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# Practical Synthesis of A Benzophenone-Based NNRT Inhibitor of HIV-1

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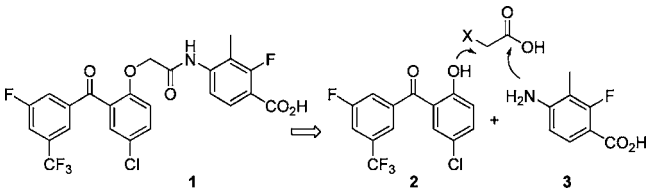
Supporting Information

**ABSTRACT:** A convergent synthesis of NNRTI 1 is described. The key step involves a direct coupling of acid chloride **4** with Grignard reagent **11** in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl] ether that moderates the reactivity of the Grignard reagent to give benzophenone **7**. An efficient 2-step process for the preparation of 2-fluoro-3-methyl-4-aminobenzoic acid (**3**) is also described.

## INTRODUCTION

Non-nucleoside reverse transcriptase inhibitors (NNRTI) represent an important class of agents for the treatment of HIV infections and AIDS.[1] Benzophenone-based NNRTIs have emerged as effective second generation inhibitors exhibiting high potency against both wild-type and resistant strains of the virus.[2] Recently, our drug discovery program produced a series of novel and potent benzophenone-based NNRTIs such as candidate **1** (Scheme 1), and we were interested in developing an efficient process for **1** on pilot plant scale.

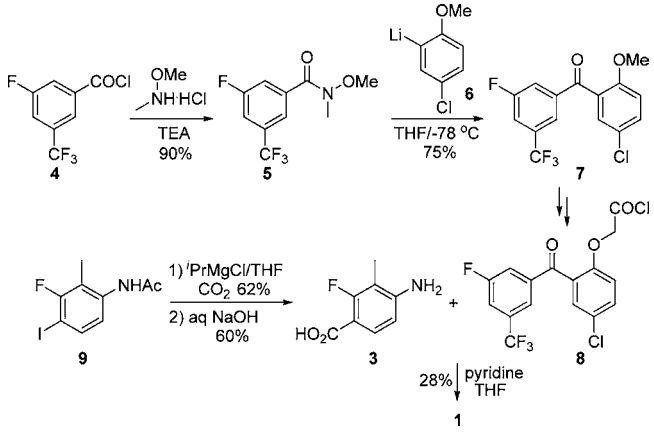
**Scheme 1. Retrosynthetic Analysis of 1**



Retrosynthetically, compound **1** can readily be disconnected to two key intermediates, benzophenone **2** and aniline **3**, with a $\alpha$-haloacetic acid derivative as a linkage (Scheme 1).

An initial synthesis of **1** involved the formation of benzophenone **2** *via* the addition of lithium species **6** to Weinreb amide **5**.[3] However, this process required an additional step for the preparation of the Weinreb reagent (Scheme 2). Intermediate **3** was formed by I/Mg exchange of iodide **9** followed by addition of gaseous $CO_2$ and hydrolysis of the acetyl protection group. This process proceeded in only moderate yield, producing unacceptable amounts of the protonated analogue of **3** as the main byproduct. The coupling of acid chloride **8** with aniline **3** gave compound **1** in only <30% yield, primarily due to the instability of acid chloride **8** under the basic conditions and the complication of the unprotected carboxylic acid group in **3**. Because of these drawbacks, this initial synthesis was not suitable for the production of large quantities of material, and a more robust synthesis was necessary to support the production of **1**.

**Scheme 2. Initial Synthesis of 1**



## RESULTS AND DISCUSSION

We investigated several approaches for the construction of benzophenone **7**. Friedel–Crafts reaction between 4-chloroanisole and acid chloride **4** in the presence of various Lewis acids gave **7** only in low yield. Similarly, Fries reaction of benzoate **10** produced phenolic benzophenone **2** in <20% yield.[4] Recently, we reported a direct, nontransition-metal-catalyzed addition of Grignard reagents to acid chlorides for the synthesis of benzophenones,[5] and therefore, we applied this methodology to the synthesis of **7**.

