

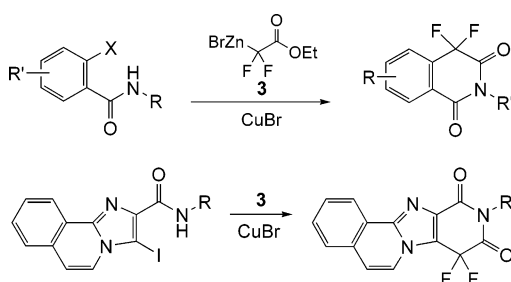
Novel  $\alpha,\alpha$ -Difluorohomophthalimides via Copper-Catalyzed Tandem Cross-Coupling–Cyclization of 2-Halobenzamides with  $\alpha,\alpha$ -Difluoro Reformatskii Reagent

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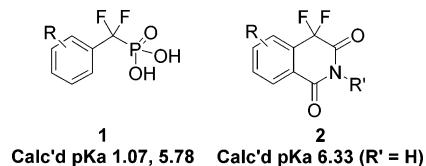
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Novel  $\alpha,\alpha$ -difluorohomophthalimides **2** were prepared by reacting *N*-substituted 2-halobenzamides with the  $\alpha,\alpha$ -difluoro Reformatskii reagent  $\text{BrZnCF}_2\text{CO}_2\text{Et}$  (**3**) in the presence of  $\text{CuBr}$  at room temperature. The synthesis involves a  $\text{CuBr}$ -mediated cross-coupling of **3** with aryl iodides or activated aryl bromides, followed by a spontaneous cyclization of the ethyl 2-benzamido- $\alpha,\alpha$ -difluoroacetate intermediates at room temperature. *N*-unsubstituted  $\alpha,\alpha$ -difluorohomophthalimides **2** ( $\text{R}' = \text{H}$ ), bearing an acidic imide proton capable of acting as a carboxylic acid bioisostere, were also prepared by reacting 3 equiv of **3** with the parent 2-iodobenzamides. Other aryl iodides such as 3-iodoimidazo[1,2-*a*]pyridine were also used for the tandem coupling–cyclization reaction.

The introduction of fluorine atoms into compounds is an important topic in organic chemistry,<sup>1</sup> and molecules containing a  $\text{CF}_2$  group adjacent to carbonyl and carboxyl moieties have widespread interest in medicinal and bioorganic chemistry.<sup>2</sup> In addition to the dramatic lowering of the  $\text{pK}_a$  of a carboxylic or phosphonic acid adjacent to a  $\text{CF}_2$  group, it has been postulated that the fluorine atoms can participate in favorable H-bonding or electrostatic interactions, particularly in protein tyrosine phosphatase (PTP) inhibitors such as **1**.<sup>3</sup> Because phosphonates **1** poorly penetrate cell membranes due to their



highly charged nature,<sup>4</sup> we were interested in expanding our PTP program<sup>5</sup> by developing general methods to prepare  $\alpha,\alpha$ -difluorohomophthalimides **2** (i.e., 4,4-difluoro-2*H*-isoquinoline-1,3-dione), where both the fluorine atoms and the weaker charge may together impart favorable biological properties. To the best of our knowledge, the preparation of  $\alpha,\alpha$ -difluorohomophthalimides **2** containing the acidic imide hydrogen has not been reported in the literature.

Direct approaches to prepare aryl  $\alpha,\alpha$ -difluorophosphonates **1** and aryl  $\alpha,\alpha$ -difluoroacetates are based on the copper-catalyzed coupling of aryl iodides with bromo- $\alpha,\alpha$ -difluorophosphonate and bromo- $\alpha,\alpha$ -difluoroacetate, respectively.<sup>6</sup> The preparation of lactams containing  $\alpha,\alpha$ -difluoromethylene carbonyl moiety has been reported by a reaction of  $\alpha$ -keto lactams with (diethylamino)sulfur trifluoride (DAST) or related reagents.<sup>7</sup> A single *N*-aryl  $\alpha,\alpha$ -difluorohomophthalimide derivative has been reported by Komoda,<sup>8</sup> by treating a  $\alpha$ -keto homophthalimide with DAST. The cyclization of *N*-allylhalo-difluoroacetamides catalyzed by  $\text{CuBr}$  provides an alternative strategy for the introduction of the  $\alpha,\alpha$ -difluoromethylene carbonyl unit.<sup>9</sup> We envisioned that a tandem  $\text{Cu(I)}$ -mediated cross-coupling of 2-halobenzamides with the  $\alpha,\alpha$ -difluoro Reformatskii reagent  $\text{BrZnCF}_2\text{CO}_2\text{Et}$  (**3**) and subsequent ring-closure of the coupling product would afford the desired  $\alpha,\alpha$ -difluorohomophthalimide, while simultaneously being mild enough to tolerate a wider variety of substituents than the highly reactive DAST conditions (Scheme 1).

