# Organocatalytic Insertion of Isatins into Aryl Difluoronitromethyl Ketones

Ransheng Ding, Pegah R. Bakhshi, and Christian Wolf*

Department of Chemistry, Georgetown University, Washington, DC 20057, United States

Ⓢ *Supporting Information*

ABSTRACT: An organocatalytic method that achieves insertion of isatins into aryl difluoronitromethyl ketones under mild conditions is described. The reaction occurs in the presence of 20 mol % of DBU and with 100% atom economy. A series of isatin derived difluoronitromethyl substituted tertiary alcohol benzoates and naphthoates were prepared in 81−99% yield. The general synthetic usefulness of these 3-hydroxyoxindole derivatives is demonstrated with the selective reduction to fluorooximes.
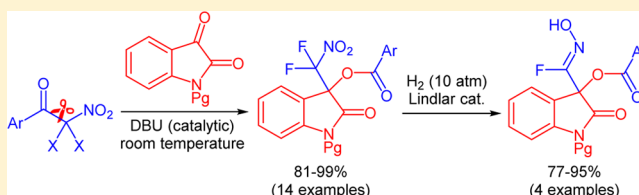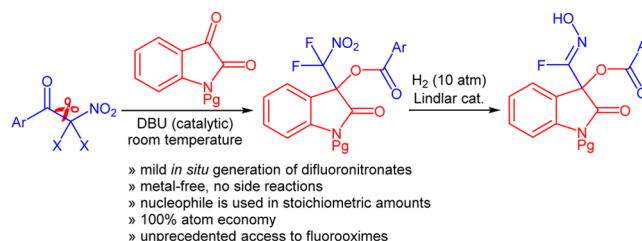
Nitroalkanes are commonly used in Henry and Michael reactions,[1] allylations,[2] arylations,[3] alkylations[4] and for the construction of amide bonds.[5] As a result of their general availability and high synthetic versatility, nitromethane and its homologues have become privileged building blocks for the formation of multifunctional target compounds and natural products. A remaining drawback of the nitroaldol reaction is that excessive amounts of the nitroalkane—the use of 5−10 equiv is common—are typically required to achieve high yields.[6] Although this might be still considered cost-effective when inexpensive nitromethane is used, it remains inefficient and produces considerable waste.

Following our longstanding interest in aldol reactions with nitroalkanes[7] and fluorinated enolates,[8] we recently introduced dihalonitronates to C−C bond formation with aldehydes using a LiBr/(*i*-Pr)₂NEt pair as catalyst.[9] Because of the high impact of fluorinated pharmaceuticals and agrochemicals, the synthesis of new organofluorines and the development of methods to make them has received widespread attention.[10] The steadily increasing structural diversity of fluorine-containing marketed pharmaceuticals and emerging drug candidates continues to provide a strong need for practical synthetic approaches. We now report an organocatalytic method that accomplishes the insertion of isatins into aryl difluoronitromethyl ketones under mild conditions based on a C−C bond cleavage−aldol reaction−acyl transfer sequence. The DBU catalyzed transformation occurs with stoichiometric amounts of the starting materials, and it produces a 3-hydroxyoxindole scaffold, an important structural motif that occurs in a variety of biologically active compounds,[11] in high yields and with 100% atom economy (Scheme 1). Moreover, we investigated the possibility to reduce the difluoronitromethyl motif and report for the first time the formation of fluorooximes.

We began our search for a mild method that achieves the insertion of an isatin scaffold into an aryl difluoronitromethyl ketone through a bond scission−aldol reaction−acyl transfer sequence by screening a variety of nucleophiles and additives

Scheme 1. Features of the DBU Catalyzed C−C Scission/ Nitronate Addition/Benzoyl Transfer Sequence

» mild *in situ* generation of difluoronitronates
» metal-free, no side reactions
» nucleophile is used in stoichiometric amounts
» 100% atom economy
» unprecedented access to fluorooximes

(Table 1). Using difluoronitroacetophenone, **1**, and *N*-benzyl isatin, **2**, as test compounds in stoichiometric amounts, we were surprised that no reaction occurred in the presence of catalytic amounts of LiBr and (*i*-Pr)₂NEt, which is in stark contrast to our experience with aldehydes (entry 1). The propensity of fluorinated nucleophiles toward decomposition and uncontrolled carbene formation, in particular in the presence of a Lewis acid, has been identified as a general problem that often impedes fluoroalkylation chemistry.[12] We, therefore, decided to probe metal-free conditions and found that the desired product **3** can be obtained when readily available *N*-nucleophiles were employed (a crystal structure of compound **3** is provided in the SI). The addition of 1 equiv of (*i*-Pr)₂NEt produced **3** in 63% yield after 48 h (entries 2−4). To our delight, **3** was formed quantitatively in the presence of Et₃N, albeit a catalytic variant still gave unsatisfactory results (entries 5−7). At this point, we rationalized that the more nucleophilic 1,8-diazabicycloundec-7-ene (DBU) would facilitate the bond scission step with **1** and thus provide an entry to an effective catalytic process.[13] Indeed, we found that the presence of 20 mol % of DBU yields quantitative formation of **3** within 24 h in both dichloromethane and chloroform. Further reduction of the DBU

Table 1. Optimization of the Isatin Insertion Reaction[a]

entry	additive (mol %)	t (h)	yield[b] (%)
1	DIPEA (20)/LiBr (20)	48	0
2	2,6-lutidine (40)	48	0
3	DMAP (50)	48	25
4	DIPEA (100)	48	63
5	Et₃N (200)	18	99
6	Et₃N (50)	24	99
7	Et₃N (20)	48	21
8	DBU (20)	24	99
9	DBU (10)	24	82
10[c]	DBU (20)	24	99

[a]Reaction conditions: A solution of **1** (0.18 mmol) and **2** (0.15 mmol) in the presence of the additive in 0.4 mL of CH_2Cl_2 was stirred at 30 °C. [b]Determined by ^1H NMR analysis. [c]$CHCl_3$ was used as solvent. DIPEA = N,N-diisopropylethylamine, DMAP = 4-dimethylamino-pyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2. Scope of the Organocatalytic Isatin Insertion into Aryl Difluoronitromethyl Ketones[a]

