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Synthesis of 3-Fluoroindoles via Photoredox Catalysis

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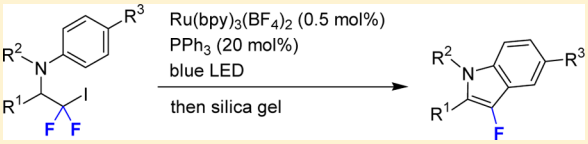
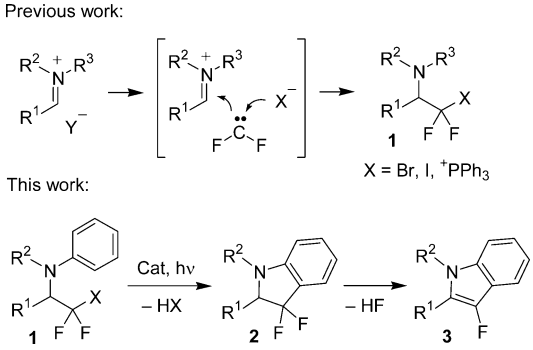
Supporting Information

ABSTRACT: A method for the synthesis of 3-fluoroindoles from *N*-arylamines substituted with the CF_2I group is described. The reaction is mediated by a ruthenium photocatalyst in the presence of a substoichiometric amount of triphenylphosphine upon irradiation with blue light. The starting *N*-arylamines are readily obtained by nucleophilic iododifluoromethylation of iminium ions.



The importance of organofluorine compounds in medicinal chemistry[1] has stimulated the development of methods for their synthesis.[2] Of particular interest are reactions allowing for assembly of molecules bearing a single fluorine atom or a fluorinated group in a specified position from simple building blocks.[1a,3] Despite significant progress in this field, synthesis of heterocycles substituted with the fluorine in a specific position still may be problematic.[4] For example, there are no general methods for the synthesis of 3-fluoroindoles. Thus, all reported approaches to 3-fluoroindoles rely on electrophilic fluorination reactions which either are accompanied by overfluorination[5] or require biased substrates such 3-stannylindoles[6] or *ortho*-alkynylanilines.[7] In this work, we describe a straightforward access to 3-fluoroindoles starting from *N*-aryliminium salts with the fluorine substituent originating from difluorocarbene[8] (Scheme 1).

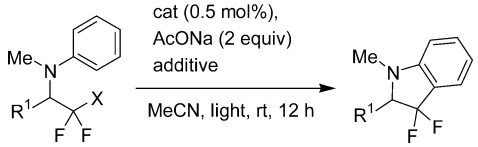
Scheme 1. Approach to the Synthesis of 3-Fluoroindoles



Recently, we reported facile methods of nucleophilic fluoroalkylation of carbonyl compounds and iminium ions affording products containing CF_2X groups,[9,10] where X is either a halogen (Br, I) or a triphenylphosphonium fragment (Scheme 1). It is also known that fluorinated iodides[11] and phosphonium salts[12] can serve as sources of fluorinated radicals under photoredox conditions.[13] Herein, we demonstrate the application of photoredox catalysis to effect cyclization of *N*-aryl-substituted amines **1** (R^3 = Ar). Difluorinated indolines **2** are the primary products of photoredox processes, whereas subsequent elimination of hydrogen fluoride would lead to the indole system.[14]

A series of substrates **1a-X** were evaluated in the presence of a photocatalyst (0.5 mol %) irradiating either with blue LED for ruthenium or with UV LED for iridium complexes (Table 1).

Table 1. Optimization Studies



1a-X, R^1 = 4-ClC_6H_4 **2a**

no.	X	cat.[a]	additive	yield of **2a**, %[b]
1	$^+PPh_3$	$Ru(bpy)_3(BF_4)_2$	–	–
2	$^+PPh_3$	$Ir(ppy)_3$	–	27
3	$^+PPh_3$	$Ru(bpy)_3(BF_4)_2$	PPh_3 (0.2 equiv)	–
4	I	$Ru(bpy)_3(BF_4)_2$	–	–
5	I	$Ir(ppy)_3$	–	<5
6	I	$Ru(bpy)_3(BF_4)_2$	PPh_3 (0.2 equiv)	98
7	I	$Ru(bpy)_3(BF_4)_2$	*i*-Pr_2NEt (0.2 equiv)	23
8	I	$Ru(bpy)_3(BF_4)_2$	*i*-Pr_2NEt (2.0 equiv)	89
9	I	$Ru(bpy)_3(BF_4)_2$	PPh_3 (0.05 equiv)	16
10	I	$Ir(ppy)_3$	PPh_3 (0.2 equiv)	79
11	I	$Ir(ppy)_3$	PPh_3 (1 equiv)	79
12	Br	$Ru(bpy)_3(BF_4)_2$	PPh_3 (0.2 equiv)	–
13	Br	$Ir(ppy)_3$	PPh_3 (0.2 equiv)	65

[a]For Ru-catalyst, blue LED; for Ir-catalyst, 400 nm LED. [b]Determined by ^{19}F NMR of reaction mixtures with 4-fluorotoluene as an internal standard.

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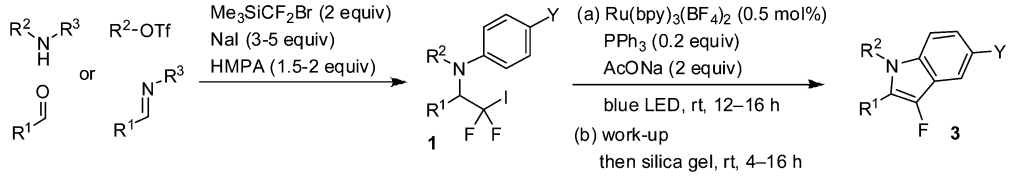
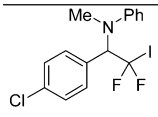
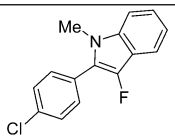
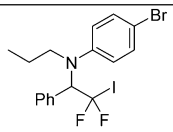
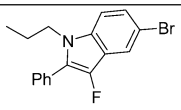
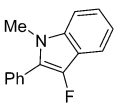
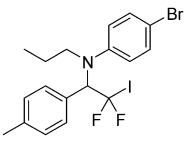
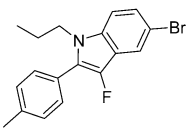
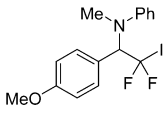
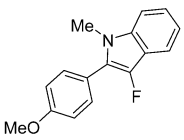
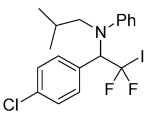
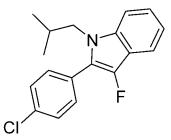
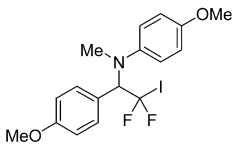
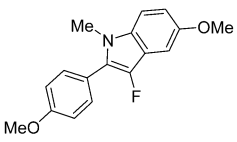
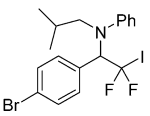
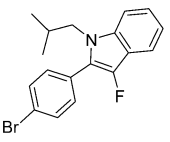
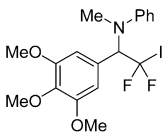
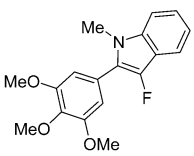
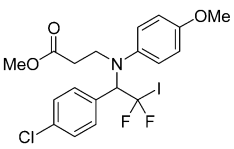
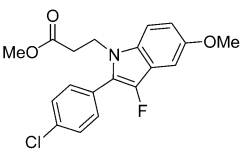
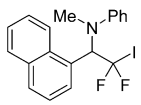
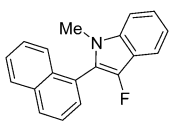
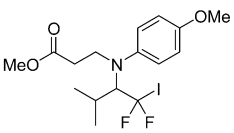
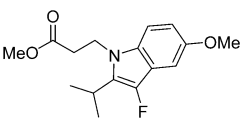
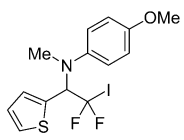
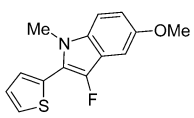
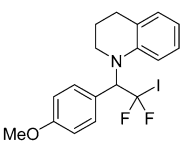
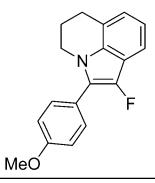
Table 2. Synthesis of 3-Fluoroindoles 3