We were pleased to find that treatment of acid chloride **4** in THF with a preformed complex of Grignard reagent **11** and bis[2-(*N*,*N*-dimethylamino)ethyl] ether (BDMAEE) at −10 to 0 °C for 1 h produced benzophenone **7** in 80% isolated yield. The process was quite efficient, and there was no need for an aqueous workup. Once the reaction was complete, filtration to remove the magnesium BDMAEE complex was followed by removal of the solvent. Crystallization from IPA/water gave the product **7** (Scheme 3). Only a small amount of overaddition

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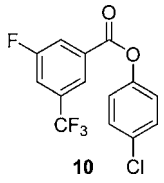

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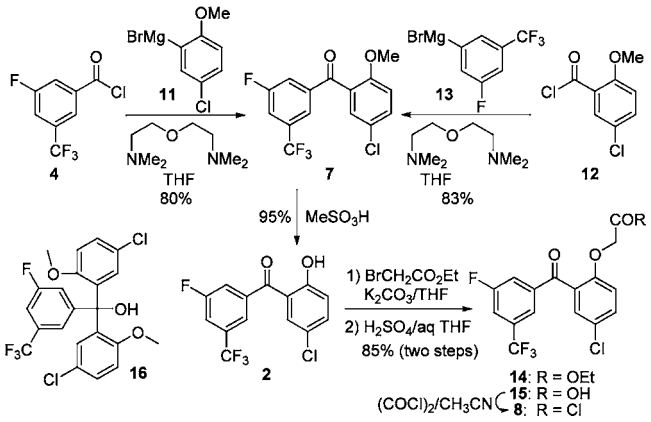
**Scheme 3. Synthesis of Benzophenone 2 by Addition of Grignard Reagents to Acid Chlorides in the Presence of BDMAEE**



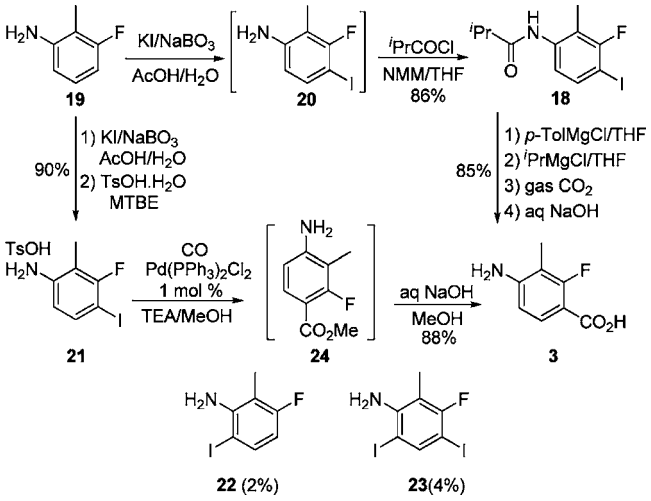
product **16** (<3%) was observed. The complexation of the Grignard reagent with BDMAEE moderated the reactivity of the aromatic magnesium species and suppressed the formation of **16**.

The alternative sequence in which the complex of Grignard reagent **13** and BDMAEE was added to acid chloride **12** gave **7** in a slightly higher isolated yield (83%). It was reported that the preparation of trifluoromethylaryl magnesium reagents could lead to an uncontrollable exothermic reaction with the potential for detonation.[6] Although Grignard reagent **13**, prepared by Br/Mg exchange of the corresponding bromide with *i*PrMgCl in THF, showed no exothermic properties on Reactive System Screening Tool (RSST), this approach to **7**, offering no advantage over the one from **4** and **11**, was not used for the scale-up. With an efficient synthesis of **7** available, demethylation of **7** to phenolic **2** was examined. Although many Lewis acid-promoted demethylation methods are available (for example, $BBr_3$),[7] we used the most practical approach, involving treatment of **7** in methanesulfonic acid at 100 °C for 4 h, which produced **2** in 95% isolated yield. The presence of the adjacent carbonyl group assisted this demethylation process. Next, the linkage between **2** and **3** was assembled by alkylation of **2** with ethyl bromoacetate in the presence of $K_2CO_3$ in THF. The crude ethyl ester **14** was hydrolyzed in aqueous THF with sulfuric acid, and free acid **15** was isolated by crystallization from a mixture of isopropylacetate and heptane (85% yield over the two steps). Acid chloride **8** was prepared in acetonitrile, and the solution was used for the subsequent coupling reaction with **3**.

Concurrently, we tried to improve the synthesis of the aniline fragment **3**. Application of Knochel's procedure (the successive addition of *p*-TolMgCl and *i*PrMgCl)[8,9] to the unprotected aniline-iodide **20** followed by the bubbling of $CO_2$ gave unacceptable amounts of the protonated product **19** (>30%) in addition to the desired **3** (see Scheme 4).