Entry	Ar	Isatin R_1 / R_2	t (h)	Insertion product	Yield (%)
1	Ph (**1**)	Bn / H (**2**)	24	**3**	99
2	**1**	Me / H (**4**)	24	**5**	99
3	**1**	Ph / H (**6**)	24	**7**	99
4	**1**	Ph / 5-Me (**8**)	24	**9**	91
5	**1**	Ph / 6-F (**10**)	24	**11**	91
6	**1**	Ph / 5-OMe (**12**)	48	**13**	91
7	**1**	Ph / 5-Cl (**14**)	48	**15**	97
8	**1**	Ph / 5,6-F_2 (**16**)	48	**17**	81
9	**1**	Ph / 5-OCF₃ (**18**)	48	**19**	85
10	1-Np (**20**)	Ph / H (**6**)	24	**21**	96
11	**20**	Ph / 6-F (**10**)	24	**22**	91
12	**20**	Ph / 6-OMe (**23**)	48	**24**	99
13	**20**	Ph / 4-Br (**25**)	24	**26**	99
14	**20**	Ph / 6-Br (**27**)	24	**28**	99

[a]General conditions: A solution of **1** or **20** (0.18 mmol), the isatin (0.15 mmol), and DBU (0.03 mmol) in 0.4 mL of $CHCl_3$ was stirred for 24–48 h.

loading, however, compromises the yield (entries 8–10). It is noteworthy that this protocol does eliminate not only the need for a Lewis acid but also the use of difluoronitromethane, which is volatile and difficult to handle, as the nitronate precursor.[14]

Having optimized the reaction conditions, we continued with the evaluation of the substrate scope (Table 2). The DBU catalyzed insertion of isatins carrying various N-protecting groups into **1** produced **3**, **5**, and **7** in almost quantitative amounts (entries 1–3).[15] We then examined N-phenylisatins with different aryl substituents R_2. The reaction of **1** with 5-methyl- and 5-methoxyisatin, **8** and **12**, or with the halogenated analogues **10** and **14** gave the cleavage–aldol reaction–acyl transfer products with more than 90% yield (entries 4–7). Employing N-phenyl 5-trifluoromethoxyisatin, **16**, and the 5,6-difluoro derivative **18** in the reaction afforded **17** and **19** in 85% and 81% yield, respectively (entries 8 and 9). Finally, we introduced α-difluoronitroacetonaphthone, **20**, as an alternative difluoronitronate precursor to the reaction sequence. The catalytic insertion of five different N-phenylisatins into **20** furnished **21**, **22**, **24**, **26**, and **28** in 91–99% yield (entries 10–14).

The reaction mechanism was investigated by ^{19}F NMR spectroscopic analysis (SI). We observed that addition of 1 equiv of DBU into a solution of difluoronitroacetophenone, **1**, in $CDCl_3$ led to the formation of the difluoronitroaceto-phenone-DBU adduct **A** showing two diastereotopic fluorine NMR signals at −88.0 and −92.1 ppm that are upfield-shifted relative to the signal of **1** at −87.3 ppm. A constant ratio between **1** and **A** (1.2:1) was established within 5 min, which indicates reversibility of this first step. Trapping of **A** with ethanol produced ethyl benzoate and led to complete conversion of both **1** and **A** to a mixture of difluoronitro-methane and difluoronitronate within 1 h according to ^{19}F NMR analysis, which further corroborates the proposed intermediate formation and reactivity of **A**.[16] Finally, ^{19}F NMR monitoring of the DBU catalyzed reaction showed that, after addition of an isatin, the intermediate **A** is first converted to **B** and subsequently to the benzoyl ester, which is the final

product of the organocatalytic isatin insertion reaction. The mechanistic studies are summarized in Scheme 2.

The incorporation of a difluoronitromethyl group into the oxindole motif is unprecedented. This prompted us to investigate the possibility of mild reduction of the nitroalkyl moiety. For this purpose, we first applied a reported procedure that uses trichlorosilane to reduce the nitro group in **3**.[17] We found that defluorination occurred and the nitrile **29** was isolated in low yields (Scheme 3). Because direct nitrile addition to isatins can be more practically accomplished by

Scheme 2. Mechanism of the Organocatalytic Isatin Insertion
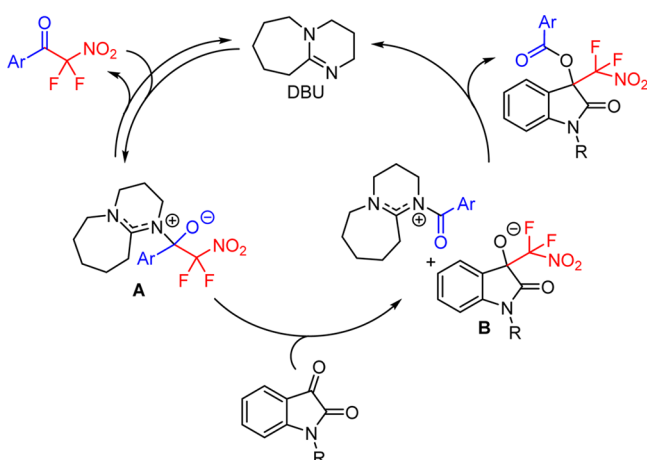
cyanobenzoylation, we turned our attention to other methods.[18] We were pleased to find that catalytic hydrogenation of **3** using the Lindlar catalyst in the presence of acetic acid and di-*tert*-butyl dicarbonate gave the (*Z*)-fluorooxime **30** in 95% yield and with excellent diastereoselectivity.[19] We were able to grow a single crystal of **30** and X-ray analysis proved the *Z*-oxime structure (see the SI). To the best of our knowledge, this is the first example of the synthesis of a fluorooxime. We believe that hydrogenation of the difluoronitromethyl moiety in **3** gives the corresponding *N*-hydroxy difluoromethylamine derivative, which is expected to spontaneously eliminate HF to form **30**.[20] When we applied the same hydrogenation procedure to compounds **5**, **13**, and **21**, we obtained the corresponding *N*-hydroxyimidoyl fluorides **31**−**33** in 77−90% yield. The fluorooximes were stored at 6 °C and showed no sign of degradation after 2 months.

In summary, we have introduced an organocatalytic method that achieves insertion of isatins into aryl difluoronitromethyl ketones. A series of isatin derived difluoronitromethyl substituted tertiary alcohol benzoates and naphthoates were prepared in excellent yields using 20 mol % of DBU as inexpensive, readily available catalyst. The irreversible cleavage−nitroaldol reaction−acyl transfer sequence occurs with 100% atom economy and at room temperature. A key feature of this protocol is that the difluoronitronate nucleophile, which is formed in situ under metal-free conditions, is used in stoichiometric amounts. This is in stark contrast to the vast majority of nitroaldol reactions that require the use of nitromethane or another nitroalkane in large excess. The synthetic utility of the reaction products was demonstrated by catalytic hydrogenation to unprecedented *N*-hydroxyimidoyl fluoride compounds.