We initially employed a series of *N*-substituted 2-iodobenzamides as substrates for the difluoroacetate ad-

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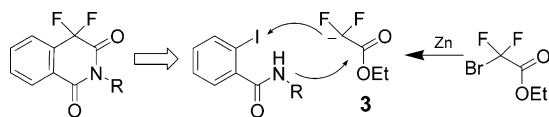
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## SCHEME 1



**TABLE 1. Formation of *N*-Substituted Difluorohomophthalimides<sup>a</sup>**

entry	R	R'	product	yield (%) <sup>b</sup>
1	Me		<b>6a</b>	88
2	Me		<b>6b</b>	85
3	Me		<b>6c</b>	81
4	H		<b>6d</b>	82
5	H		<b>6e</b>	90
6	H		<b>6f</b>	90

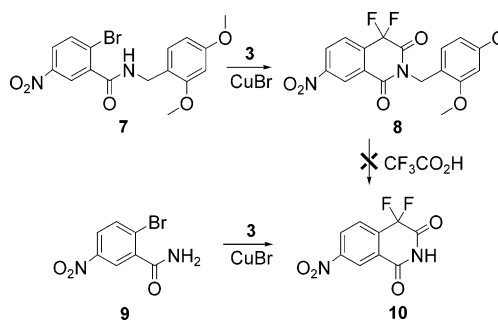
<sup>a</sup> All reactions were carried out with 2-iodobenzamides **4** (0.15 mmol), CuBr (0.12 mmol), and bromozinc- $\alpha,\alpha$ -difluoroacetate **3** in DMF (0.36 mmol) at room temperature for 18 h. <sup>b</sup> Yields of isolated products.

dition to assess whether there were steric or electronic aspects precluding ring closure. Thus, several 2-iodobenzamides **4a–f** were prepared from 2-iodobenzoic acid (for **4a–d**) or 2-iodohippuric acid (for **4e,f**) and the corresponding amines with diphenylphosphoryl azide (DPPA) as the coupling agent.<sup>10</sup>  $\alpha,\alpha$ -Difluoro Reformatskii reagent **3** was prepared from activated zinc dust and ethyl bromodifluoroacetate in DMF.<sup>11</sup> When the cross-coupling of **4a–f** and **3** was carried out in the presence of CuBr, the expected ethyl 2-benzamido- $\alpha,\alpha$ -difluoroacetates **5** were not observed. Instead, we were pleased to observe that the *N*-substituted  $\alpha,\alpha$ -difluorohomophthalimides **6a–f** were formed as the sole products after a normal reaction workup (Table 1). This transformation may be interpreted as a spontaneous cyclization of the *o*- $\alpha,\alpha$ -difluoroacetate intermediate **5** formed after the initial iodine displacement. Clearly, the facile formation of **6** results from the electron-withdrawing *o*- $\alpha,\alpha$ -difluoroacetate group of **5**, since the preparation of homophthalimides without the two  $\alpha$ -fluorine atoms generally requires fairly drastic conditions, such as heating to 140

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(11) The yield of zinc reagent **3** in DMF was estimated to be ca. 75% according to the deuteriolysis of the zinc reagent **3**, and less than 10% of homocoupling product was obtained (GC-MS analysis).