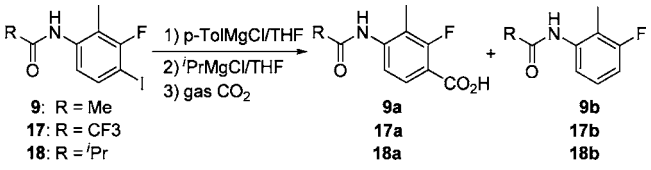
To develop an efficient approach for I/Mg exchange and subsequent carboxylation, we investigated the protected aniline–iodide derivatives **9**, **17**, and **18** in this transformation. The

**Scheme 4. Synthesis of Aniline Fragment 3**



successive addition of *p*-TolMgCl (10 min) and *i*PrMgCl (20 min) to **9** followed by the bubbling of $CO_2$ to the resulting dimagnesium derivative gave the desired **9a** in only 62% isolated yield together with 34% of the protonated **9b**. When I/Mg exchange was allowed to age for prolonged times of 40 and 60 min prior to the addition of $CO_2$, respectively (entries 2 and 3, Table 1), a trend of increased conversion to the protonated

**Table 1. I/Mg Exchange for Carboxylation**



**9**: R = Me
**17**: R = CF3
**18**: R = *i*Pr

**9a** **17a** **18a** **9b** **17b** **18b**

| entry | iodide | time for I/Mg exchange (min) | yield of **a** (%)[a] | yield of **b** (%)[a] |
|---|---|---|---|---|
| 1 | **9** | 20 | 62 | 34 |
| 2 | **9** | 40 | 50 | 45 |
| 3 | **9** | 60 | 41 | 53 |
| 4 | **17** | 20 | 92 | 5 |
| 5 | **18** | 20 | 90 | 5 |
| 6 | **18** | 44 | 88 | 6 |

[a]Isolated by flash chromatography on silica gel.

product **9b** was observed. This may reflect the internal quench of the resulting magnesium species by the active acetyl protons.[10] When trifluoroacetamide **17**, which lacks acidic $\alpha$-protons, was subjected to the same reaction sequence, there was a significant reduction in the formation of the protonated product, and the desired carboxylic acid **17a** was isolated in 92% yield. Interestingly, isobutyramide **18** gave the carboxylic acid **18a** in 90% isolated yield with only 5% of protonated **18b** under the same conditions, even with a prolonged aging for I/Mg exchange. One explanation might be that the steric demand of the isopropyl group may have inhibited the internal quench of the resulting magnesium species by the presence of the active $\alpha$-proton.[11] Considering the cost of isobutyryl chloride vs TFAA, we had an efficient synthesis of **3** using isobutyramide **18** as a key intermediate. Thus, after iodination of aniline **19** with KI/$NaBO_3$ in a mixture of AcOH and water,[12] the crude solid **20** was treated with isobutyryl chloride in the presence of NMM to give **18** in 86% yield after crystallization from MTBE/heptane.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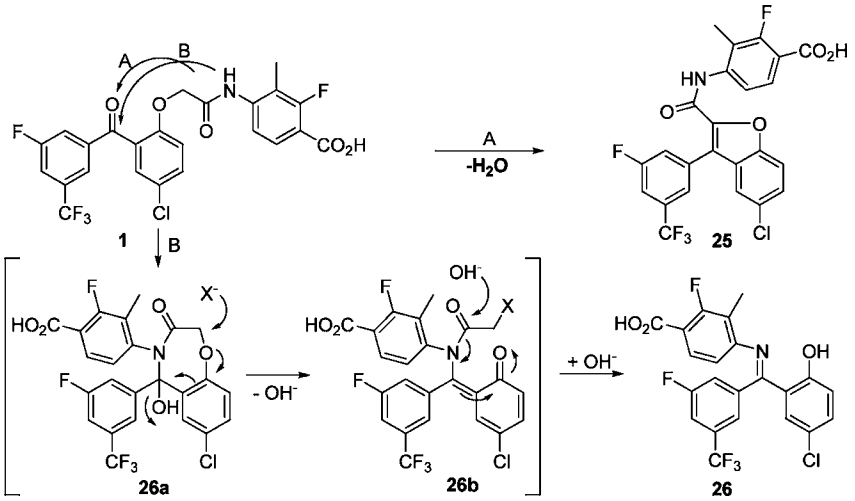
**Scheme 5. Possible Pathways to Byproducts 24 and 25 from 1**



The metalation-carbonylation sequence produced the acid, which was not isolated but used as a crude **18a** in toluene. Extraction into aqueous NaOH then served as a purification step to remove byproduct, such as protonated **18b**. Deprotection of the isobutyramide of this aqueous solution at 80 °C for 8 h, followed by neutralization with aqueous HCl, gave **3** in 85% overall yield (Scheme 4).