■ EXPERIMENTAL SECTION

General Information. All commercially available reagents and solvents were used without further purification unless otherwise noted. Chloroform was dried over activated 4 Å molecular sieves prior to use as solvent. NMR spectra were obtained at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR), and 376 MHz (^{19}F NMR) in CDCl$_3$. Chemical shifts are reported in ppm relative to tetramethylsilane. Difluoronitroacetophenone **1** and isatins **8**, **10**, **12**, **14**, **16**, **18**, **23**, **25**, and **27** were synthesized as described in the literature.[9,21] Reaction products were purified by column chromatography on silica using a flash purification system as described below.

Synthesis of 1-Difluoronitroacetonaphthone, 20. To a solution of 1-naphthoylnitromethane[22] (410.0 mg, 1.90 mmol) in anhydrous acetonitrile (15 mL) were added Selectfluor (1451.0 mg, 4.18 mmol) and anhydrous potassium phosphate (443.5 mg, 2.09 mmol). The reaction was stirred at room temperature for 2 days and monitored by F NMR. Upon completion, the mixture was poured onto saturated aqueous ammonium chloride solution (100 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by chromatography using 2−8% hexanes/ethyl acetate as mobile phase to give 1-difluoronitroacetonaphthone (450.0 mg, 1.79 mmol) as a yellow oil in 94% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.65 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.74 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.96 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.15 (ddd, *J* = 7.6, 3.6, 2.4 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.74 (dd, *J* = 8.7, 1.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 115.4 (t, *J*$_{C-F}$ = 302.4 Hz), 124.1, 125.0, 126.0, 127.6, 129.1, 130.0, 131.0, 131.2 (t, *J*$_{C-F}$ = 5.1 Hz), 134.0, 137.0, 180.6 (t, *J*$_{C-F}$ = 25.5

Scheme 3. Reduction of the Difluoronitromethylated Oxindoles 3, 5, 13, and 21
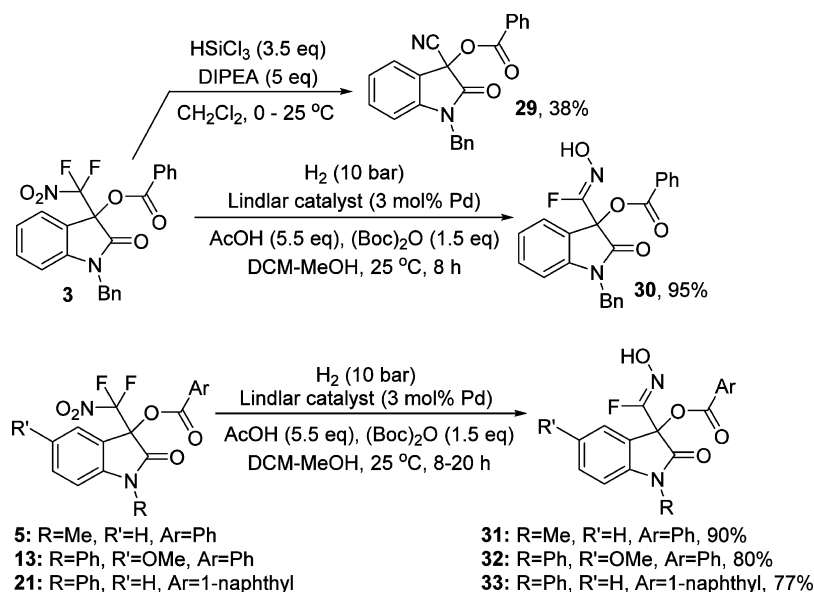
Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ −85.34 (s, 2F). Anal. Calcd for $C_{12}H_7F_2NO_3$: C, 57.38; H, 2.81; N, 5.58. Found: C, 57.32; H, 2.91; N, 5.60.

General Procedure for Isatin Insertion into Aryl Difluoronitromethyl Ketones. To a solution of the isatin (0.15 mmol), difluoronitroacetophenone (36.2 mg, 0.18 mmol), or difluoronitroacetonaphthone (45.3 mg, 0.18 mmol) in anhydrous chloroform (0.4 mL) was added DBU (4.6 mg, 0.03 mmol) under a nitrogen atmosphere. The reaction was stirred at room temperature for 24−48 h. Upon completion, the mixture was dry-loaded on silica gel and purified by chromatography using 5−10% hexanes/ethyl acetate as mobile phase.

Hydrogenation Procedure. A solution of **3** or **21** (0.16 mmol) and di-*tert*-butyl dicarbonate (52.4 mg, 0.24 mmol) in dichloromethane (2 mL) was transferred to a glass-lined hydrogenation apparatus containing the Lindlar catalyst (3 mol % Pd) and glacial acetic acid (50 μL, 0.87 mmol) in methanol (6 mL). The apparatus was charged with H₂ (10 bar) and stirred at room temperature for 7−20 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The residue was dry-loaded on silica gel and purified by flash chromatography using 15−25% hexanes/ethyl acetate as mobile phase.

***N*-Benzyl 3-Cyano-2-oxoindolin-3-yl Benzoate, 29.** A solution of **3** (70.1 mg, 0.16 mmol) and diisopropylethylamine (139.3 μL, 0.8 mmol) in dichloromethane (5 mL) was cooled to 0 °C, and then trichlorosilane (56.7 μL, 0.56 mmol) was added. The mixture was stirred for 8 h and concentrated under reduced pressure. The crude product was purified by flash chromatography using 5−15% hexanes/ethyl acetate as mobile phase to give 22.3 mg of **29** (0.06 mmol, 38%) of a white solid, Mp 136.8−139.4 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.94 (d, J = 15.7 Hz, 1H), 5.01 (d, J = 15.7 Hz, 1H), 6.75 (dd, J = 8.0, 0.9 Hz, 1H), 7.03 (dd, J = 7.6, 1.0 Hz, 1H), 7.24−7.43 (m, 7H), 7.45 (dd, J = 8.3, 7.6 Hz, 2H), 7.59 (dd, J = 8.0, 1.0 Hz, 1H), 8.13 (dd, J = 7.4, 1.0 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 44.0, 70.4, 109.5, 113.8, 123.1, 124.4, 125.6, 127.3, 127.7, 128.4, 128.8, 129.0, 130.1, 130.2, 133.5, 135.3, 143.7, 165.8, 172.3. Anal. Calcd for $C_{23}H_{16}N_2O_3$: C, 74.99; H, 4.38; N, 7.60. Found: C, 75.31; H, 4.63; N, 7.49.