## SCHEME 2



°C.<sup>12</sup> Derivative **6a** bearing a dimethoxybenzyl (DMB) protecting group was intended to serve as precursor to the unsubstituted parent ring system. DMF appears to be superior to THF as the reaction solvent, since CuBr is completely soluble in DMF while only partially soluble in THF. It was found that 0.7–0.8 equiv of CuBr gave the best results in most cases, while considerable amounts of the corresponding 2-bromobenzamides were generated as byproduct when >1 equiv of CuBr was used, presumably via iodide exchange. Through a series of model reactions not shown here, we have observed 2-bromobenzamides to be poor substrates for the copper-mediated coupling reaction with **3**. Although we have made to date only a modest number of examples of *N*-substituted  $\alpha,\alpha$ -difluoro homophthalimides, the reaction scheme appears quite general and tolerant of a variety of substituents.

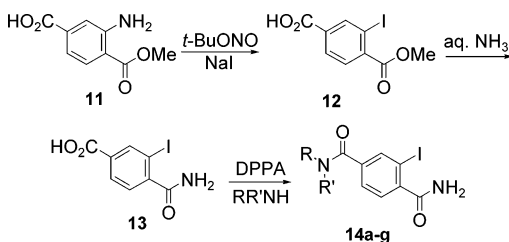
Having demonstrated the feasibility of the synthetic route, we next turned to the preparation of  $\alpha,\alpha$ -difluorohomophthalimides **2** ( $R' = H$ ) containing an acidic *N*-H proton on the imide nitrogen. Initial attempts to remove the DMB protecting group of **6a** with TFA were unsuccessful under a variety of conditions. Homophthalimide **8**, chosen as a more stringent deprotection model and as a typical intermediate of a planned library of homophthalimides, was prepared from 2-bromo-5-nitrobenzoic acid.<sup>13</sup> Unfortunately, compound **8** remained unchanged after standard DMB removal procedures, even upon treatment with neat  $CF_3CO_2H$  at 60 °C for 48 h (Scheme 2). The unusual stability of the fluorinated imide **8** to  $CF_3CO_2H$  may be explained by the high electron deficiency at the imide nitrogen due to the strong electron-withdrawing effects of the fluorine atoms, and is in agreement with the general difficulties associated with removal of a DMB group from the related phthalimides and maleimide rings.<sup>14</sup> Fortunately, the desired  $\alpha,\alpha$ -difluorohomophthalimide **10** could be readily prepared in 88% isolated yield by the reaction of aryl bromide **9** with 3 equiv of bromozinc- $\alpha,\alpha$ -difluoroacetate **3** and 0.8 equiv of CuBr at room temperature. This result suggests that the primary benzamide **9** can be used in the same way as the secondary benzamides **4** and **7** in the

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(13) In contrast to model studies with 2-bromobenzamides lacking any additional electron withdrawing group on the ring, copper-mediated nucleophilic addition of **3** to 2-bromo-5-nitrobenzamide was found to afford high yields of the expected cross-coupling reaction products.

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## SCHEME 3



coupling–cyclization process when an excess of **3** is used, and the requirement for excess amounts of **3** is likely due to the acidic imide proton of the product quenching **3**. The structure of **10** was confirmed by MS and  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR analysis. The  $^{13}\text{C}$ – $^{19}\text{F}$  coupling constant ( $J = 236$  Hz) of the  $\alpha$ -carbon atom with the  $\alpha,\alpha$ -gem-fluorine atoms was measured in the  $^{13}\text{C}$  NMR of **10**. The chemical shift of the imide proton ( $\delta$  12.6 ppm) was also observed in the  $^1\text{H}$  NMR of **10**, and the downfield chemical shift reflects the increased acidity of the imide proton. The  $\text{p}K_{\text{a}}$  of the imide proton of **10** was determined to be 4.11 by a potentiometric titration in DMSO/ $\text{H}_2\text{O}$  (1:4) according to the methods developed by Bates and Benet,<sup>15</sup> which was in close agreement with the calculated  $\text{p}K_{\text{a}}$  of 4.23 for **10**.<sup>16</sup> Both the experimental and calculated  $\text{p}K_{\text{a}}$  values indicate that the fluorinated **10** is greatly more acidic than the nonfluorinated analogue (calculated  $\text{p}K_{\text{a}}$  8.90), and thus the increased acidity of the imide proton makes the  $\alpha,\alpha$ -difluorohomophthalimides **2** a potential carboxylic acid bioisotere.