An alternative approach for the introduction of the carboxylate of **3** by carbonylation of iodo-aniline **20** was also identified (Scheme 4).[13] It was observed that iodination of **19** with KI/$NaBO_3$ in a mixture of AcOH and water was both regio- and chemoselective, producing **20** together with only 2% of regioisomer **22** and 4% of diiodide **23**. Formation of the *p*-toluenesulfonic acid salt by treatment of crude **20** in MTBE gave pure **21**, free of regioisomer **22** and diiodide **23**. Carbonylation of **21** was performed with 1 mol % of $Pd(PPh_3)_2Cl_2$ in the presence of TEA in methanol at 60 °C under CO at atmospheric pressure for 8 h. The resulting crude **24** in methanol which contained about 10 area % of dimer, trimer by HPLC was directly saponified to give **3** in 88% isolated yield.

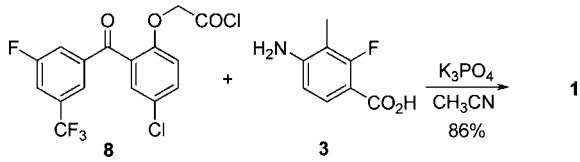
The coupling of acid chloride **8** and aniline **3** bearing an unprotected carboxylic acid was performed next. When inorganic bases such as sodium hydroxide or organic bases such as pyridine were used for the coupling, a low to moderate yield of **1** was obtained. We observed two major byproducts, **25** (4−8%) and **26** (~10%), generated from **1** through proposed pathways A and B, respectively, in the presence of base, as rationalized in Scheme 5. The formation of these two byproducts and the instability of **8** under the conditions led to a moderate recovery of **1** as described in the initial synthesis (Scheme 2).

We had recently developed a general and efficient method for the coupling of acyl chlorides and amino derivatives, which utilized potassium phosphate tribasic as base.[14] With this mild condition, the coupling of **8** and **3** was performed using $K_3PO_4$ as base in acetonitrile to give product **1** in 86% yield as shown in Scheme 6. The poor solubility of $K_3PO_4$ in acetonitrile may reduce the basicity of the reaction mixture, minimizing side reactions.

## SUMMARY AND CONCLUSION

In summary, we have developed a concise, robust process for the production of NNRTI **1**. The synthesis involves a direct coupling of acid chloride with Grignard reagent for the synthesis of benzophenone in the presence of BDMAEE that moderates the reactivity of the Grignard reagent to circumvent the overaddition. Furthermore, a mild and efficient coupling of acid chloride with aniline **3** bearing a nonprotected carboxylic acid was utilized. NNRTI 1 was produced on pilot plant scale for development activities.

**Scheme 6. Coupling of Acid Chloride 8 with Aniline 3 to 1**



## EXPERMENTAL SECTION

**General.** HPLC monitoring for all reactions was carried out with the use of a commercially available reverse-phase column (Zorbax Eclipse XDB-C8) eluted with 0.05% TFA in water (A) and 0.05% TFA in acetonitrile (B) according to the following conditions: flow rate of 1.0 mL/min.; wavelength of 254 nm; column temperature of 20 °C; injection volume of 5 μL; at $t$ = 0 min, 10% eluent B; at $t$ = 4 min, 30% eluent B; at $t$ = 10 min, 90% eluent B; at $t$ = 11 min, 95% eluent B; at $t$ = 16 min, 95% eluent B. Relative retention time: 1 for comound **1**; 1.08 for **2**; 0.54 for **3**; 1.11 for **7**; 1.11 for **14**; 0.99 for **15**; 0.93 for **18**; 0.81 for **18a**; 0.68 for **18b**; 0.88 for **20**/**21**; 0.90 for **22**; 1.07 for **23**; 0.98 for **25**; 1.06 for **26**. Grignard reagent **11** was purchased from commercial sources.