***N*-Benzyl 3-(Difluoronitromethyl)-2-oxoindolin-3-yl Benzoate, 3.** N-Benzyl isatin (35.6 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 64.9 mg (0.15 mmol, 99%) of a white solid, Mp 127.3−129.8 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.98 (d, J = 15.9 Hz, 1H), 5.12 (d, J = 15.9 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 7.09 (dd, J = 7.6, 7.6 Hz, 1H), 7.28−7.45 (m, 7H), 7.49 (dd, J = 8.2, 7.4 Hz, 2H), 7.64 (dd, J = 8.0, 1.0 Hz, 1H), 8.08 (dd, J = 7.1, 0.8 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 45.1, 77.7 (t, J_{C-F} = 26.0 Hz), 110.7, 119.0, 120.3 (t, J_{C-F} = 294.6 Hz), 123.7, 125.0, 127.4, 127.6, 128.1, 128.9, 129.1, 130.5, 132.7, 134.6, 134.6, 144.6, 163.0, 166.7. ¹⁹F NMR (376 MHz, CDCl₃): δ −96.07 (d, J = 169.2 Hz, 1F), −95.62 (d, J = 169.9 Hz, 1F). Anal. Calcd for $C_{23}H_{16}F_2N_2O_5$: C, 63.02; H, 3.68; N, 6.39. Found: C, 62.91; H, 3.96; N, 6.39.

***N*-Methyl 3-(Difluoronitromethyl)-2-oxoindolin-3-yl Benzoate, 5.** N-Methyl isatin (24.2 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 53.3 mg (0.15 mmol, 98%) of a white solid, Mp 167.1−169.2 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.35 (s, 3H), 6.98 (d, J = 7.9 Hz, 1H), 7.12 (dd, J = 7.6, 7.6 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.43−7.54 (m, 3H), 7.63 (dd, J = 8.5, 1.1 Hz, 1H), 8.04 (dd, J = 7.4, 1.0 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 27.3, 77.5 (t, J_{C-F} = 25.9 Hz), 109.6, 119.1, 120.2 (t, J_{C-F} = 294.5 Hz), 123.7, 125.0, 127.6, 128.9, 130.4, 132.9, 134.5, 145.5, 163.1, 166.6. ¹⁹F NMR (376 MHz, CDCl₃): δ −96.09 (d, J = 169.6 Hz, 1F), −95.62 (d, J = 169.6 Hz, 1F). Anal. Calcd for $C_{17}H_{12}F_2N_2O_5$: C, 56.36; H, 3.34; N, 7.73. Found: C, 56.47; H, 3.49; N, 7.53.

***N*-Phenyl 3-(Difluoronitromethyl)-2-oxoindolin-3-yl Benzoate, 7.** N-Phenyl isatin (33.5 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general

procedure described above, and the reaction was stirred for 24 h. Flash purification gave 62.4 mg (0.15 mmol, 98%) of a white solid, Mp 109.2−112.1 °C. ¹H NMR (400 MHz, CDCl₃): δ 6.85 (d, J = 7.9 Hz, 1H), 7.14 (dd, J = 7.7, 7.7 Hz, 1H), 7.37−7.46 (m, 2H), 7.46−7.55 (m, 5H), 7.58 (dd, J = 8.3, 7.6 Hz, 2H), 7.64 (dd, J = 8.2, 1.2 Hz, 1H), 8.09 (dd, J = 7.6, 1.0 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 77.6 (t, J_{C-F} = 25.5 Hz), 110.8, 118.7, 120.4 (t, J_{C-F} = 294.5 Hz), 124.1, 125.2, 127.0, 127.7, 128.9, 129.2, 130.1, 130.5, 132.8, 133.7, 134.6, 146.0, 163.3, 166.0. ¹⁹F NMR (376 MHz, CDCl₃): δ −95.94 (d, J = 169.1 Hz, 1F), −95.34 (d, J = 169.2 Hz, 1F). Anal. Calcd for $C_{22}H_{14}F_2N_2O_5$: C, 62.27; H, 3.33; N, 6.60. Found: C, 61.96; H, 3.43; N, 6.32.

***N*-Phenyl 3-(Difluoronitromethyl)-5-methyl-2-oxoindolin-3-yl Benzoate, 9.** N-Phenyl 5-methylisatin (35.6 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 61.2 mg (0.14 mmol, 93%) of a white amorphous solid. ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H), 6.75 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.23 (s, 1H), 7.43−7.52 (m, 5H), 7.57 (dd, J = 8.3, 6.5 Hz, 2H), 7.65 (dd, J = 6.4, 1.6 Hz, 1H), 8.09 (dd, J = 8.3, 1.4 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 21.1, 77.7 (t, J_{C-F} = 24.9 Hz), 110.6, 118.6, 120.4 (t, J_{C-F} = 295.4 Hz), 125.7, 126.9, 127.7, 128.9, 129.0, 130.0, 130.5, 133.2, 133.8, 134.0, 134.5, 143.6, 163.2, 165.9. ¹⁹F NMR (376 MHz, CDCl₃): δ −95.93 (d, J = 168.9 Hz, 1F), −95.34 (d, J = 169.2 Hz, 1F). Anal. Calcd for $C_{23}H_{16}F_2N_2O_5$: C, 63.02; H, 3.68; N, 6.39. Found: C, 63.39; H, 4.01; N, 6.18.

***N*-Phenyl 3-(Difluoronitromethyl)-5-fluoro-2-oxoindolin-3-yl Benzoate, 11.** N-Phenyl 6-fluoroisatin (36.2 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 60.2 mg (0.14 mmol, 91%) of a white amorphous solid. ¹H NMR (400 MHz, CDCl₃): δ 6.57 (dd, J = 8.8, 2.3 Hz, 1H), 6.81 (dd, J = 8.7, 2.3 Hz, 1H), 7.41 (dd, J = 8.4, 5.1 Hz, 1H), 7.46−7.54 (m, 5H), 7.59 (dd, J = 7.7, 6.5 Hz, 2H), 7.5 (dd, J = 6.3, 1.5 Hz, 1H), 8.07 (dd, J = 8.0, 1.4 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 77.8 (t, J_{C-F} = 25.0 Hz), 99.8 (d, J_{C-F} = 28.5 Hz), 110.8 (d, J_{C-F} = 23.3 Hz), 114.1 (d, J_{C-F} = 3.1 Hz), 120.2 (t, J_{C-F} = 295.8 Hz), 126.9, 127.1 (d, J_{C-F} = 10.5 Hz), 127.5, 128.9, 129.5, 130.3, 130.5, 133.2, 134.7, 148.0 (d, J_{C-F} = 12.2 Hz), 163.3, 165.6 (d, J_{C-F} = 252.5 Hz), 166.1. ¹⁹F NMR (376 MHz, CDCl₃): δ −103.69 (ddd, J = 8.8, 8.7, 5.2 Hz, 1F), −95.89 (d, J = 169.5 Hz, 1F), −95.25 (d, J = 169.5 Hz, 1F). Anal. Calcd for $C_{22}H_{13}F_3N_2O_5$: C, 59.74; H, 2.96; N, 6.33. Found: C, 59.93; H, 3.22; N, 6.12.