starting	product		yield, %[a]	starting	product		yield, %[a]
		**3a**	98			**3h**	98
		**3b**	98			**3i**	92
		**3c**	89			**3j**	81
		**3d**	90			**3k**	90
		**3e**	97			**3l**	87
		**3f**	80			**3m**	86
		**3g**	85			**3n**	88

[a]Isolated yield for the conversion of **1** to **3**.

Reactions were performed in acetonitrile using sodium acetate as a basic scavenger, and the mixtures were analyzed by ^{19}F NMR. In a reaction of phosphonium salt, no product was formed with the ruthenium catalyst, whereas *fac*-Ir(ppy)$_3$ was markedly more efficient (entries 1 and 2). When iodosubstituted substrate **1a-I** was used, traces of product **2a** were observed, with the starting iodide being virtually unconsumed (entries 4 and 5). Surprisingly, addition of 20 mol % of triphenylphosphine to both ruthenium and iridium catalysts had a profound effect, and product **2a** was formed in high yields (entries 6 and 10). The ruthenium system was particularly effective in affording the product in a virtually quantitative yield. Bromo-substituted starting compound **1a-Br** was less efficient compared to an iodo-counterpart (entries 12 and 13). When Hünig's base, a typical reductive additive in photoredox processes,[15] was used instead of phosphine, the product was formed in low yield (entry 7). However, with 2 equiv of Hünig's base, complete conversion of the starting substrate was noted along with the high yield of the product (entry 8). It is likely that acetic acid formed during the reaction scavenges the amine base (pK_a = 11.51), whereas less basic phosphine (pK_a = 2.73) remains unprotonated and can be employed in substoichiometric amounts.

The isolation of difluoroindoline **2a** by chromatography on silica gel was unsuccessful, since a significant portion of the product underwent elimination of hydrogen fluoride leading to corresponding 3-fluoroindole. Surprisingly, numerous attempts to intentionally cause dehydrofluorination by treatment of **2a** with mild bases or acids did not furnish complete conversion.

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Finally, for the isolation of indole, dehydrofluorination was performed by simple stirring of a solution of the crude indoline with silica gel for 4−16 h at room temperature.

Accordingly, under the optimized conditions, a series of iododifluoromethylated amines **1** were converted into 3-fluoroindoles **3** (Table 2). Starting substrates **1** were obtained by iododifluoromethylation of *in situ* generated iminium ions using a combination of Me_3SiCF_2Br and NaI as a source for the CF_2I carbanion.[9c,16] Various substrates bearing aromatic, heteroaromatic, and aliphatic substituents worked well in this reaction. Substrates having methoxy or halogen groups provided indoles **3** in high yields. A tetrahydroquinoline derivative furnished tricyclic product **3n**.

To probe the reaction mechanism, the light/dark experiment for the reaction of **1a-I** under standard conditions was performed (Figure 1). The reaction stops during periods when the light

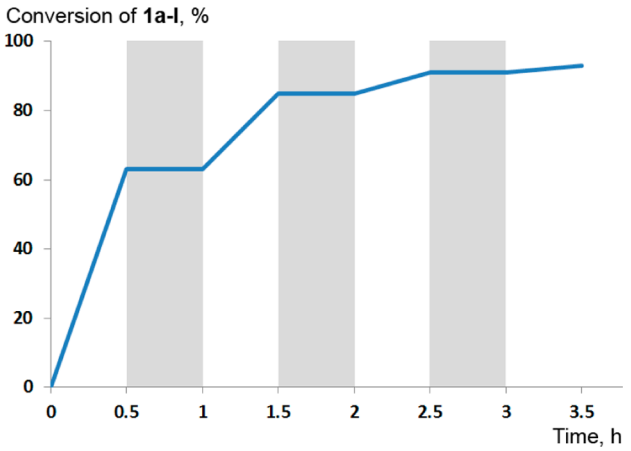


Figure 1. Conversion of **1a-I** in the light/dark sequence. Dark periods are shown in gray.

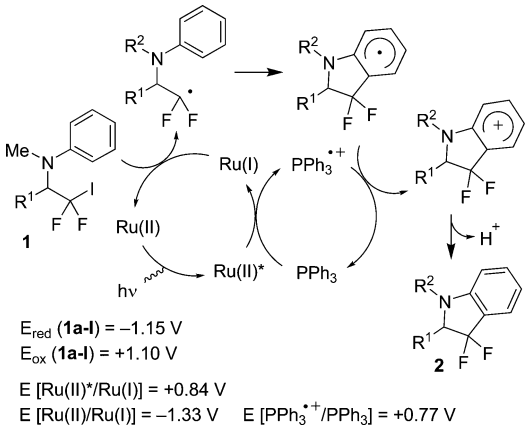
is turned off and proceeds when irradiation is resumed. This result excludes a light-initiated chain process and suggests the involvement of the photocatalyst in the reaction.

To evaluate the feasibility of electron transfer steps, the redox potentials of compound **1a-I** were measured by cyclic voltammetry (CV). Thus, the reduction potential of −1.15 V corresponding to the CF_2I-fragment and oxidation potential of +1.10 V corresponding to the aniline fragment were obtained (all values are given vs S.C.E.; see Supporting Information for CV curves). The oxidation potential of triphenylphosphine was measured to be +0.77 V. Taken together, these data allow for the proposed mechanism shown in Scheme 2. The reductive quenching of exited photocatalyst by triphenylphosphine provides Ru(I), which reduces the substrate generating the difluorinated radical. Subsequent intramolecular attack of the radical onto the aromatic ring followed by oxidation by a phosphine radical cation and elimination of the proton affords product **2**.

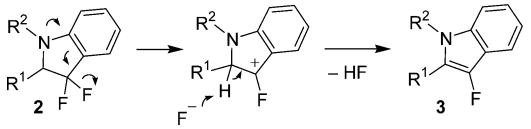
Concerning the mechanism of hydrogen fluoride elimination from indolines **2**, we propose that it starts from cleavage of the carbon−fluorine bond, which is facilitated by mesomeric donation from the *ortho*-nitrogen. Finally, elimination of a proton assisted by the fluoride anion leads to a stable indole system (Scheme 3).