A series of *N*-unsubstituted  $\alpha,\alpha$ -difluorohomophthalimides with a free imide proton were prepared in an analogous manner with 2-iodobenzamides as precursor (Scheme 3). Due to a scarcity of available 2-iodobenzamides, we prepared a key 2-iodobenzamide containing a distal carboxylic acid. Thus, methyl 4-carboxyl-2-iodobenzoate **12**<sup>17</sup> was prepared from methyl 4-carboxyl-2-aminobenzoate **11** by a diazotization with *tert*-butyl nitrite in  $\text{CH}_3\text{CN}/\text{DMSO}$  (1:1) followed by an iodide displacement with NaI in the same reaction medium. The conversion of ester **12** to **13** was effected by amidation with aqueous ammonium hydroxide. Acid **13** was coupled with a variety of amines by using DPPA as the coupling agent to afford the 2,4-disubstituted aryl iodides **14a–g**.

Iodides **14a–g** were reacted as before with 3 equiv of **3** and 0.8 equiv of CuBr to give the *N*-unsubstituted  $\alpha,\alpha$ -difluorohomophthalimides **15a–g**. The yields of **15a–g** after purification were 70–93%, as summarized in Table 2. The reaction proceeds with good to excellent yields for substrates bearing a variety of functionalities such as an ester, amide, sulfonamide, and nitro group. It is interesting to note that neither the formation of the acidic imide proton in the products nor the presence of an acidic sulfonamide proton in the substrate (entry 3) interferes with the overall transformation.

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(16) The  $\text{p}K_{\text{a}}$  of **10** and other compounds were calculated with Daylight software from Daylight Chemical Information Systems, Inc.

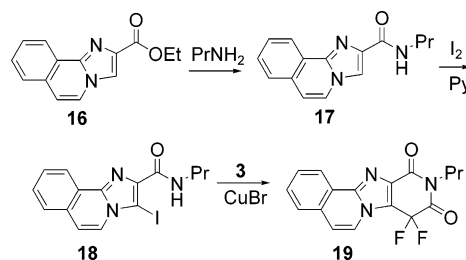
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TABLE 2. Formation of  $\alpha,\alpha$ -Difluorohomophthalimides<sup>a</sup>

entry	Amine	product	yield (%) <sup>b</sup>
1		<b>15a</b>	90
2		<b>15b</b>	92
3		<b>15c</b>	70
4		<b>15d</b>	77
6		<b>15e</b>	89
7		<b>15f</b>	83
8		<b>15g</b>	93

<sup>a</sup> All reactions were carried out with 2-iodobenzamides **4** (0.12–0.15 mmol), CuBr (0.10–0.12 mmol), and bromozinc- $\alpha,\alpha$ -difluoroacetate **3** in DMF (0.36–0.45 mmol) at room temperature for 24 h. <sup>b</sup> Yields of isolated products.

## SCHEME 4



The reaction was then extended to other aryl iodides such as 3-iodoimidazo[1,2- $\alpha$ ]pyridine (Scheme 4). Under the same conditions, 3-iodoimidazo[1,2- $\alpha$ ]pyridine **18** exhibited a reactivity similar to that of **4** and **14**; the desired product **19**, however, was obtained along with ca. 20% of **17** when **3** was added to a mixture of **18** and CuBr as before. It was envisioned that a zinc–iodide exchange between **3** and **18** generated an aryl anion intermediate, which was protonated during the workup to give **17** as a byproduct. To circumvent this problem, a homogeneous solution of **3** with CuBr in DMF was prepared in situ at  $-30$  °C and reacted with the aryl iodide **18**. The product **19** was obtained in 80% yield from **18**, and only a small amount of **17** (usually less than 2%) was detected by HPLC.