***N*-Phenyl 3-(Difluoronitromethyl)-5-methoxy-2-oxoindolin-3-yl Benzoate, 13.** N-Phenyl 5-methoxyisatin (38.0 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above and the reaction was stirred for 48 h. Flash purification gave 65.5 mg (0.14 mmol, 96%) of a yellow amorphous solid. ¹H NMR (400 MHz, CDCl₃): δ 3.77 (s, 3H), 6.79 (d, J = 8.7 Hz, 1H), 6.93 (dd, J = 8.7, 2.6 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 7.43−7.53 (m, 6H), 7.6 (dd, J = 8.7, 7.4 Hz, 2H), 7.65 (dd, J = 8.7, 1.3 Hz, 1H), 8.09 (dd, J = 7.3, 1.3 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 56.0, 77.8 (t, J_{C-F} = 25.1 Hz), 111.5, 111.9, 117.4, 119.7, 120.3 (t, J_{C-F} = 294.4 Hz), 126.8, 127.6, 128.9, 129.0, 130.0, 130.5, 133.9, 134.6, 139.2, 156.8, 163.2, 165.7. ¹⁹F NMR (376 MHz, CDCl₃): δ −95.94 (d, J = 169.6 Hz, 1F), −95.38 (d, J = 169.2 Hz, 1F). Anal. Calcd for $C_{23}H_{16}F_2N_2O_6$: C, 60.80; H, 3.55; N, 6.17. Found: C, 60.69; H, 3.66; N, 6.08.

***N*-Phenyl 3-(Difluoronitromethyl)-5-chloro-2-oxoindolin-3-yl Benzoate, 15.** N-Phenyl 5-chloroisatin (38.6 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 48 h. Flash purification gave 62.4 mg (0.14 mmol, 91%) of a pale yellow amorphous solid. ¹H NMR (400 MHz, CDCl₃): δ 6.80 (dd, J = 8.3, 2.8 Hz, 1H), 7.38 (dd, J = 8.5, 2.2 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.46−7.55 (m, 5H), 7.58 (dd, J = 7.8, 7.5 Hz, 2H), 7.66 (dd, J = 8.0, 1.7 Hz, 1H), 8.09 (dd, J = 7.6, 1.5 Hz, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 77.2 (t, J_{C-F} = 24.9 Hz), 111.9, 120.0 (t, J_{C-F} = 294.3 Hz), 120.2, 125.6, 126.9, 127.3, 129.0, 129.4, 129.5, 130.2, 130.6,

132.8, 133.3, 134.8, 144.6, 163.3, 165.6. ^{19}F NMR (376 MHz, CDCl$_3$): δ −95.64 (d, J = 170.3 Hz, 1F), −95.11 (d, J = 170.3 Hz, 1F). Anal. Calcd for C$_{22}$H$_{13}$ClF$_2$N$_2$O$_5$: C, 57.59; H, 2.86; N, 6.11. Found: C, 57.36; H, 3.21; N, 5.77.

N-Phenyl 3-(Difluoronitromethyl)-5,6-difluoro-2-oxoindolin-3-yl Benzoate, 17. N-Phenyl 5,6-difluoroisatin (38.9 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 48 h. Flash purification gave 56.0 mg (0.12 mmol, 81%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.69 (dd, J = 9.8, 6.3 Hz, 1H), 7.32 (dd, J = 8.6, 7.5 Hz, 1H), 7.44−7.55 (m, 5H), 7.60 (dd, J = 8.3, 6.8 Hz, 2H), 7.66 (dd, J = 7.3, 1.3 Hz, 1H), 8.07 (dd, J = 8.2, 1.3 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 101.4 (d, $J_{\text{C-F}}$ = 23.9 Hz), 113.8 (dd, $J_{\text{C-F}}$ = 6.2, 4.5 Hz), 115.3 (d, $J_{\text{C-F}}$ = 21.2 Hz), 120.0 (t, $J_{\text{C-F}}$ = 295.9 Hz), 126.9, 127.2, 129.0, 129.7, 130.4, 130.6, 133.2, 134.9, 143.0 (dd, $J_{\text{C-F}}$ = 9.8, 2.8 Hz), 147.4 (dd, $J_{\text{C-F}}$ = 247.2, 13.6 Hz), 153.4 (dd, $J_{\text{C-F}}$ = 255.0, 13.7 Hz), 163.3, 165.7. ^{19}F NMR (376 MHz, CDCl$_3$): δ −142.23 (ddd, J = 19.9, 8.6, 6.1 Hz, 1F), −128.04 (ddd, J = 19.8, 9.8, 7.3 Hz, 1F), −95.79 (d, J = 170.3 Hz, 1F), −95.22 (d, J = 170.3 Hz, 1F). Anal. Calcd for C$_{22}$H$_{12}$F$_4$N$_2$O$_5$: C, 57.40; H, 2.63; N, 6.09. Found: C, 57.38; H, 2.78; N, 5.97.