**(5-Chloro-2-methoxyphenyl)[3-fluoro-5-(trifluoromethyl)phenyl]methanone (7).** To a 1 M solution of 2-methoxy-5-chloromagnesium bromide (**11**) (4520 mL, 4.52 mol) in THF was added bis[2-(*N*,*N*-dimethylamino)ethyl] ether (723 g, 4.52 mol) at 0 °C over 30 min. The resulting mixture was transferred to a solution of 3-fluoro-5-trifluoromethylbenzoyl chloride (**4**) (1000 g, 4.42 mol) in THF (2000 mL) at −5 to 0 °C over 30 min. After being stirred at −5 to 0 °C for 1 h, the mixture was filtered. The filter cake was washed with THF (700 mL). The combined organics were concentrated to ~3000 mL, and IPA (3500 mL) was added. The solution was concentrated to ~2300 mL. To this solution was added water (500 mL) at 60 °C over 30 min, and the slurry was cooled to 20 °C over 30 min.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After being stirred at 20 °C for 2 h, the solids were collected by filtration and dried in an oven to give **7** as white crystals (1200 g, 80%). mp 93−95 °C; $^1$H NMR (500 MHz, $CDCl_3$) 7.82 (s, 1H), 7.66 (d, $J$ = 8.5 Hz, 1H), 7.53 (d, $J$ = 7.5 Hz, 1H), 7.49 (d, $J$ = 9.0 Hz, 1H), 7.42 (s, 1H), 6.97 (d, $J$ = 9.0 Hz, 1H), 3.71 (s, 3H); $^{13}$C NMR (500 MHz, $CDCl_3$) 192.1, 162.4 (d, $J$ = 249.3 Hz), 156.0, 140.4 (d, $J$ = 6.4 Hz), 132.8, 132.7 (dq, $J$ = 7.5, 33.6 Hz), 129.7, 128.4, 126.3, 122.9 (q, $J$ = 272.3), 122.1 (m), 119.5 (d, $J$ = 22.4), 116.9 (m), 113.3, 55.3; HRMS calculated for $C_{15}H_9ClF_4O_2$ $[M + H]^+$: 333.0299, Found: 333.0306.

A small amount of **16** was isolated by flash chromatography on silica gel: mp 134−135 °C; $^1$H NMR (400 MHz, $CDCl_3$) 7.82 (s, 1H), 7.81−7.65 (m, 1H), 7.35−7.29 (m, 3H), 7.19 (d, $J$ = 2.8 Hz, 2H), 6.86 (d, $J$ = 7.2 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) 167.5 (q, $J$ = 3.0 Hz), 161.9 (d, $J$ = 246.0 Hz), 155.1, 149.9 (d, $J$ = 7.0 Hz), 133.8 (d, $J$ = 8.0 Hz), 133.0, 129.4, 129.0, 126.5 (d, $J$ = 2.0 Hz), 126.3, 121.1 (d, $J$ = 24.0 Hz), 116.5 (d, $J$ = 24.0 Hz), 113.3, 79.0 (d, $J$ = 1.0 Hz), 55.7; HRMS calculated for $C_{22}H_{16}F_4Cl_2O_3$ $[M + H]^+$: 474.0413, Found: 474.0413.

**5-Chloro-2-(hydroxyphenyl)[3-fluoro-5-(trifluoromethyl)phenyl]methanone (2).** A solution of **7** (1000 g, 3.01 mol) in methanesulfonic acid (2000 mL) was heated to 100 °C for 12 h. The solution was cooled to room temperature, and toluene (5000 mL) was added. The mixture was washed with water (3500 mL × 2), and the organic was concentrated to ∼2000 mL. IPA (3000 mL) was added, and the solution was concentrated to ∼2500 mL. This operation was repeated one more time. To this solution was added water (4500 mL) at 50 °C over 60 min, and the slurry was cooled to 20 °C over 60 min. After being stirred at 20 °C for 2 h, the solids were collected by filtration and dried in an oven to give **2** as light yellow crystals (910 g, 95%). mp 85−87 °C; $^1$H NMR (500 MHz, $CDCl_3$) 11.55 (s, 1H), 7.73 (s, 1H), 7.59 (d, $J$ = 8.0 Hz, 1H), 7.55 (d, $J$ = 7.5 Hz, 1H), 7.50 (d, $J$ = 9.0 Hz, 1H), 7.43 (s, 1H), 7.07 (d, $J$ = 9.0 Hz, 1H); $^{13}$C NMR (500 MHz, $CDCl_3$) 197.4, 162.1 (d, $J$ = 251.1 Hz), 161.9, 140.0 (d, $J$ = 6.6 Hz), 137.2, 133.4 (dq, $J$ = 7.5, 33.6 Hz), 131.6, 124.0, 122.6 in 85% (q, $J$ = 272.3 Hz), 121.5 (m), 120.6, 119.4 (d, $J$ = 22.8 Hz), 118.9, 116.5 (m); HRMS calcd for $C_{15}H_9ClF_4O_2$ $[M + H]^+$: 333.0299, Found: 333.0306.