In summary, we have discovered a mild and efficient method for the preparation of novel  $\alpha,\alpha$ -difluorohomophthalimides utilizing available 2-halobenzamides as starting materials. Both the *N*-substituted and parent un-

substituted  $\alpha,\alpha$ -difluorohomophthalimides **2** have been synthesized by the tandem cross-coupling–cyclization process. The reaction proceeds in good to excellent yields for a variety of 2-iodoarylamides bearing diverse functionalities, and represents a novel method for the synthesis of fluorinated heterocyclic compounds. The unsubstituted  $\alpha,\alpha$ -difluorohomophthalimide **10** shows moderate acidity ( $pK_a$  4.11) in aqueous solution, and we anticipate that this new acid mimetic will find broad application in medicinal chemistry. Efforts at conducting the described chemistry on the solid phase and the evaluation of biological activity of compounds from this class will be reported in due course.

## Experimental Section

**Preparation of Bromozinc- $\alpha,\alpha$ -difluoroacetate **3**.** To a mixture of zinc dust (1.1 g, 17 mmol) and anhydrous DMF (2.0 mL) in an oven-dried vial was added trifluoroacetic acid (20  $\mu$ L) under  $N_2$ . The mixture was stirred at room temperature for 5 min, and DMF (12 mL) was added. A solution of ethyl bromo- $\alpha,\alpha$ -difluoroacetate (566 mg, 2.8 mmol) in DMF (3 mL) was added to the reaction mixture at room temperature, and the vial was shaken until it warmed (ca. 5–10 min). The mixture was then shaken for another 2 h and was centrifuged to give a clear solution of bromozinc- $\alpha,\alpha$ -difluoroacetate **3** in DMF. The actual concentration of **3** in DMF was estimated to be ca. 0.12 M.<sup>11</sup>

**General Procedure for the Preparation of  $\alpha,\alpha$ -difluorohomophthalimide (**6**).** To a mixture of *o*-iodoarylamide (**4**) (0.15 mmol) and CuBr (0.12 mmol) in an oven-dried vial was added a solution of bromozinc- $\alpha,\alpha$ -difluoroacetate **3** in DMF (3 mL, 0.36 mmol) under  $N_2$ . After the mixture was stirred at room temperature for 18 h, a solution of 2 N aqueous ammonium chloride (5 mL) and  $CH_2Cl_2$  (5 mL) were added. The aqueous layer was washed with  $CH_2Cl_2$ , and the combined organic layers were washed with brine, eluted through a short pad of  $SiO_2$  to removed inorganic residues, and concentrated under reduced pressure. The residue was dissolved in  $CH_3CN$  and purified by preparative HPLC on a  $C_{18}$  column to give **6** with >99% purity as determined by HPLC analysis.

**2-(2,4-Dimethoxybenzyl)-4,4-difluoro-7-methylisoquinoline-1,3(2H,4H)-dione (**6a**).** Colorless powder (47 mg, 88%). <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  2.48 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 5.18 (s, 2H), 6.41 (m, 2H), 7.13 (d,  $J$  = 8.8 Hz, 1H), 7.60 (d,  $J$  = 8.0 Hz, 1H), 7.76 (d,  $J$  = 8.0 Hz, 1H), 8.03 (s, 1H); <sup>13</sup>C NMR  $\delta$  21.64, 39.99, 55.52, 98.79, 104.38, 106.27, 116.40, 125.72, 128.21, 128.45, 128.69, 129.72, 129.95, 135.42, 143.28, 158.63, 160.76, 162.05, 162.67; MS (ESI, positive) calcd for  $C_{19}H_{17}F_2NO_4$  361.11, found 362.1 (M + H)<sup>+</sup>, 384.0 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{19}H_{17}F_2NO_4$  (361.11): C, 63.15; H, 4.74; N, 3.88. Found: C, 62.81; H, 4.70; N, 3.85.