N-Phenyl 3-(Difluoronitromethyl)-5-trifluoromethoxy-2-oxoindolin-3-yl Benzoate, 19. N-Phenyl 5-trifluoromethoxyisatin (46.1 mg, 0.15 mmol) and difluoronitroacetophenone (36.2 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 48 h. Flash purification gave 64.3 mg (0.13 mmol, 84%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.86 (d, J = 8.7 Hz, 1H), 7.29 (dd, J = 8.6, 2.8 Hz, 1H), 7.33 (d, J = 2.8 Hz, 1H), 7.47−7.53 (m, 5H), 7.59 (dd, J = 8.2, 7.7 Hz, 2H), 7.66 (dd, J = 7.9, 1.7 Hz, 1H), 8.08 (dd, J = 8.4, 1.3 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 77.79 (t, $J_{\text{C-F}}$ = 24.6 Hz), 111.60, 119.21, 119.97, 119.99 (t, $J_{\text{C-F}}$ = 294.9 Hz), 120.49 (q, $J_{\text{C-F}}$ = 257.0 Hz), 125.91, 126.92, 127.21, 129.00, 129.55, 130.28, 130.59, 133.28, 134.87, 144.58, 145.41 (q, $J_{\text{C-F}}$ = 1.9 Hz), 163.32, 165.74. ^{19}F NMR (376 MHz, CDCl$_3$): δ −95.82 (d, J = 169.9 Hz, 1F), −95.30 (d, J = 169.9 Hz, 1F), −58.52 (s, 3F). Anal. Calcd for C$_{23}$H$_{13}$F$_5$N$_2$O$_6$: C, 54.34; H, 2.58; N, 5.51. Found: C, 54.73; H, 2.93; N, 5.30.

N-Phenyl 3-(Difluoronitromethyl)-2-oxoindolin-3-yl 1-Naphthoate, 21. N-Phenyl isatin (33.5 mg, 0.15 mmol) and difluoronitroacetonaphthone (45.3 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 68.7 mg (0.14 mmol, 97%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.89 (dd, J = 8.0, 1.4 Hz, 1H), 7.15 (dd, J = 7.7, 1.6 Hz, 1H), 7.42 (dd, J = 8.8, 7.6 Hz, 1H), 7.46−7.63 (m, 9H), 7.89 (dd, J = 8.0, 2.1 Hz, 1H), 8.12 (dd, J = 8.1, 1.7 Hz, 1H), 8.49 (dd, J = 7.2, 1.6 Hz, 1H), 8.81 (dd, J = 8.6, 2.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 77.7 (t, $J_{\text{C-F}}$ = 24.6 Hz), 110.8, 118.9, 120.5 (t, $J_{\text{C-F}}$ = 294.7 Hz), 123.6, 124.1, 124.8, 125.2, 125.5, 126.7, 127.1, 128.6, 128.9, 129.2, 130.1, 131.7, 132.3, 132.8, 133.7, 133.9, 135.5, 146.1, 163.6, 166.2. ^{19}F NMR (376 MHz, CDCl$_3$): δ −95.80 (d, J = 169.0 Hz, 1F), −95.06 (d, J = 169.0 Hz, 1F). Anal. Calcd for C$_{26}$H$_{16}$F$_2$N$_2$O$_5$: C, 65.82; H, 3.40; N, 5.90. Found: C, 65.86; H, 3.55; N, 5.82.

N-Phenyl 3-(Difluoronitromethyl)-6-fluoro-2-oxoindolin-3-yl 1-Naphthoate, 22. N-Phenyl 6-fluoroisatin (36.2 mg, 0.15 mmol) and difluoronitroacetonaphthone (45.3 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 70.4 mg (0.14 mmol, 95%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.61 (dd, J = 8.8, 2.3 Hz, 1H), 6.83 (ddd, J = 8.7, 8.7, 2.3 Hz, 1H), 7.45 (dd, J = 8.4, 5.1 Hz, 1H), 7.49−7.64 (m, 8H), 7.89 (dd, J = 8.4, 1.5 Hz, 1H), 8.13 (dd, J = 8.2, 1.6 Hz, 1H), 8.47 (dd, J = 7.4, 1.3 Hz, 1H), 8.80 (dd, J = 8.4, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 77.6 (t, $J_{\text{C-F}}$ = 24.6 Hz), 99.8 (d, $J_{\text{C-F}}$ = 28.5 Hz), 110.8 (d, $J_{\text{C-F}}$ = 23.3 Hz), 114.3 (d, $J_{\text{C-F}}$ = 3.3 Hz), 120.4 (t, $J_{\text{C-F}}$ = 294.8 Hz), 123.4, 124.8, 125.4, 126.8, 126.9, 127.0 (d, $J_{\text{C-F}}$ = 10.2 Hz), 128.7, 128.9, 129.5, 130.2, 131.7, 132.4, 133.3, 133.9, 135.6, 148.0 (d, $J_{\text{C-F}}$ = 12.2 Hz),163.6, 165.6 (d, $J_{\text{C-F}}$ = 252.3 Hz) 166.3. ^{19}F NMR (376 MHz, CDCl$_3$): δ −103.84 (ddd, J = 8.8, 8.7, 5.1 Hz, 1F), −95.75 (d, J = 169.3 Hz, 1F), −94.98

(d, J = 169.3 Hz, 1F). Anal. Calcd for C$_{26}$H$_{15}$F$_3$N$_2$O$_5$: C, 63.42; H, 3.07; N, 5.69. Found: C, 63.50; H, 3.28; N, 5.63.

N-Phenyl 3-(Difluoronitromethyl)-6-methoxy-2-oxoindolin-3-yl 1-Naphthoate, 24. N-Phenyl 6-methoxyisatin (38.0 mg, 0.15 mmol) and difluoronitroacetonaphthone (45.3 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 48 h. Flash purification gave 73.4 mg (0.15 mmol, 97%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.77 (s, 3H), 6.40 (d, J = 2.3 Hz, 1H), 6.62 (dd, J = 8.5, 2.3 Hz, 1H), 7.38 (dd, J = 8.4, 1.0 Hz, 1H), 7.47−7.63 (m, 8H), 7.89 (dd, J = 8.1, 1.5 Hz, 1H), 8.11 (dd, J = 8.2, 2.0 Hz, 1H), 8.47 (dd, J = 7.4, 1.3 Hz, 1H), 8.82 (dd, J = 8.8, 1.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 55.8, 77.7 (t, $J_{\text{C-F}}$ = 24.6 Hz), 98.3, 108.5, 110.3, 120.6 (t, $J_{\text{C-F}}$ = 296.0 Hz), 123.9, 124.8, 125.6, 126.4, 126.7, 127.1, 128.6, 128.9, 129.2, 130.1, 131.7, 132.2, 133.7, 133.9, 135.4, 147.6, 163.5, 163.7, 166.7. ^{19}F NMR (376 MHz, CDCl$_3$): δ −95.82 (d, J = 168.4 Hz, 1F), −95.01 (d, J = 168.4 Hz, 1F). Anal. Calcd for C$_{27}$H$_{18}$F$_2$N$_2$O$_6$: C, 64.29; H, 3.60; N, 5.55. Found: C, 64.30; H, 3.61; N, 5.52.

