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Organocatalytic Insertion of Isatins into Aryl Difluoronitromethyl Ketones

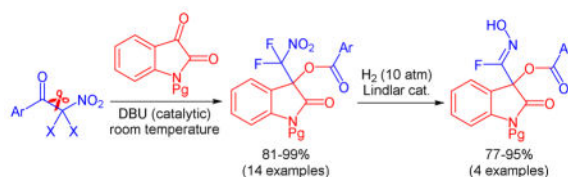
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Abstract

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 was prepared in 81–99% yield. The general synthetic usefulness of these 3-hydroxyoxindole derivatives is demonstrated with the selective reduction to fluorooximes.

Graphical abstract



Nitroalkanes are commonly used in Henry and Michael reactions,¹ allylations,² arylations,³ alkylations⁴ 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 equivalents 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 nitroalkanes⁷ 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

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Supporting Information Available. NMR spectra and crystallographic details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 (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 one equivalent of (*i*-Pr)₂NEt produced **3** in 63% yield after 48 hours (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 hours in both dichloromethane and chloroform. Further reduction of the DBU loading, however, compromises the yield (entries 8–10). It is noteworthy that this protocol does not only eliminate 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 R₂. 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 -difluoronitroacetophenone, **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 ¹⁹F NMR spectroscopic analysis (SI). We observed that addition of one equivalent of DBU into a solution of difluoronitroacetophenone, **1**, in CDCl₃ led to the formation of the

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 (^1H 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**, **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-difluoronitroacetophenone, 20—To a solution of 1-naphthoynitromethane **22** (410.0 mg, 1.90 mmol) in anhydrous acetonitrile (15 mL) was 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-difluoronitroacetophenone (450.0 mg, 1.79 mmol) as a yellow oil in 94% yield. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 115.4 (t, $J_{\text{C-F}} = 302.4$ Hz), 124.1, 125.0, 126.0, 127.6, 129.1, 130.0, 131.0, 131.2 (t, $J_{\text{C-F}} = 5.1$ Hz), 134.0, 137.0, 180.6 (t, $J_{\text{C-F}} = 25.5$ Hz). ^{19}F NMR (376 MHz, CDCl_3): δ -85.34 (s, 2F). Anal. Calcd. for $\text{C}_{12}\text{H}_7\text{F}_2\text{NO}_3$: 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 difluoronitroacetophenone (45.3 mg, 0.18 mmol) in anhydrous chloroform (0.4 mL) was added DBU (4.6 mg, 0.03 mmol) under nitrogen atmosphere. The reaction was stirred at room temperature for 24 – 48 hours. 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 H_2 (10 bar) and stirred at room temperature for 7 – 20 hours. 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 μ L, 0.8 mmol) in dichloromethane (5 mL) was cooled to 0°C and then trichlorosilane (56.7 μ L, 0.56 mmol) was added. The mixture was stirred for 8 hours 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, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 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 $\text{C}_{23}\text{H}_{16}\text{N}_2\text{O}_3$: 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 hours. Flash purification gave 64.9 mg (0.15 mmol, 99%) of a white solid, Mp 127.3 – 129.8 °C. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 45.1, 77.7 (t, $J_{\text{C-F}}$ = 26.0 Hz), 110.7, 119.0, 120.3 (t, $J_{\text{C-F}}$ = 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. ^{19}F NMR (376 MHz, CDCl_3): δ -96.07 (d, J = 169.2 Hz, 1F), -95.62 (d, J = 169.9 Hz, 1F). Anal. Calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 53.3 mg (0.15 mmol, 98%) of a white solid, Mp 167.1 – 169.2 °C. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 27.3, 77.5 (t, $J_{\text{C-F}}$ = 25.9 Hz), 109.6, 119.1, 120.2 (t, $J_{\text{C-F}}$ = 294.5 Hz), 123.7, 125.0, 127.6, 128.9, 130.4, 132.9, 134.5, 145.5, 163.1, 166.6. ^{19}F NMR (376 MHz, CDCl_3): δ -96.09 (d, J = 169.6 Hz, 1F), -95.62 (d, J = 169.6 Hz, 1F). Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 62.4 mg (0.15 mmol, 98%) of a white solid, Mp 109.2 – 112.1 °C. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 77.6 (t, $J_{\text{C-F}}$ =