In summary, a method for the synthesis of 3-fluoroindoles from difluoroiodomethyl-substituted amines under photoredox conditions is described. The use of a ruthenium(II) photocatalyst in combination with triphenylphosphine to generate a

Scheme 2. Proposed Mechanism



Scheme 3. Proposed Mechanism for Indole Formation



difluorinated radical is the key feature responsible for the reaction efficiency.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an argon atmosphere. Acetonitrile was distilled from CaH_2. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and the time-of-flight (TOF) mass analyzer. The measurements were done in a positive ion mode (interface capillary voltage −4500 V) or in a negative ion mode (3200 V); the mass range was from m/z 50 to m/z 3000. For blue light irradiation, a strip of light emitting diodes (2835-120LED-1M-BLUE 12 V) was used. Column chromatography was carried out employing silica gel (230−400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualized by using UV and/or aq. $KMnO_4$ solution. (Bromodifluoromethyl)-trimethylsilane[16a] was obtained according to a literature procedure.

Measurement of Redox Potentials by Cyclic Voltammetry (CV). Voltammetric studies were carried out in a temperature-controlled (25 °C) cell (V = 10 mL) with a scan rate of 0.1 V·s^{-1}. A platinum wire (diameter 1 mm) in a Teflon casing was used as the working electrode. A saturated calomel electrode (S.C.E.) separated from the solution being studied by a salt bridge filled with the supporting electrolyte (0.1 M Et_4NClO_4 in MeCN) was used as the reference electrode. A platinum plate (S = 3 cm^2) was used as the counter electrode.

Tris(2,2′-bipyridine)ruthenium(II) Tetrafluoroborate. Obtained by a modified literature procedure.[17] A mixture of ruthenium chloride hydroxide (2 g, 9 mmol), hydrocloric acid (5 mL of aqueous 30% solution), and ethanol (10 mL) was refluxed for 3 h. Then, volatiles were evaporated under vacuum. Chloroform (5 mL) was added to the residue, and volatiles were evaporated under vacuum. The residue was treated with ethylene glycol (30 mL) and 2,2′-bipyridine (4.2 g, 27 mmol), and the mixture was refluxed for 3 h. The heating was discontinued, and a solution of $NaBF_4$ (4.9 g, 45 mmol) in water (2 mL) was added. The mixture was cooled and kept overnight in a refrigerator at 0 °C to effect crystallization. The precipitate was filtered off, washed with ethanol (3 × 10 mL), and dried affording 5.5 g of red powder (82%). Mp > 200 °C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 8.82 (d, J = 8.3 Hz, 6H), 8.22−8.10 (m, 6H), 7.73 (d, J = 5.0 Hz, 6H), 7.57−7.48 (m, 6H). $^{13}C\{^1H\}$ NMR (50 MHz, $(CD_3)_2SO$), δ: 156.6, 151.2, 138.0, 127.9, 124.5, 96.8.

*N-[2-Bromo-1-(4-chlorophenyl)-2,2-difluoroethyl]-N-methyl-N-phenylamine (**1a-Br**).* Prepared according to a literature procedure[9b]

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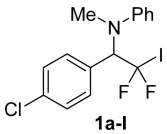
from *p*-chlorobenzaldehyde (2.0 mmol) and *N*-methylaniline (2.2 mmol); yield 526 mg (73%). Colorless oil. Chromatography: hexane. R_f 0.24 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (s, 4H), 7.34 (dd, J = 8.7 Hz, 7.3 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 6.92 (t, J = 7.3 Hz, 1H), 5.60 (dd, J = 14.0, 12.6 Hz, 1H), 2.77 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 149.9, 134.7, 132.0 (t, J = 1.4 Hz), 130.2 (t, J = 2.3 Hz), 129.6, 129.0, 123.9 (dd, J = 316.1, 314.4 Hz), 119.5, 114.5, 71.4 (dd, J = 22.7 Hz, 20.1 Hz), 33.8 (t, J = 2.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −49.1 (dd, J = 165.3, 12.6 Hz, 1F), −50.1 (dd, J = 165.3, 14.0 Hz, 1F). HRMS (ESI): calcd for $C_{15}H_{14}BrClF_2N$ (M + H) 361.9940; found 361.9954.

Synthesis of Iododifluoromethyl-Susbtituted Amines. *General Procedure 1.* Methyl triflate (274 μL, 2.5 mmol) was added to a solution of imine (2 mmol) in acetonitrle (3 mL), and the mixture was stirred at room temperature for 2 h. The mixture was cooled with an ice/water bath, and NaI (900 mg, 6 mmol), Me_3SiCF_2Br (650 μL, 4 mmol), and HMPA (696 μL, 4 mmol) were successively added. The cooling bath was removed, and the mixture was stirred at room temperature for 8 h. For the workup, saturated aq. Na_2CO_3 (2 mL) was added, and the mixture was washed with EtOAc/hexane (1/1, 3 × 5 mL). The combined organic layers were filtered through Na_2SO_4 and concentrated under vacuum, and the residue was purified by column chromatography.

General Procedure 2. Me_3SiCl (0.51 mL, 4.0 mmol) was added dropwise to a vigorously stirred mixture of NaI (1.50 g, 10.0 mmol), 1,8-bis(dimethylamino)naphthalene (428 mg, 2.0 mmol), *N*-alkyl-*N*-arylamine (2.0 mmol), aldehyde (2.0 mmol), and acetonitrile (4 mL) at 0 °C. Then, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The reaction flask was immersed into an ice/water cooling bath, and Me_3SiCF_2Br (610 mg, 3.0 mmol) and HMPA (523 μL, 3.0 mmol) were added successively. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The reaction mixture was worked up by successive addition of a hexane/CH_2Cl_2 mixture (4/1, 8 mL), saturated aqueous Na_2CO_3 (4 mL), and water (4 mL). The organic layer was separated, and the aqueous layer was washed with the hexane/CH_2Cl_2 mixture (4/1, 2 × 8 mL). The combined organic layers were washed with 1.0 M aqueous $NaHSO_4$ (4 mL), while the acidic aqueous layer was washed with the hexane/CH_2Cl_2 mixture (4/1, 2 × 8 mL). All organic layers were combined, filtered through Na_2SO_4, and concentrated under vacuum, and the residue was purified by column chromatography.

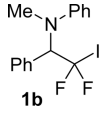
*N-(1-4-Chorophenyl)-2,2-difluoro-2-iodoethyl)-N-methylaniline (**1a-l**).* According to General procedure 1, from *N*-[(4-chlorophenyl)-



1a-l

methylene]-*N*-phenylamine, yield 415 mg (51%). Yellow oil. Chomatography: hexanes/EtOAc, 20/1. R_f 0.60 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50−7.31 (m, 6H), 7.10−6.90 (m, 3H), 5.63 (t, J = 14.5 Hz, 1H), 2.84 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 149.7, 134.6, 131.7, 130.4 (t, J = 2.3 Hz), 129.5, 129.0, 119.4, 114.5, 105.1 (dd, J = 323.6, 322.8 Hz), 73.7 (dd, J = 20.7, 19.5 Hz), 34.0 (t, J = 2.3 Hz). ^{19}F NMF (282 MHz, $CDCl_3$) δ: −42.7 (dd, J = 180.1, 14.5 Hz, 1F), −43.6 (dd, J = 182.3, 14.5 Hz, 1F). HRMS (ESI): calcd for $C_{15}H_{14}ClF_2IN$ (M + H) 407.9822; found 407.9812.