N-Phenyl 3-(Difluoronitromethyl)-4-bromo-2-oxoindolin-3-yl 1-Naphthoate, 26. N-Phenyl 4-bromoisatin (45.3 mg, 0.15 mmol) and difluoronitroacetonaphthone (45.3 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 74.3 mg (0.14 mmol, 90%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.80 (dd, J = 7.7, 1.1 Hz, 1H), 7.20−7.32 (m, 2H), 7.48−7.65 (m, 8H), 7.91 (dd, J = 8.0, 2.0 Hz, 1H), 8.14 (dd, J = 8.2, 1.6 Hz, 1H), 8.62 (dd, J = 7.4, 1.3 Hz, 1H), 8.84 (dd, J = 8.7, 1.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 79.98 (dd, $J_{\text{C-F}}$ = 26.0, 22.9 Hz), 109.66, 118.26, 119.97, 120.26 (dd, $J_{\text{C-F}}$ = 301.2, 295.0 Hz), 122.81, 124.69, 125.40, 126.57, 127.04, 128.51, 128.65, 128.76, 129.41, 130.08, 131.67, 132.65, 133.16, 133.18, 133.81, 135.43, 147.53, 163.40, 165.79. ^{19}F NMR (376 MHz, CDCl$_3$): δ −91.99 (d, J = 163.1 Hz, 1F), −90.97 (d, J = 163.0 Hz, 1F). Anal. Calcd for C$_{26}$H$_{15}$BrF$_2$N$_2$O$_5$: C, 56.44; H, 2.73; N, 5.06. Found: C, 56.55; H, 3.05; N, 4.95.

N-Phenyl 3-(Difluoronitromethyl)-6-bromo-2-oxoindolin-3-yl 1-Naphthoate, 28. N-Phenyl 6-bromoisatin (45.3 mg, 0.15 mmol) and difluoronitroacetonaphthone (45.3 mg, 0.18 mmol) were employed in the general procedure described above, and the reaction was stirred for 24 h. Flash purification gave 77.8 mg (0.14 mmol, 94%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.01 (d, J = 1.9 Hz, 1H), 7.27−7.35 (m, 2H), 7.49−7.65 (m, 8H), 7.90 (dd, J = 7.9, 1.2 Hz, 1H), 8.13 (dd, J = 8.3, 1.4 Hz, 1H), 8.46 (dd, J = 7.6, 1.2 Hz, 1H), 8.79 (dd, J = 8.6, 1.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 77.8 (t, $J_{\text{C-F}}$ = 24.6 Hz), 114.3, 117.2, 120.2 (t, $J_{\text{C-F}}$ = 294.7 Hz), 123.1, 123.3, 124.8, 125.4, 126.4, 126.8, 127.0, 127.1, 128.8, 129.0, 129.6, 130.3, 131.7, 132.4, 133.2, 133.9, 135.7, 147.2, 163.6, 166.0. ^{19}F NMR (376 MHz, CDCl$_3$): δ −95.68 (d, J = 169.4 Hz, 1F), −94.97 (d, J = 169.5 Hz, 1F). Anal. Calcd for C$_{26}$H$_{15}$BrF$_2$N$_2$O$_5$: C, 56.44; H, 2.73; N, 5.06. Found: C, 56.52; H, 3.10; N, 4.85.

N-Benzyl (Z)-3-(Fluoro(hydroxyimino)methyl)-2-oxoindolin-3-yl Benzoate, 30. N-Benzyl 3-(difluoronitromethyl)-2-oxoindolin-3-yl benzoate (70.1 mg, 0.16 mmol) was employed in the catalytic hydrogenation procedure described above, and the reaction was stirred for 7 h. Flash purification gave 61.7 mg (0.15 mmol, 95%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.99 (d, J = 15.9 Hz, 1H), 5.10 (d, J = 15.9 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 7.05 (dd, J = 7.6, 1.0 Hz, 1H), 7.27 (dd, J = 7.8, 1.2 Hz, 2H), 7.31−7.38 (m, 2H), 7.39−7.49 (m, 5H), 7.62 (dd, J = 5.6, 1.5 Hz, 1H), 8.08 (dd, J = 8.3, 1.3 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 44.8, 77.7, 110.4, 123.3, 123.4, 124.5, 127.3, 127.9, 128.4, 128.7, 129.0, 130.4, 131.3, 134.1, 135.1, 143.4, 148.43 (d, $J_{\text{C-F}}$ = 342.2 Hz), 163.9, 169.13 (d, $J_{\text{C-F}}$ = 3.2 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −79.21 (s, 1F). Anal. Calcd for C$_{23}$H$_{17}$FN$_2$O$_4$: C, 68.31; H, 4.24; N, 6.93. Found: C, 68.11; H, 4.46; N, 6.89.

N-Methyl (Z)-3-(Fluoro(hydroxyimino)methyl)-2-oxoindolin-3-yl Benzoate, 31. N-Methyl-3-(difluoronitromethyl)-2-oxoindolin-3-yl benzoate (43.5 mg, 0.12 mmol) was employed in the catalytic hydrogenation procedure described above, and the reaction mixture was stirred for 8 h. Flash purification gave 35.3 mg (0.11 mmol, 90%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.33 (s,

3H), 6.95 (d, *J* = 7.9 Hz, 1H), 7.10 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.37–7.50 (m, 4H), 7.59 (dd, *J* = 7.7, 1.5 Hz, 1H), 8.03 (dd, *J* = 7.5, 1.2 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): 27.2, 77.8, 109.3, 123.2, 123.5, 124.7, 128.4, 128.7, 130.4, 131.5, 134.1, 144.4, 148.30 (d, J_{C-F} = 342.4 Hz), 164.0, 169.1 (d, J_{C-F} = 3.0 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −79.2 (s, 1F). Anal. Calcd for C$_{17}$H$_{13}$FN$_2$O$_4$: C, 62.20; H, 3.99; N, 8.53. Found: C, 62.37; H, 3.68; N, 8.32.

N-Phenyl (Z)-3-(Fluoro(hydroxyimino)methyl)-5-methoxy-2-oxoindolin-3-yl Benzoate, 32. *N*-Phenyl 3-(difluoronitromethyl)-5-methoxy-2-oxoindolin-3-yl benzoate (44.0 mg, 0.1 mmol) was employed in the catalytic hydrogenation procedure described above, and the mixture was stirred for 8 h. Flash purification gave 33.3 mg (0.08 mmol, 80%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.77 (s, 3H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 8.3, 7.6 Hz, 2H), 7.49–7.55 (m, 5H), 7.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.09 (dd, *J* = 7.5, 1.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): 56.0, 77.9, 111.2, 111.4, 116.2, 124.0, 126.7, 126.9, 128.4, 128.7, 129.9, 130.4, 134.1, 134.4, 138.2, 148.3 (d, J_{C-F} = 342.6 Hz), 156.7, 164.1, 168.3 (d, J_{C-F} = 2.7 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −79.4 (s, 1F). Anal. Calcd for C$_{23}$H$_{17}$FN$_2$O$_5$: C, 65.71; H, 4.08; N, 6.66. Found: C, 65.75; H, 3.69; N, 6.41.