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. ^{19}F NMR (376 MHz, CDCl_3): δ -95.94 (d, $J = 169.1$ Hz, 1F), -95.34 (d, $J = 169.2$ Hz, 1F). Anal. Calcd. for $\text{C}_{22}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 61.2 mg (0.14 mmol, 93%) of a white amorphous solid. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 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. ^{19}F NMR (376 MHz, CDCl_3): δ -95.93 (d, $J = 168.9$ Hz, 1F), -95.34 (d, $J = 169.2$ Hz, 1F). Anal. Calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 60.2 mg (0.14 mmol, 91%) of a white amorphous solid. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 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. ^{19}F NMR (376 MHz, CDCl_3): 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 $\text{C}_{22}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 65.5 mg (0.14 mmol, 96%) of a yellow amorphous solid. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 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. ^{19}F NMR (376 MHz, CDCl_3): δ -95.94 (d, $J = 169.6$ Hz, 1F), -95.38 (d, $J = 169.2$ Hz, 1F). Anal. Calcd. for $\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_6$: 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 hours. Flash purification gave 62.4 mg (0.14 mmol, 91%) of a pale yellow amorphous solid. ^1H NMR (400 MHz, CDCl_3): 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). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 77.2 (t, $J_{\text{C-F}} = 24.9$ Hz), 111.9, 120.0 (t, $J_{\text{C-F}} = 294.3$ 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 $\text{C}_{22}\text{H}_{13}\text{ClF}_2\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 56.0 mg (0.12 mmol, 81%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{22}\text{H}_{12}\text{F}_4\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 64.3 mg (0.13 mmol, 84%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{23}\text{H}_{13}\text{F}_5\text{N}_2\text{O}_6$: 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 difluoronitroacetophenone (45.3 mg, 0.18 mmol) were employed in the general procedure described above and the reaction was stirred for 24 hours. Flash purification gave 68.7 mg (0.14 mmol, 97%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{26}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_5$: 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 difluoronitroacetone (45.3 mg, 0.18 mmol) were employed in the general procedure described above and the reaction was stirred for 24 hours. Flash purification gave 70.4 mg (0.14 mmol, 95%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{26}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_5$: 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 difluoronitroacetone (45.3 mg, 0.18 mmol) were employed in the general procedure described above and the reaction was stirred for 48 hours. Flash purification gave 73.4 mg (0.15 mmol, 97%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{27}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_6$: 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 difluoronitroacetone (45.3 mg, 0.18 mmol) were employed in the general procedure described above and the reaction was stirred for 24 hours. Flash purification gave 74.3 mg (0.14 mmol, 90%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{26}\text{H}_{15}\text{BrF}_2\text{N}_2\text{O}_5$: 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 difluoronitroacetone (45.3 mg, 0.18 mmol) were employed in the general procedure described above and the reaction was stirred for 24 hours. Flash purification gave 77.8 mg (0.14 mmol, 94%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{26}\text{H}_{15}\text{BrF}_2\text{N}_2\text{O}_5$: 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 hours. Flash purification gave 61.7 mg (0.15 mmol, 95%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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 $\text{C}_{23}\text{H}_{17}\text{FN}_2\text{O}_4$: 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 hours. Flash purification gave 35.3 mg (0.11 mmol, 90%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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, $J_{\text{C-F}}$ = 342.4 Hz), 164.0, 169.1 (d, $J_{\text{C-F}}$ = 3.0 Hz). ^{19}F NMR (376 MHz, CDCl_3): δ -79.2 (s, 1F). Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}_4$: 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 hours. Flash purification gave 33.3 mg (0.08 mmol,

80%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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, $J_{\text{C-F}}$ = 342.6 Hz), 156.7, 164.1, 168.3 (d, $J_{\text{C-F}}$ = 2.7 Hz). ^{19}F NMR (376 MHz, CDCl_3): δ -79.4 (s, 1F). Anal. Calcd. for $\text{C}_{23}\text{H}_{17}\text{FN}_2\text{O}_5$: 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 hours. Flash purification gave 54.3 mg (0.12 mmol, 77%) of a white amorphous solid. ^1H 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). $^{13}\text{C}\{^1\text{H}\}$ 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, $J_{\text{C-F}}$ = 342.2 Hz), 164.7, 168.6 (d, $J_{\text{C-F}}$ = 2.9 Hz). ^{19}F NMR (376 MHz, CDCl_3): δ -78.8 (s, 1F). Anal. Calcd. for $\text{C}_{26}\text{H}_{17}\text{FN}_2\text{O}_4$: C, 70.90; H, 3.89; N, 6.36. Found: C, 70.70; H, 4.09; N, 6.36.