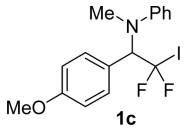
*N-(2,2-Difluoro-2-iodo-1-phenylethyl)-N-methylaniline (**1b**).* According to General procedure 1, from *N*-(phenylmethylene)-*N*-



1b

phenylamine, yield 522 mg (70%). Yellow oil. Chromatography: hexanes/EtOAc, 20/1. R_f 0.26 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.29 (m, 7H), 7.01 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 6.8 Hz, 1H), 5.63 (t, J = 14.8 Hz,, 1H), 2.81 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 149.9, 133.3, 129.5, 129.1 (t, J = 2.3 Hz), 128.8, 128.6, 119.1, 114.4, 105.6 (dd, J = 323.6 Hz, 319.0 Hz), 74.1 (dd, J = 21.8, 19.5 Hz), 34.1 (t, J = 2.3 Hz). ^{19}F NMF (282 MHz, $CDCl_3$) δ: −42.2 (dd, J = 180.2, 14.8 Hz, 1F), −43.3 (dd, J = 180.2, 14.8 Hz, 1F). HRMS (ESI): calcd for $C_{15}H_{15}F_2IN$ (M + H) 374.0212; found 374.0207.

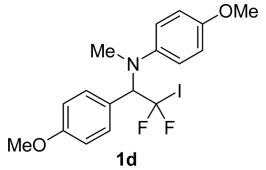
*N-(2,2-Difluoro-2-iodo-1-(4-methoxyphenyl)ethyl)-N-methylaniline (**1c**).* According to General procedure 1, from *N*-[(4-



1c

methoxyphenyl)methylene]-*N*-phenylamine, yield 500 mg (62%). Yellow oil. Chromatography: from hexanes/EtOAc, 20/1. R_f 0.46 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.33 (m, 4H), 7.07 (d, J = 8.0 Hz, 2H), 7.02−6.88 (m, 3H), 5.66 (dd, J = 14.1, 14.1 Hz, 1H), 3.88 (s, 3H), 2.87 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 159.6, 149.9, 130.4 (t, J = 2.2 Hz), 129.4, 125.2 (t, J = 1.9 Hz), 119.0, 114.4, 114.0, 106.1 (dd, J = 324.0, 323.2 Hz), 73.7 (dd, J = 20.7, 18.4 Hz), 55.6, 34.0. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −42.0 (dd, J = 180.1, 14.1 Hz, 1F), −43.8 (dd, J = 178.0, 14.1 Hz, 1F). HRMS (ESI): calcd for $C_{16}H_{17}F_2INO$ (M + H) 404.0317; found 404.0310.

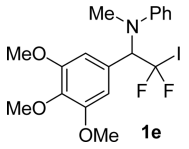
*N-(2,2-Difluoro-2-iodo-1-(4-methoxyphenyl)ethyl)-4-methoxy-N-methylaniline (**1d**).* According to General procedure 1, from



1d

N-(4-methoxyphenyl)-*N*-[(4-methoxyphenyl)methylene]amine, yield 450 mg (52%). Yellow oil. Chromatography: hexanes/EtOAc, 15/1. R_f 0.26 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.5 Hz, 2H), 7.05−6.81 (m, 6H), 5.34 (t, J = 15.1 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.76 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 159.7, 153.5, 144.7, 130.6 (t, J = 2.3 Hz), 125.0, 117.4, 114.7, 114.0, 107.2 (dd, J = 323.6, 323.0 Hz), 76.1 (dd, J = 21.8, 18.4 Hz), 55.7, 55.4, 34.8. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −42.8 (dd, J = 178.0, 15.1 Hz, 1F), −44.0 (dd, J = 178.0, 15.1 Hz, 1F). HRMS (ESI): calcd for $C_{17}H_{19}F_2INO_2$ (M + H) 434.0423; found 434.0410.

*N-[2,2-Difluoro-2-iodo-1-(3,4,5-trimethoxyphenyl)ethyl]-N-methyl-N-phenylamine (**1e**).* According to General procedure 2 from



1e

3,4,5-trimethoxybenzaldehyde and *N*-methylaniline, yield 485 mg (52%). Colorless oil. Chromatography: hexane/EtOAc, 7/1. R_f 0.31 (hexane/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (t, J = 7.8 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 6.89 (t, J = 7.3 Hz, 1H), 6.60 (s, 2H), 5.50 (t, J = 14.4 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 6H), 2.82 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 153.3, 150.0, 138.5, 129.5, 128.6, 119.3, 114.7, 106.7, 105.5 (t, J = 323.2 Hz), 74.2 (dd, J = 20.7, 18.9 Hz), 61.0, 56.4, 34.2. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −41.9 (dd, J = 180.1, 14.4 Hz, 1F), −43.4 (dd, J = 180.1, 14.4 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{20}F_2INO_3Na$ (M + Na) 486.0348; found 486.0324.

*N-[2,2-Difluoro-2-iodo-1-(1-naphthyl)ethyl]-N-methyl-N-phenylamine (**1f**).* According to General procedure 2 from 1-naphthaldehyde and *N*-methylaniline, yield 637 mg, (75%). White crystals. Mp 125−126 °C. Chromatography: CH_2Cl_2/hexane, from 1/7 to 1/3.

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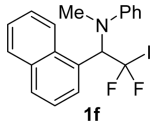
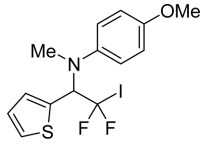


1f

R_f 0.31 (CH_2Cl_2/hexane, 1/7). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, J = 7.3 Hz, 1H), 7.92 (t, J = 7.6 Hz, 2H), 7.62−7.32 (m, 6H), 7.08 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 7.3 Hz, 1H), 6.27 (dd, J_{H-F} = 23.3 Hz, J = 5.5 Hz, 1H), 2.72 (d, J = 0.9 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 148.9, 134.1, 132.4 (t, J = 1.7 Hz), 129.9 (dd, J = 5.2 Hz, 2.3 Hz), 129.6, 129.2, 128.0, 127.9, 127.2, 126.1, 124.8, 123.3, 118.8, 113.39, 113.37, 105.3 (dd, J = 327.6 Hz, 316.7 Hz), 69.3 (t, J = 18.4 Hz,), 34.2 (d, J = 2.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −39.0 (dd, J = 180.6, 5.5 Hz, 1F), −50.0 (dd, J = 180.6, 23.3 Hz, 1F). HRMS (ESI): calcd for $C_{19}H_{17}F_2IN$ (M + H) 424.0368; found 424.0346.

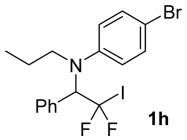
*N-(2,2-Difluoro-2-iodo-1(thiophen-2-yl)ethyl)-4-methoxy-N-methylaniline (**1g**).* According to General procedure 1 from



1g

N-(4-methoxyphenyl)-*N*-[thien-2-ylmethylene]amine, yield 417 mg (51%). Yellow crystals. Mp 29−30 °C. Chromatography: hexanes/EtOAc, 20/1. R_f 0.33 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (d, J = 5.6 Hz, 1H), 7.22−7.17 (m, 1H), 7.06 (t, J = 4.7 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 5.57 (dd, J = 14.7, 13.3 Hz, 1H), 3.82 (s, 3H), 2.86 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 153.8, 144.1, 134.1, 128.3 (t, J = 2.3 Hz), 127.0, 126.1, 117.8, 114.7, 105.5 (dd, J = 323.6, 323.6 Hz), 72.8 (dd, J = 21.8, 19.5 Hz), 55.7, 34.6 (t, J = 2.3 Hz). ^{19}F NMF (282 MHz, $CDCl_3$) δ: −43.0 (dd, J = 180.2, 13.3 Hz, 1F), −44.7 (dd, J = 180.1, 14.7 Hz, 1F). HRMS (ESI): calcd for $C_{14}H_{14}F_2INOS$ (M^+) 408.9803; found 408.9821.