N-Phenyl (Z)-3-(Fluoro(hydroxyimino)methyl)-2-oxoindolin-3-yl 1-Naphthoate, 33. *N*-Phenyl 3-(difluoronitromethyl)-2-oxoindolin-3-yl 1-naphthoate (75.9 mg, 0.16 mmol) was employed in the catalytic hydrogenation procedure described above, and the reaction was stirred for 7 h. Flash purification gave 54.3 mg (0.12 mmol, 77%) of a white amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.88 (d, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.46 (m, 1H), 7.49–7.62 (m, 8H), 7.87 (dd, *J* = 8.0, 2.1 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.9 Hz, 1H), 8.43 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.83 (d, *J* = 8.6, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 77.8, 110.5, 123.2, 123.8, 124.6, 124.8, 125.8, 126.6, 127.1, 128.4, 128.8, 128.9, 129.9, 131.3, 131.6, 131.8, 133.9, 134.2, 134.8, 144.9, 148.50 (d, J_{C-F} = 342.2 Hz), 164.7, 168.6 (d, J_{C-F} = 2.9 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −78.8 (s, 1F). Anal. Calcd for C$_{26}$H$_{17}$FN$_2$O$_4$: C, 70.90; H, 3.89; N, 6.36. Found: C, 70.70; H, 4.09; N, 6.36.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02704.

NMR spectra and crystallographic details (PDF)
Crystallographic data for **30** (CIF)
Crystallographic data for **3** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cw27@georgetown.edu.

ORCID Ⓘ

Christian Wolf: 0000-0002-4447-3753

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley: New York, 2001.

(2) (a) Tsuji, J.; Yamada, T.; Minami, L.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995. (b) Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2687–2689. (c) Trost, B. M.; Surivet, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122–3124. (d) Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 4250–4257.

(3) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106–111.

(4) (a) Seebach, D.; Lehr, F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 505–506. (b) Katritzky, A. R.; Kashmiri, M. A.; De Ville, G. Z.; Patel, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 90–96. (c) Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 9942–9945.

(5) (a) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027–1032. (b) Schwieter, K. E.; Shen, B.; Shackleford, J. P.; Leighty, M. W.; Johnston, J. N. *Org. Lett.* **2014**, *16*, 4714–4717. (c) Schwieter, K. E.; Johnston, J. N. *Chem. Sci.* **2015**, *6*, 2590–2595.

(6) Stoichiometric nitroaldol reactions: (a) Majhi, A.; Kadam, S. T.; Kim, S.-S. *Bull. Korean Chem. Soc.* **2009**, *30*, 1767–1770. (b) Soengas, R. G.; Silva, A. M. S. *Synlett* **2012**, *23*, 873–876. (c) Rokhum, L.; Bez, G. *Can. J. Chem.* **2013**, *91*, 300–306.

(7) (a) Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834. (b) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724–4727. (c) Xu, H.; Wolf, C. *Chem. Commun.* **2010**, *46*, 8026–8028. (d) Xu, H.; Wolf, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 12249–12252.

(8) (a) Zhang, P.; Wolf, C. *J. Org. Chem.* **2012**, *77*, 8840–8844. (b) Zhang, P.; Wolf, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7869–7873. (c) Balaraman, K.; Moskowitz, M.; Liu, Y.; Wolf, C. *Synthesis* **2016**, *48*, 2376–2384.

(9) Ding, R.; Wolf, C. *Chem. Commun.* **2016**, *52*, 3576–3579.

(10) (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826–870. (b) Mei, H.; Acena, J. L.; Soloshonok, V. A.; Roeschenthaler, G.-V.; Han, J.; Xie, C. *Eur. J. Org. Chem.* **2015**, *2015*, 6401–6412. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432–2506.

(11) (a) Ren, Q.; Huang, J.; Wang, L.; Li, W.; Liu, H.; Jiang, X.; Wang, J. *ACS Catal.* **2012**, *2*, 2622–2625. (b) Duan, Z.; Han, J.; Qian, P.; Zhang, Z.; Wang, Y.; Pan, Y. *Org. Biomol. Chem.* **2013**, *11*, 6456–6459. (c) Saidalimu, I.; Fang, X.; He, X.-P.; Liang, J.; Yang, X.; Wu, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5566–5570. (d) Prathima, P. S.; Rajesh, P.; Rao, J. V.; Kailash, U. S.; Sridhar, B.; Rao, M. M. *Eur. J. Med. Chem.* **2014**, *84*, 155–159.

(12) Ni, C.; Hu, J. *Chem. Soc. Rev.* **2016**, *45*, 5441–5454.

(13) Kaljurand, I.; Kuett, A.; Soovaeli, L.; Rodima, T.; Maeemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019–1028.

(14) (a) Bissell, E. R. *J. Org. Chem.* **1963**, *28*, 1717–1720. (b) Butler, P.; Golding, B. T.; Laval, G.; Loghmani-Khouzani, H.; Ranjbar-Karimi, R.; Sadeghi, M. M. *Tetrahedron* **2007**, *63*, 11160–11166.

(15) The reaction also occurs with unprotected isatin; however, the insertion product was isolated in only 60% yield.

(16) Ethanol and **1** do not react in the absence of DBU.

(17) Orlandi, M.; Tosi, F.; Bonsignore, M.; Benaglia, M. *Org. Lett.* **2015**, *17*, 3941–3943.

(18) Esmaeili, A. A.; Ghalandarabad, S. A.; Zangouei, M. *Tetrahedron Lett.* **2012**, *53*, 5605–5607.

(19) The (*E*)-diastereomer was not detected by NMR analysis.

(20) The −NH-C(R)F− moiety is unstable: Annedi, S. C.; Li, W.; Samson, S.; Kotra, L. P. *J. Org. Chem.* **2003**, *68*, 1043–1049.

(21) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.

(22) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Gromova, A. V.; Witek, R.; Steel, P. J. *J. Org. Chem.* **2005**, *70*, 9211–9214.