Supplementary Material

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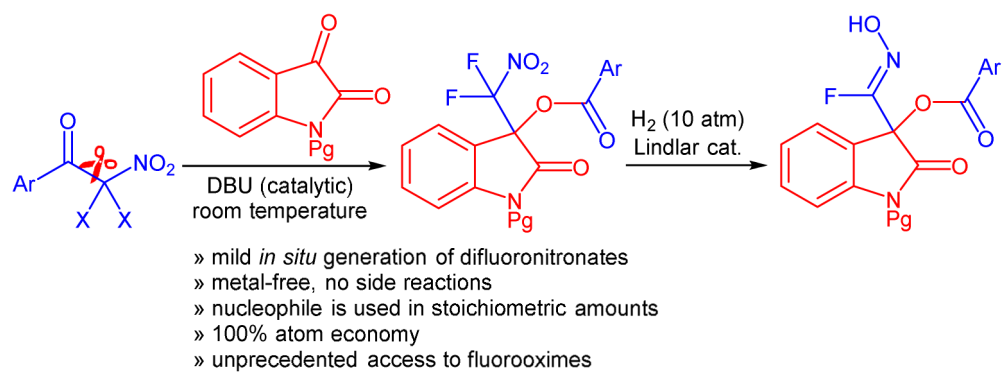
Acknowledgments

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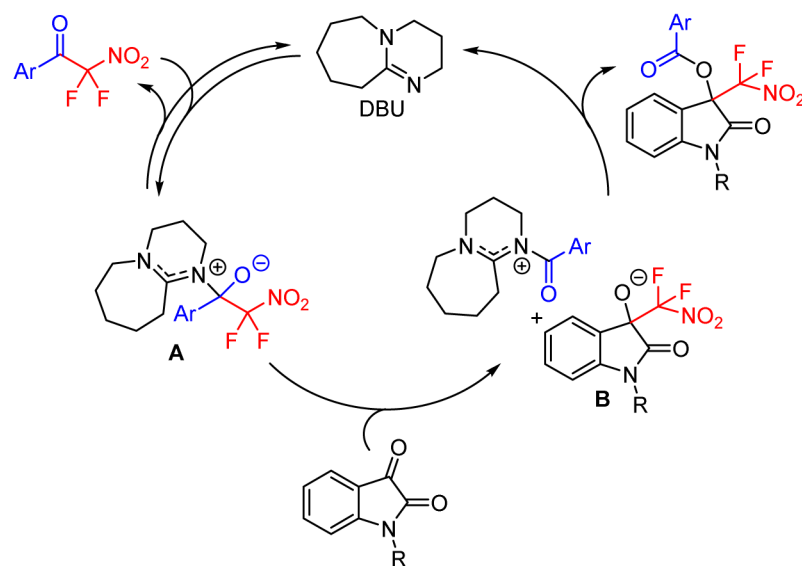
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15. The reaction also occurs with unprotected isatin, however, the insertion product was isolated in only 60% yield.
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19. The (*E*)-diastereomer was not detected by NMR analysis.
20. The –NH-C(R)F-moiety is unstable: Annedi SC, Li W, Samson S, Kotra LP. *J Org Chem.* 2003; 68:1043–1049. [PubMed: 12558433]
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**Scheme 1.**

Features of the DBU catalyzed C-C scission/nitronate addition/benzoyl transfer sequence.



Scheme 2.
Mechanism of the organocatalytic isatin insertion.