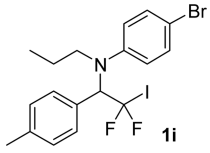
*N-(4-Bromophenyl)-N-(2,2-difluoro-2-iodo-1-phenylethyl)-N-propylamine (**1h**).* According to General procedure 2 from



1h

benzaldehyde and *N*-(4-bromophenyl)-*N*-propylamine, yield 551 mg (57%). Pale yellow crystals. Mp 90−91 °C. Chromatography: hexane. R_f 0.32 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J = 9.1 Hz, 2H), 7.38 (s, 4H), 6.87 (d, J = 9.1 Hz, 2H), 5.45 (dd, J = 16.9, 12.8 Hz, 1H), 3.15 (ddd, J = 14.9, 9.4, 5.5 Hz, 1H), 2.98 (ddd, J = 14.7, 9.5, 5.2 Hz, 1H), 1.54−1.37 (m, 1H), 1.34−1.13 (m, 1H), 0.72 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 147.4, 133.8 (t, J = 2.3 Hz), 132.2, 129.3 (dd, J = 2.9, 1.7 Hz), 128.8, 128.7, 118.5, 112.0, 105.4 (dd, J = 324.7, 320.7 Hz), 75.6 (dd, J = 20.7, 17.8 Hz), 48.2, 20.1, 11.3. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −42.1 (dd, J = 179.5, 12.8 Hz, 1F), −45.5 (dd, J = 179.5, 16.9 Hz, 1F). HRMS (ESI): calcd for $C_{17}H_{18}BrF_2IN$ (M + H) 481.9610; found 481.9622.

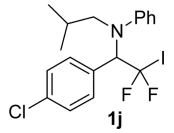
*N-(4-Bromophenyl)-N-[2,2-difluoro-2-iodo-1-(4-methylphenyl)-ethyl]-N-propylamine (**1i**).* According to General procedure 2 from



1i

4-methylbenzaldehyde and *N*-(4-bromophenyl)-*N*-propylamine, yield 672 mg (68%). Colorless oil. Chromatography: hexane. R_f 0.29 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J = 9.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 9.2 Hz, 2H), 5.41 (dd, J = 17.4, 12.4 Hz, 1H), 3.15 (ddd, J = 15.1, 9.5, 5.6 Hz, 1H), 2.99 (ddd, J = 14.6, 9.5, 5.1 Hz, 1H), 2.38 (s, 3H), 1.54−1.37 (m, 1H), 1.34−1.15 (m, 1H), 0.73 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 147.5, 138.6, 132.1, 130.7 (t, J = 2.3 Hz), 129.4, 129.2 (dd, J = 2.3, 1.7 Hz), 118.5, 111.9, 105.7 (dd, J = 324.4, 320.9 Hz), 75.5 (dd, J = 20.7, 18.4 Hz), 48.2, 21.3, 20.1, 11.4. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −41.8 (dd, J = 180.1, 12.4 Hz, 1F), −45.7 (dd, J = 180.1, 17.4 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{20}BrF_2IN$ (M + H) 495.9767; found 495.9792.

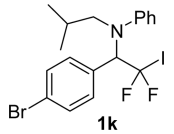
*N-[1-(4-Chlorophenyl)-2,2-difluoro-2-iodoethyl]-N-isobutyl-N-phenylamine (**1j**).* According to General procedure 2 from



1j

4-chlorobenzaldehyde and *N*-isobutylaniline, yield 555 mg (62%). Colorless oil. Chromatography: hexane. R_f 0.29 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40−7.34 (m, 6H), 7.08 (d, J = 7.8 Hz, 2H), 7.00 (t, J = 7.3 Hz, 1H), 5.31 (dd, J_{H-F} = 18.5 Hz, J = 11.7 Hz, 1H), 2.90 (dd, J = 13.5, 8.0 Hz, 1H), 2.73 (dd, J = 13.5, 6.2 Hz, 1H), 1.66−1.85 (m, 1H), 0.89 (d, J = 6.4 Hz, 3H), 0.60 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 149.1, 134.5, 132.3, 131.0, 129.2, 128.8, 121.8, 120.5, 105.6 (dd, J = 323.5, 320.7 Hz), 78.8 (t, J = 19.2 Hz), 54.3, 25.5, 20.6, 20.3. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −41.3 (dd, J = 178.0, 11.7 Hz, 1F), −46.0 (dd, J = 178.0, 18.5 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{20}ClF_2IN$ (M + H) 450.0292; found 450.0273.

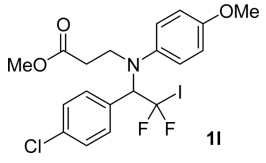
*N-[1-(4-Bromophenyl)-2,2-difluoro-2-iodoethyl]-N-isobutyl-N-phenylamine (**1k**).* According to General procedure 2 from



1k

4-bromobenzaldehyde and *N*-isobutylaniline, yield 635 mg (64%). Colorless oil. Chromatography: hexane. R_f 0.30 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, J = 8.2 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 7.00 (t, J = 7.1 Hz, 1H), 5.27 (dd, J_{H-F} = 18.3, J = 11.9 Hz, 1H), 2.88 (dd, J = 13.5, 8.0 Hz, 1H), 2.72 (dd, J = 13.7, 6.0 Hz, 1H), 1.66−1.83 (m, 1H), 0.88 (d, J = 6.4 Hz, 3H), 0.60 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 149.1, 132.8 (t, J = 2.6 Hz), 131.8, 131.3 (t, J = 2.0 Hz), 129.3, 122.8, 121.9, 120.7, 105.6 (dd, J = 324.1, 320.7 Hz), 78.9 (dd, J = 20.1, 17.8 Hz), 54.4 (t, J = 1.7 Hz), 25.5, 20.6, 20.3. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −41.3 (dd, J = 178.0, 11.9 Hz, 1F), −46.0 (dd, J = 178.0, 18.3 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{20}BrF_2IN$ (M + H) 495.9767; found 495.9740.

*Methyl N-[1-(4-Chlorophenyl)-2,2-difluoro-2-iodoethyl]-N-(4-methoxyphenyl)-β-alaninate (**1l**).* According to General procedure



1l

2 from 4-chlorobenzaldehyde and methyl *N*-(4-methoxyphenyl)-β-alaninate, yield 701 mg (69%). Pale yellow oil. Chromatography: from CH_2Cl_2/hexane (1/2) to CH_2Cl_2. R_f 0.54 (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.98 (dd, J = 15.6 Hz, 14.2 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 3H), 3.60−3.47 (m, 1H), 3.28 (dd, J = 13.7, 8.2, 5.5 Hz, 1H), 2.48−2.24 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 172.4, 155.8, 140.6, 134.7,

DOI: 10.1021/acs.joc.6b02344
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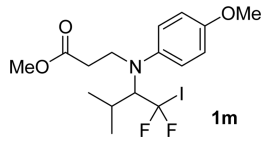
131.8, 131.0 (t, J = 2.0 Hz), 128.8, 123.6, 114.6, 106.6 (dd, J = 322.7 Hz, 321.0 Hz), 78.2 (dd, J = 20.9 Hz, 18.1 Hz), 55.6, 51.7, 45.0, 33.2. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −42.5 (dd, J = 179.1, 14.2 Hz, 1F), −45.9 (dd, J = 179.1, 15.6 Hz, 1F). HRMS (ESI): calcd for $C_{19}H_{19}ClF_2INO_3Na$ (M + Na) 531.9958; found 531.9940.

