro-2,3-hydroindol-3-ylidene)acetonitrile (6c).

^{19}F NMR (254 MHz, CDCl$_3$) δ −71.30 (dd, *J*=22.36, 9.15 Hz); MS (*m/z*) 216 (M$^+$), 172, 154, 145; HRMS [(EI): *m/z* calcd for $C_{12}H_9FN_2O$, 216.0699; found, 216.0694.

3.4. Direct anodic synthesis of compound 5e in the presence of a few drops of water

Electrolysis of compound **2e** (0.2 mmol) was carried out in a 0.3 M solution of Et$_4$NF-4HF in acetonitrile (4 ml) containing distilled water (0.1 ml). The electrolysis was performed in an undivided cell at room temperature until the starting substrate was completely consumed that was monitored by TLC. Following short column first, the reaction mixture was purified by chromatography on silica gel using hexane/AcOEt (5/1, v/v) to simply give compound **5e**.

3.4.1. Methyl (1-acetyl-2-fluoro-3-hydroxy-2,3-dihydro-3-indolyl)acetate (5e) trans-form.

Colorless oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.41 (s, Ac−3H), 2.96 (dd, 1H, *J*=17.55, 4.86 Hz), 3.20 (dd, 1H, *J*=17.28, 6.75 Hz), 3.84 (s, OMe−3H), 4.38 (s, OH), 6.21 (d, 1H, *J*=62.65 Hz), 7.17 (td, Ar−1H, *J*=7.56, 0.81 Hz), 7.32–7.43 (m, Ar−2H), 8.20 (d, Ar−1H, *J*=8.10 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ 61.67 (d, 1F, *J*=62.75 Hz); ^{13}C NMR (68 MHz, CDCl$_3$) δ 23.29 (d, CH$_3$, *J*=42.38 Hz), 49.57 (d, CH$_2$, *J*=32.88 Hz), 51.43 (CH$_3$), 53.52 (C), 102.66 (d, C−F, *J*=167.87 Hz), 123.52, 125.86, 130.20, 132.12 (CH), 129.87, 141.75 (C), 169.33, 173.18 (d, *J*=2.78 Hz) (C=O); MS (*m/z*) 267 (M$^+$), 247 (M$^+$, −F), 225, 205, 173, 145, 130, 117; HRMS (EI): *m/z* calcd for $C_{13}H_{14}FNO_4$, 267.0907; found, 267.0923.

3.5. Dehydrofluorination of trans-2,3-difluoro-2,3-dihydroindole derivative 4e

To a stirring solution of the compound **4e** (1 mmol) in dry solvent (DMF, MeCN, etc.) (10 ml) was added various bases with 10 mmol (10 equiv). The reaction mixture was stirred at room temperature for some hours. Following produced piperidyl hydrofluoride salt was

removed through filtration, almost pure product **6e** was obtained in good yield. Regrettably, it was difficult to further purify the crude due to conversion to compound **6e″**. In the case of utilizing alcohol (MeOH) as solvent in dehydrofluorination reaction, compound **6e′** was obtained in 61 or 71% yield.

3.5.1. Methyl 2-(1-acetyl-2-fluoroindolin-3-ylidene)acetate 6e.

Yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.48 (s, Ac−3H), 3.85 (s, OMe−3H), 6.48 (dd, 1H, *J*=5.95, 1.35 Hz), 7.14 (td, 1H, *J*=7.56, 0.81 Hz), 7.32 (dd, 1H, *J*=60.76, 1.08 Hz), 7.43 (dt, 1H, *J*=15.66, 1.08), 7.54 (d, 1H, *J*=7.83 Hz), 8.24 (d, 1H, *J*=8.10 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −53.35 (dd, *J*=59.19, 5.59 Hz); MS (*m/z*) 249 (M$^+$), 231, 207, 189, 172, 148, 130. Elemental analysis could not carried out because of its instability.

3.6. Defluorination of difluorinated compound 3d and 3e

To a solution of the compounds **3d** and **3e** in dry solvent (MeOH, DMF, etc.) was added appropriate bases, respectively. The reaction mixture was stirred at room temperature for 1−13.5 h. The reaction was halted once starting substrates were completely consumed (checked by TLC). After taking off extra solvent through evaporation under reduced pressure, compound **7** and **8** were determined by ^{19}F NMR and GC−MS.

3.6.1. 1-Acetyl-3-fluoroindole (7).

White solid: mp 52−53 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.58 (s, Ac−3H), 7.20 (d, 1H, *J*=2.70 Hz), 7.32 (td, Ar−1H, *J*=7.56, 1.08 Hz), 7.41 (td, Ar−1H, *J*=7.29, 1.08 Hz), 7.59 (dd, Ar−1H, *J*=7.83, 2.70 Hz), 8.43 (d, Ar−1H, *J*=8.10 Hz); ^{19}F NMR (254 MHz, CDCl$_3$) δ −90.48 (s, 1F); ^{13}C NMR (68 MHz, CDCl$_3$) 23.85 (CH$_3$), 107.27 (d, *J*=27.80 Hz), 116.75, 117.08 (d, *J*=2.71 Hz), 123.87, 126.54 (CH), 121.00 (d, *J*=18.31 Hz), 132.93 (C), 148.79 (d, *J*=254.25 Hz) (C−F), 168.39 (C=O); MS (*m/z*) 177 (M$^+$), 135. HRMS (ESI-TOF): *m/z* [M+Na$^+$] calcd for $C_{10}H_8FNONa$, 200.0488; found, 200.0482.

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