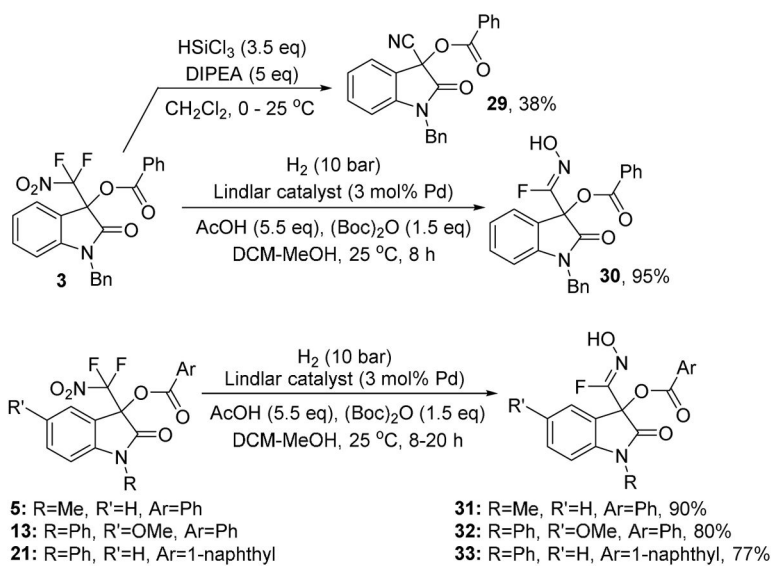
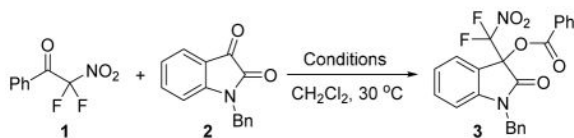
**Scheme 3.**Reduction of the difluoronitromethylated oxindoles **3**, **5**, **13** and **21**.

Table 1

Optimization of the isatin insertion reaction.



Entry	Additive (mol %)	t (h)	Yield ^a (%)
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	Et ₃ N (200)	18	99
6	Et ₃ N (50)	24	99
7	Et ₃ N (20)	48	21
8	DBU (20)	24	99
9	DBU (10)	24	82
10 ^b	DBU (20)	24	99

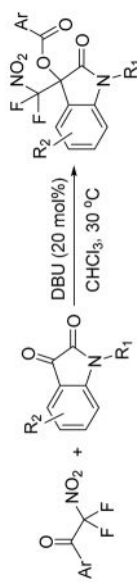
Reaction conditions: A solution of **1** (0.18 mmol) and **2** (0.15 mmol) in the presence of the additive in 0.4 mL of CH₂Cl₂ was stirred at 30 °C.

^aDetermined by ¹H NMR analysis.

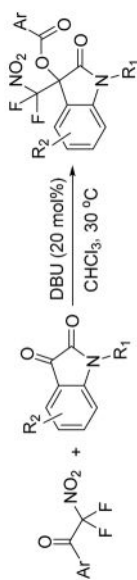
^bCHCl₃ was used as solvent. DIPEA = *N,N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2

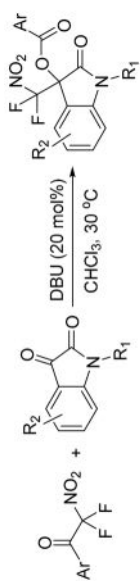
Scope of the organocatalytic isatin insertion into aryl difluoronitromethyl ketones



Entry	Ar	Isatin R ₁ /R ₂	t (h)	Insertion product	Yield (%)
1	Ph (1)	Bn/H (2)	24		99
2	1	Me/H (4)	24		99
3	1	Ph/H (6)	24		99
4	1	Ph/5-Me (8)	24		91
5	1	Ph/6-F (10)	24		91



Entry	Ar	Isatin R ₁ /R ₂	t (h)	Insertion product	Yield (%)
6	1	Ph/5-OMe (12)	48		91
7	1	Ph/5-Cl (14)	48		97
8	1	Ph/5,6-F ₂ (16)	48		81
9	1	Ph/5-OCF ₃ (18)	48		85
10	1-Np (20)	Ph/H (6)	24		96



Entry	Ar	Isatin R ₁ /R ₂	t (h)	Insertion product	Yield (%)
11	20	Ph/6-F (10)	24		91
12	20	Ph/6-OMe (23)	48		99
13	20	Ph/4-Br (25)	24		99
14	20	Ph/6-Br (27)	24		99

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 CHCl₃ was stirred for 24–48 hours.