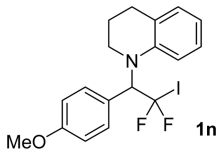
*Methyl N-{1-[Difluoro(iodo)methyl]-2-methylpropyl}-N-(4-methoxyphenyl)-β-alaninate (**1m**).* According to General procedure



1m

2 from isobutyraldehyde and methyl *N*-(4-methoxyphenyl)-β-alaninate, yield 287 mg (33%). Colorless oil. Chromatography: CH_2Cl_2/hexane, from 1/2 to CH_2Cl_2. R_f 0.53 (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.92−6.82 (m, 4H), 3.78 (s, 3H), 3.71 (t, J = 7.8 Hz, 2H), 3.69 (s, 3H), 3.58 (dd, J_{H-F} = 18.8 Hz, J = 9.4, 6.6 Hz, 1H), 2.74−2.55 (m, 2H), 2.44−2.26 (m, 1H), 1.17−1.10 (m, 3H), 0.98 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 172.7, 153.4, 141.9, 117.9, 114.8, 109.8 (dd, J = 327.3, 325.0 Hz), 78.0 (t, J = 19.8 Hz), 55.7, 51.8, 40.8 (d, J = 2.9 Hz), 32.7, 29.6, 21.7, 20.6 (dd, J = 6.0, 2.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$), δ: −30.7 (d, J = 178.0 Hz, 1F), −40.7 (dd, J = 178.0, 18.8 Hz, 1F). HRMS (ESI): calcd for $C_{16}H_{23}F_2INO_3$ (M + H) 442.0685; found 442.0669.

*1-[2,2-Difluoro-2-iodo-1-(4-methoxyphenyl)ethyl]-1,2,3,4-tetrahydroquinoline (**1n**).* According to General procedure 2 from

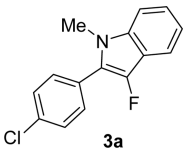


1n

4-methoxybenzaldehyde and 1,2,3,4-tetrahydroquinoline, yield 439 mg (51%). Pale yellow oil. Chromatography: CH_2Cl_2/hexane, 1/2. R_f 0.42 (CH_2Cl_2/hexane, 1/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J = 8.7 Hz, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H), 5.65 (dd, J = 17.4, 12.4 Hz, 1H), 3.84 (s, 3H), 3.32 (ddd, J = 11.2, 8.1, 3.1 Hz, 1H), 3.05 (ddd, J = 11.2, 7.7, 3.5 Hz, 1H), 2.85−2.63 (m, 2H), 1.94−1.79 (m, 1H), 1.68−1.54 (m, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), δ: 159.7, 144.9, 130.7 (dd, J = 2.9 Hz, 1.7 Hz), 130.0, 127.3, 125.5 (t, J = 2.3 Hz), 123.8, 117.8, 114.1, 112.1 (d, J = 2.3 Hz), 106.0 (dd, J = 324.7, 322.4 Hz), 71.6 (dd, J = 20.7, 18.4 Hz), 55.4, 44.8 (t, J = 2.0 Hz), 28.3, 21.8. ^{19}F NMR (282 MHz, $CDCl_3$), δ: −41.4 (dd, J = 180.1, 12.4 Hz, 1F), −44.8 (dd, J = 178.0, 17.4 Hz, 1F). HRMS (ESI): calcd for $C_{18}H_{19}F_2INO$ (M + H) 430.0474; found 430.0463.

Synthesis of Indoles 3 (General Procedure 3). A test tube containing sodium acetate (82 mg, 1 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol) was evacuated and filled with argon. Then, a solution of iodide **1** (0.5 mmol) in acetonitrile (2 mL) was injected, and $Ru(bpy)_3(BF_4)_2$ (2 mg) was added; the mixture was irradiated with a strip of blue LED for 12−16 h (since diods provide heat when working, the reaction tube was immersed into a glass vessel cooled with circulating room temperature water; the cooling vessel was wrapped with the LED strip). For the workup, water (2 mL) was added, and the mixture was washed with EtOAc/hexane (1/2, 3 × 5 mL). The organic phases were combined, silica gel (5 g) was added, and the mixture was stirred for 4−14 h at room temperature (TLC control). The solvent was evaporated to dryness under vacuum, and the residual silica gel was transferred onto a packed chromatography column followed by elution.

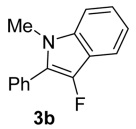
*2-(4-Chlorophenyl)-3-fluoro-1-methyl-1H-indole (**3a**).* Reaction time 12 h; treatment with silica gel 4 h; yield 126 mg (97%).



3a

White crystals. Mp 112−114 °C. Chromatography: hexanes/EtOAc, 15/1. R_f 0.35 (hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (d, J = 7.8 Hz, 1H), 7.57−7.41 (m, 4H), 7.40−7.24 (m, 2H), 7.24−7.14 (m, 1H), 3.68 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 142.2 (d, J = 245.5 Hz), 134.3 (d, J = 3.4 Hz), 131.1 (d, J = 2.3 Hz), 127.5 (d, J = 3.4 Hz), 125.2, 122.5 (d, J = 20.7 Hz), 121.5 (d, J = 15.0 Hz), 120.1, 117.1 (d, J = 2.3 Hz), 116.8, 109.8 (d, J = 2.3 Hz), 31.2. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −175.6 (s, 1F). HRMS (ESI): calcd for $C_{15}H_{12}FClN$ (M + H) 260.0623; found 260.0637.

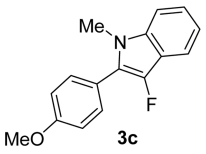
*3-Fluoro-1-methyl-2-phenyl-1H-indol (**3b**).* Reaction time 12 h; treatment with silica gel 4 h; yield 110 mg (98%). White crystals.



3b

Mp 73−75 °C. Chromatography: hexanes/EtOAc, 15/1. R_f 0.33 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88−7.12 (m, 9H), 3.73 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 141.9 (d, J = 245.5 Hz), 134.0 (d, J = 5.7 Hz), 129.9, 129.0 (d, J = 3.4 Hz), 128.8, 128.2, 123.7 (d, J = 20.7 Hz), 122.8, 119.9, 117.1, 116.8 (d, J = 3.4 Hz), 109.7 (d, J = 2.3 Hz), 31.1. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −176.3 (s, 1F). HRMS (ESI): calcd for $C_{15}H_{13}FN$ (M + H) 226.1017; found 226.1027.

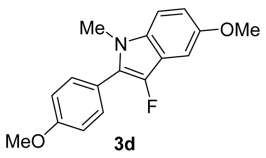
*3-Fluoro-2-(4-methoxyphenyl)-1-methyl-1H-indole (**3c**).* Reaction time 12 h; treatment with silica gel 4 h; yield 114 mg (89%).



3c

White crystals. Mp 110−112 °C. Chromatography: hexanes/EtOAc, 20/1. R_f 0.46 (hexanes/EtOAc, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 7.39−7.12 (m, 3H), 7.06 (d, J = 8.2 Hz, 2H), 3.89 (s, 3H), 3.67 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 159.7, 141.4 (d, J = 243.2 Hz), 133.7 (d, J = 5.7 Hz), 131.3 (d, J = 2.3 Hz), 123.6 (d, J = 21.8 Hz), 122.5, 121.4 (d, J = 3.4 Hz), 119.8, 117.0 (d, J = 16.1 Hz), 116.7 (d, J = 3.5 Hz), 114.4, 109.6, 55.5, 31.0. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −177.3 (s, 1F). Anal. calcd for $C_{16}H_{14}FNO$ (255.29): C, 75.28; H, 5.53; N, 5.49. Found: C, 75.39; H, 5.53; N, 5.50.