**4,4-Difluoro-7-nitroisoquinoline-1,3(2H,4H)-dione (**10**).** The 2-bromobenzamide **9** (612 mg, 2.5 mmol) and CuBr (258.2, 1.8 mmol) were reacted with bromozinc- $\alpha,\alpha$ -difluoroacetate **3** in DMF (62 mL, 7.5 mmol) under the same conditions, and the crude product was purified on a  $SiO_2$  column (MeOH/ $CHCl_3$ , 2:98) to give **10** (480 mg, 80%) as light yellow powder. <sup>1</sup>H NMR ( $CD_3SOCD_3$ )  $\delta$  8.20 (d,  $J$  = 8.4 Hz, 1H), 8.60–8.65 (m, 2H); <sup>13</sup>C NMR  $\delta$  105.23 (t,  $J_{CF}$  = 236 Hz), 122.83, 127.91, 127.96, 128.05, 128.08, 129.20, 136.35, 136.60, 136.84, 150.21, 161.10, 161.87, 162.16, 162.45; <sup>19</sup>F NMR  $\delta$  –18.65; MS (ESI, negative) calcd for  $C_9H_4F_2N_2O_4$  242.01, found 240.9 (M – H)<sup>+</sup>. Anal. Calcd for  $C_9H_4F_2N_2O_4$  (242.01): C, 44.64; H, 1.67; N, 11.57. Found: C, 44.97; H, 1.78; N, 11.45.

**4-(Aminocarbonyl)-3-iodobenzoic Acid (**13**).** To a solution of NaI (18.0 g, 120 mmol) in  $CH_3CN$  (100 mL) were added a solution of methyl 4-carboxyl-2-aminobenzoate (**11**) (8.98 g, 46 mmol) in  $CH_3CN$ /DMSO (1:1, 16 mL) and *tert*-butyl nitrite (6.8 g, 66 mmol). To the above solution was slowly added trifluoroacetic acid (0.6 mL) under stirring at room temperature. The mixture was slowly heated to 65 °C over 45 min and stirred at 65 °C for another 1 h. The reaction mixture was concentrated

under reduced pressure and diluted with  $CHCl_3$ . The organic layer was washed with brine, dried over  $MgSO_4$ , and concentrated under reduced pressure. The crude ester **12** (6.12 g, 20 mmol) was dissolved in 28% ammonium hydroxide (80 mL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and acidified with 3 N aqueous HCl to pH 3. The resulting precipitates were collected and washed with cold water and ether to give acid **13** (3.78 g, 90%) as a light yellow powder. <sup>1</sup>H NMR ( $CD_3SOCD_3$ )  $\delta$  7.44 (d,  $J$  = 8.0 Hz, 1H), 7.96 (dd,  $J$  = 8.0, 1.8 Hz, 1H), 8.34 (m, 1H); <sup>13</sup>C NMR  $\delta$  93.16, 128.15, 129.12, 132.82, 140.03, 147.35, 165.79, 170.48; MS (ESI, negative) calcd for  $C_8H_6INO_3$  209.94, found 290.0 (M – H)<sup>+</sup>.

**General Procedure for the Preparation of  $\alpha,\alpha$ -difluorohomophthalimides (**15**).** Iodobenzamides **14** (0.12–0.15 mmol) and CuBr (0.10–0.12 mmol) were reacted with bromozinc- $\alpha,\alpha$ -difluoroacetate **3** in DMF (0.36–0.45 mmol) under the same conditions. The crude products were purified by preparative HPLC on a  $C_{18}$  column to give **15** with >99% purity as determined by HPLC analysis.

***N*-[2-(2-Chlorophenyl)ethyl]-4,4-difluoro-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-6-carboxamide (**15a**).** Colorless powder (51 mg, 90%). <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  3.12 (t,  $J$  = 7.2 Hz, 2H), 4.68 (t,  $J$  = 7.2 Hz, 2H), 7.22 (m, 2H), 7.30–7.39 (m, 2H), 8.18 (m, 1H), 8.27 (m, 2H); <sup>13</sup>C NMR  $\delta$  32.87, 39.84, 124.53, 127.02, 128.13, 128.75, 129.42, 130.80, 131.21, 134.04, 136.83, 140.34, 153.02, 153.30, 166.48; MS (ESI, negative and positive) calcd for  $C_{18}H_{13}ClF_2N_2O_3$  378.06, found 377.0 (M – H)<sup>+</sup>, 379.2 (M + H)<sup>+</sup>, 401.1 (M + Na)<sup>+</sup>. Anal. Calcd for  $C_{18}H_{13}ClF_2N_2O_3$  (378.06): C, 57.08; H, 3.46; N, 7.40. Found: C, 56.98; H, 3.52; N, 7.38.