*3-Fluoro-5-methoxy-2-(4-methoxyphenyl)-1-methyl-1H-indole (**3d**).* Reaction time 12 h; treatment with silica gel 4 h; yield 128 mg



3d

(90%). White crystals. Mp 99−100 °C. Chromatography: hexanes/EtOAc, 10/1. R_f 0.26 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, J = 8.2 Hz, 2H), 7.29−7.18 (m, 1H), 7.13−7.00 (m, 3H), 6.88 (d, J = 9.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.64 (s, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$) δ: 159.6, 154.4, 141.6 (d, J = 241.3 Hz), 131.2, 129.3 (d, J = 5.7 Hz), 124.3 (d, J = 21.3 Hz), 121.5 (d, J = 4.3 Hz), 116.9 (d, J = 15.6 Hz), 114.3, 113.2, 110.7, 97.8 (d, J = 2.8 Hz), 56.0, 55.4, 31.0. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −177.6 (s, 1F). Anal. calcd for $C_{17}H_{16}FNO_2$ (285.31): C, 71.56; H, 5.65; N, 4.91. Found: C, 71.62; H, 5.63; N, 5.00.

*3-Fluoro-1-methyl-2-(3,4,5-trimethoxyphenyl)-1H-indole (**3e**).* Reaction time 12 h; treatment with silica gel 4 h; yield 153 mg (97%). White crystals. Mp 136−137 °C. Chromatography: hexanes/EtOAc, 5/1. R_f 0.34 (hexanes/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, J = 8.6 Hz, 1H),7.39−7.24 (m, 2H), 7.21−7.14 (m, 1H), 6.74 (s, 2H), 3.94 (s, 3H), 3.93 (s, 6H), 3.70 (s, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$) δ: 153.5, 141.6 (d, J = 244.4 Hz),

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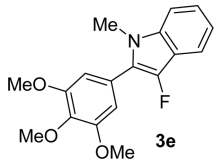
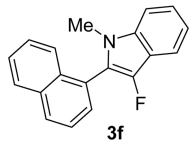


3e

124.3 (d, J = 3.5 Hz), 123.9, 123.6 (d, J = 20.7 Hz), 122.8, 116.8 (d, J = 16.1 Hz), 116.6 (d, J = 2.3 Hz), 109.6 (d, J = 2.3 Hz), 109.1, 107.4, 105.8, 61.0, 56.3, 31.0. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −175.9 (s, 1F). HRMS (ESI): calcd for $C_{18}H_{19}FNO_3$ (M + H) 316.1343; found 316.1338.

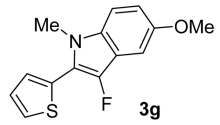
3-Fluoro-1-methyl-2-(naphthalen-1-yl)-1H-indole ***(3f)***. Reaction time 16 h; treatment with silica gel 14 h; yield 110 mg (80%).



3f

Light yellow crystals. Mp 111−112 °C. Chromatography: hexanes/CH_2Cl_2, 10/1. R_f 0.32 (hexanes/CH_2Cl_2, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11−7.89 (m, 2H), 7.77 (d, J = 7.5 Hz, 2H), 7.71−7.19 (m, 7H), 3.50 (s, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 142.3 (d, J = 245.5 Hz), 133.9, 133.8, 132.9, 130.0, 129.7, 128.6, 127.0, 126.4 (d, J = 2.3 Hz), 126.3, 126.0, 125.4, 122.7, 121.9 (d, J = 23.0 Hz), 119.9, 117.0 (d, J = 2.3 Hz), 116.9 (d, J = 16.1 Hz), 109.7, 30.7. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −174.3 (s, 1F). HRMS (ESI): calcd for $C_{19}H_{15}FN$ (M + H) 276.1186; found 276.1183.

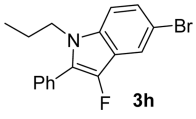
3-Fluoro-5-methoxy-1-(tiophen-2-yl)-1H-indole ***(3g)***. Reaction time 12 h; treatment with silica gel 4 h; yield 111 mg (85%).



3g

Yellow crystals. Mp 80−81 °C. Chromatography: hexanes/EtOAc, 15/1. R_f 0.30 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (d, J = 5.1 Hz, 1H), 7.31 (d, J = 3.3 Hz, 1H), 7.25−7.18 (m, 2H), 7.08 (d, J = 1.8 Hz, 1H), 6.96 (dd, J = 9.0, 2.5 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$) δ: 154.4, 142.2 (d, J = 245.5 Hz), 129.8 (d, J = 5.0 Hz), 129.5 (d, J = 5.7 Hz), 127.9 (d, J = 3.4 Hz), 127.6, 126.8, 118.0 (d, J = 20.7 Hz), 116.4 (d, J = 14.9 Hz), 114.2, 110.7, 97.8 (d, J = 2.3 Hz), 55.9, 31.1. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −172.0 (s, 1F). HRMS (ESI): calcd for $C_{14}H_{13}FNOS$ (M + H); 262.0696; found 262.0692.

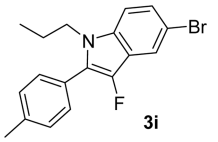
5-Bromo-3-fluoro-2-phenyl-1-propyl-1H-indole ***(3h)***. Reaction time 12 h; treatment with silica gel 4 h; yield 163 mg (98%).



3h

Yellow oil. Chromatography: hexanes/CH_2Cl_2, 20/1. R_f 0.32 (hexanes/CH_2Cl_2, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (d, J = 1.9 Hz, 1H), 7.63−7.42 (m, 5H), 7.35 (dd, J = 8.0 Hz, 2.2 Hz, 1H), 7.25 (dd, J = 9.2, 2.8 Hz, 1H), 4.06 (t, J = 7.2 Hz, 2H), 1.65 (sext, J = 7.8 Hz, 2H), 0.75 (t, J = 7.2 Hz, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 141.0 (d, J = 245.5 Hz), 131.8 (d, J = 4.6 Hz), 139.9, 128.9, 128.8, 128.6, 125.5, 124.8 (d, J = 19.5 Hz), 119.4 (d, J = 3.4 Hz), 118.6 (d, J = 16.1 Hz), 113.0, 111.8, 45.7, 23.3, 11.3. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −175.8 (s, 1F). HRMS (ESI): calcd for $C_{17}H_{16}FNBr$ (M + H) 334.0425; found 334.0420.

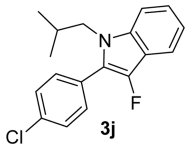
5-Bromo-3-fluoro-1-propyl-2-(p-tolyl)-1H-indole ***(3i)***. Reaction time 12 h; treatment with silica gel 4 h; yield 159 mg (92%). Yellow oil. Chromatography: hexanes/CH_2Cl_2, 20/1. R_f 0.36 (hexanes/CH_2Cl_2, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 (d, J = 2.4 Hz, 1H), 7.48−7.31 (m, 5H), 7.25 (dd, J = 8.6 Hz, 2.0 Hz, 1H),



3i

4.07 (t, J = 7.7 Hz, 2H), 2.49 (s, 3H), 1.67 (sext, J = 7.4 Hz, 2H), 0.78 (t, J = 6.8 Hz, 3H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 140.6 (d, J = 244.4 Hz), 138.6, 131.7 (d, J = 5.7 Hz), 129.8, 129.6, 125.8 (d, J = 3.4 Hz), 125.3, 124.9 (d, J = 20.7 Hz), 119.2 (d, J = 3.4 Hz), 118.7 (d, J = 14.9 Hz), 112.9, 111.7, 45.6, 23.3, 21.4, 11.2. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −176.0 (s, 1F). HRMS (ESI): calcd for $C_{18}H_{18}FNBr$ (M + H) 346.0601; found 346.0599.

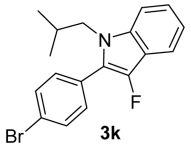
2-(4-Cholorophenyl)-3-fluoro-1-isobutyl-1H-indole ***(3j)***. Reaction time 14 h; treatment with silica gel 4 h; yield 122 mg (81%).



3j

Pale yellow oil. Chromatography: hexanes. R_f 0.25 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, J = 8.3 Hz, 1H), 7.62−7.16 (m, 7H), 4.01 (d, J = 7.6 Hz, 2H), 2.11−1.93 (m, 1H), 0.73 (d, J = 6.6 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 142.3 (d, J = 245.5 Hz), 134.2, 133.7 (d, J = 5.7 Hz), 131.3, 129.1, 128.0 (d, J = 3.4 Hz), 122.9, 122.5 (d, J = 19.5 Hz), 120.0, 117.0 (d, J = 16.1 Hz), 116.9 (d, J = 2.3 Hz), 110.6, 51.2, 29.2, 20.1. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −175.7 (s, 1F). HRMS (ESI): calcd for $C_{18}H_{17}FClN$ (M) 301.1028; found 301.1029.

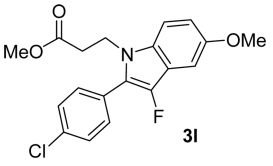
2-(4-Bromophenyl)-3-fluoro-1-isobutyl-1H-indole ***(3k)***. Reaction time 15 h; treatment with silica gel 4 h; yield 156 mg (90%).



3k

Yellow oil. Chromatography: hexanes/CH_2Cl_2, 20/1. R_f 0.38 (hexanes/CH_2Cl_2, 20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78−7.62 (m, 3H), 7.48−7.38 (m, 3H), 7.33 (t, J = 6.7 Hz, 1H), 6.23 (t, J = 7.7 Hz, 1H), 4.00 (d, J = 7.4 Hz, 2H), 2.10−1.91 (m, 1H), 0.71 (d, J = 6.0 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 142.3 (d, J = 245.5 Hz), 133.7 (d, J = 5.7 Hz), 132.0, 131.4, 128.5 (d, J = 3.4 Hz), 122.9, 122.4 (d, J = 20.6 Hz), 122.4, 120.0, 117.0 (d, J = 16.1 Hz), 116.9 (d, J = 2.3 Hz), 110.6, 51.1, 29.1, 20.0. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −175.6 (s, 1F). HRMS (ESI): calcd for $C_{18}H_{18}FNBr$ (M + H) 346.0601; found 346.0607.

Methyl 3-[2-(Chlorophenyl)-3-fluoro-5-methoxy-1H-indol-1-yl]-propanoate ***(3l)***. Reaction time 12 h; treatment with silica gel 4 h;



3l

yield 157 mg (87%). Yellow crystals. Mp 66−67 °C. Chromatography: hexanes/EtOAc, 5/1. R_f 0.27 (hexanes/EtOAc, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40−7.28 (m, 4H), 7.16 (dd, J = 9.2, 2.7 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 6.83 (dd, J = 9.2, 2.8 Hz, 1H), 4.27 (t, J = 7.3 Hz, 2H), 3.75 (s, 3H), 3.44 (s, 3H), 2.37 (t, J = 7.3 Hz, 2H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 171.1, 154.6, 142.6 (d, J = 246.7 Hz), 134.4, 130.8 (d, J = 2.3 Hz), 129.2, 128.8 (d, J = 5.7 Hz), 127.3 (d, J = 3.4 Hz), 122.3 (d, J = 19.5 Hz), 117.7 (d, J = 15.0 Hz), 114.2, 111.2, 98.1 (d, J = 2.3 Hz), 55.7, 51.8, 39.8, 34.1. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −174.4 (s, 1F). HRMS (ESI): calcd for $C_{19}H_{18}ClFNO_3$ (M + H) 362.0954; found 362.0943.

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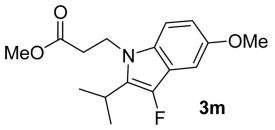
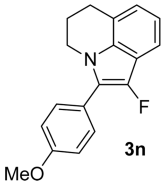
*Methyl 3-(3-Fluoro-2-isopropyl-5-methoxy-1H-indol-1-yl)-propanoate (**3m**).* Reaction time 12 h; treatment with silica gel was



3m

omitted since the indole was formed directly after the reaction; yield 126 mg (86%). Yellow oil. Chromatography: hexanes/EtOAc, 10/1. R_f 0.28 (hexanes/EtOAc, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (dd, J = 9.1, 2.3 Hz, 1H), 6.76 (d, J = 2.3 Hz, 1H), 6.71 (dd, J = 9.1, 2.6 Hz, 1H), 4.35 (t, J = 7.3 Hz, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 3.15–3.99 (m, 1H), 2.69 (t, J = 7.8 Hz, 2H), 1.43 (d, J = 7.5 Hz, 6H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 171.5, 154.2, 141.7 (d, J = 239.8 Hz), 128.2, 127.9, 126.8 (d, J = 5.7 Hz), 117.8 (d, J = 16.1 Hz), 112.3, 110.2 (d, J = 2.3 Hz), 97.8, 55.9, 52.0, 39.0, 25.2 (d, J = 3.4 Hz), 21.8 (d, J = 3.4 Hz). ^{19}F NMF (282 MHz, $CDCl_3$) δ: −175.5 (s, 1F). HRMS (ESI): calcd for $C_{16}H_{20}FNO_3Na$ (M + Na) 316.1319; found 316.1317.

*1-Fluoro-2-(4-methoxyphenyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]-quinoline (**3n**).* Reaction time 12 h; treatment with silica gel 4 h;



3n

yield 124 mg (88%). White crystals. Mp 126–127 °C. Chromatography: hexanes/EtOAc, 15/1. R_f 0.35 (hexanes/EtOAc, 15/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57–7.40 (m, 3H), 7.14–7.00 (m, 3H), 6.95 (d, J = 7.1 Hz, 1H), 4.09 (t, J = 5.5 Hz, 2H), 3.89 (s, 3H), 3.03 (t, J = 6.0 Hz, 2H), 2.23 (quint, J = 6.0 Hz, 2H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ: 159.5, 141.3 (d, J = 244.2 Hz), 130.5 (d, J = 2.3 Hz), 122.3 (d, J = 21.3 Hz), 121.7 (d, J = 2.3 Hz), 121.6, 119.9, 119.3, 114.4, 114.2 (d, J = 2.3 Hz), 55.5, 43.1, 25.1, 23.1. ^{19}F NMF (282 MHz, $CDCl_3$) δ: −177.0 (s, 1F). HRMS (ESI): calcd for $C_{18}H_{17}FNO$ (M + H) 282.1289; found 282.1299.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02344.

Copies of NMR spectra for all compounds and CV curves for **1a-I**, $Ru(bpy)_3(BF_4)_2$, and PPh_3 (PDF)

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Notes

The authors declare no competing financial interest.

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