**3-Iodo-*N*-propylimidazo[2,1- $\alpha$ ]isoquinoline-2-carboxamide (**18**).** Iodine (570 mg, 2.25 mmol) was added to a solution of **17** (283 mg, 1.12 mmol) in pyridine (2.5 mL), the mixture was stirred at 60 °C for 6 h, and pyridine was evaporated under reduced pressure. The mixture was dissolved in  $CH_2Cl_2$  and washed with 2 N aqueous  $Na_2S_2O_3$  solution and water. The organic layer was concentrated, and the crude product was dissolved in  $CH_3CN$  and purified by preparative HPLC on a  $C_{18}$  column to give **18** as light yellow powder (386 mg, 91%). <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  1.00 (t,  $J$  = 7.3 Hz, 3H), 1.68 (m, 2H), 3.44 (m, 2H), 7.20 (d,  $J$  = 7.5 Hz, 1H), 7.62–7.69 (m, 2H), 7.72–7.76 (m, 1H), 7.76–7.82 (b, 1H), 8.03 (d,  $J$  = 7.5 Hz, 1H), 8.60 (m, 1H); <sup>13</sup>C NMR  $\delta$  11.66, 23.14, 41.31, 11533, 123.42, 123.61, 127.48, 129.05, 129.75, 130.55, 137.72, 145.33, 162.08; MS (ESI, positive) calcd for  $C_{15}H_{14}IN_3O$  379.02, found 380.0 (M + H)<sup>+</sup>. Anal. Calcd for  $C_{15}H_{14}IN_3O$  (379.02): C, 47.51; H, 3.72; N, 11.08. Found: C, 47.21; H, 3.78; N, 10.93.

**7,7-Difluoro-9-propyl-7H-6a,9,11-triazabenzoc[ $\alpha$ ]fluorene-8,10-dione (**19**).** A solution of bromozinc- $\alpha,\alpha$ -difluoroacetate **3** (4.1 mL, 0.5 mmol) was added to a slurry of CuBr (35 mg, 0.25 mmol) in anhydrous DMF (1 mL) at –30 °C under  $N_2$ . After the mixture was stirred at –30 °C for 30 min, a solution of **18** (95 mg, 0.25 mmol) in DMF (1.5 mL) was slowly added. After this solution was stirred at room temperature for 18 h, a solution of 2 N aqueous ammonium chloride (12 mL) and  $CH_2Cl_2$  (10 mL) were added. The aqueous layer was extracted with  $CH_2Cl_2$ , and the combined organic layers were washed with brine and concentrated under reduced pressure. The residue was dissolved in  $CH_3CN$  and purified by preparative HPLC on  $C_{18}$  column to give **19** as colorless powder (66 mg, 80%). <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$  0.99 (t,  $J$  = 7.3 Hz, 3H), 1.68 (m, 2H), 3.99 (m, 2H), 7.38 (d,  $J$  = 7.5 Hz, 1H), 7.71–7.82 (m, 3H), 8.08 (d,  $J$  = 7.1 Hz, 1H), 8.82 (m, 1H); <sup>13</sup>C NMR  $\delta$  11.30, 21.39, 42.61, 117.37, 121.71, 123.61, 125.14, 127.64, 129.75, 130.56, 131.01, 147.47, 158.45, 162.52; MS (ESI, positive) calcd for  $C_{17}H_{13}F_2N_3O_2$  329.10, found 330.1 (M + H)<sup>+</sup>. Anal. Calcd for  $C_{17}H_{13}F_2N_3O_2$  (329.10): C, 62.00; H, 3.98; N, 12.76. Found: C, 61.43; H, 4.03; N, 12.61.

**Supporting Information Available:** Experimental procedures and compound characterization (<sup>1</sup>H and <sup>13</sup>C NMR, HPLC, and MS) for all the compounds described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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