**[4-Chloro-2-(3-fluoro-5-trifluoromethylbenzoyl)-phenoxy]acetic Acid (15).** To a mixture of **2** (900 g, 2.82 mol) and potassium carbonate (390 g, 2.82 mol) in THF (5000 mL) was added ethyl bromoacetate (490 g, 2.88 mol). The resulting mixture was heated to reflux for 2 h. After being cooled to 20 °C, the mixture was filtered through a pad of Celite (150 g), and the filter cake was washed with THF (100 mL). The combined organics layer of ethyl [4-chloro-2-(3-fluoro-5-trifluoromethylbenzoyl)phenoxy]acetate (**14**) in THF was used directly for the preparation of **15** without isolation. A small amount of **14** was isolated by flash chromatography on silica gel as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) 7.90 (s, 1H), 7.73 (d, $J$ = 8.4 Hz, 1H), 7.51 (d, $J$ = 8.0 Hz, 1H), 7.44 (m, 2H), 6.80 (m, 1H), 4.51 (s, 2H), 4.17 (q, $J$ = 7.2 Hz, 2H), 1.21 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (400 MHz, $CDCl_3$) 191.9 (d, $J$ = 2.0 Hz), 167.5, 162.4 (d, $J$ = 249.0 Hz), 161.1, 140.3 (d, $J$ = 7.0 Hz), 132.7 (dq, $J$ = 7.5, 33.6 Hz), 132.6, 130.1, 129.0, 127.4, 122.9 (q, $J$ = 272.0 Hz), 122.2 (m), 120.1 (d, $J$ = 22.0 Hz), 117.0 (m), 113.7, 65.5, 61.6, 14.0; HRMS calcd for $C_{18}H_{13}ClF_4O_4$ $[M + NH_4]^+$: 422.0776, Found: 422.0790.

To the THF solution of **14** was added 46% sulfuric acid (2920 g, 13.9 mol). The resulting mixture was heated to reflux for 6 h. A distillation was performed to ∼3500 mL, and isopropyl acetate (5000 mL) was added. The mixture was washed with water (3000 mL × 2) and concentrated to ∼2000 mL. To this solution was added heptane (5000 mL), and a distillation was performed to ∼2000 mL. An additional amount of heptane (5000 mL) was added at 20 °C over 30 min, and the white solid was collected by filtration to give **15** (904 g, 85%). mp 148−150 °C; $^1$H NMR (500 MHz, MeOD-$d_4$) 7.91 (s, 1H), 7.79 (d, $J$ = 8.5 Hz, 1H), 7.69 (d, $J$ = 8.0 Hz, 1H), 7.54 (d, $J$ = 9.0 Hz, 1H), 7.45 (s, 1H), 7.06 (d, $J$ = 9.0 Hz, 1H), 4.63 (s, 2H); $^{13}$C NMR (500 MHz, MeOD-$d_4$) 193.5 (d, $J$ = 2.0 Hz), 171.0, 163.9 (d, $J$ = 247.9 Hz), 155.9, 142.0 (d, $J$ = 6.6 Hz), 133.8, 133.7 (dq, $J$ = 7.5, 33.6 Hz), 130.8, 130.1, 127.9, 124.5 (q, $J$ = 270.1 Hz), 123.1 (m), 121.1 (d, $J$ = 22.8 Hz), 118.0 (m), 115.5, 66.0; HRMS calcd for $C_{16}H_9ClF_4O_4$ $[M + NH_4]^+$: 394.0463, Found: 394.0483.

**2-Fluoro-3-methyl-4-(isobutyryl)aminophenyl Iodide (18).** To a mixture of 2-methyl-3-fluoroaniline (**19**) (400 g, 3.20 mol) and $NaBO_3{\cdot}4H_2O$ (492 g, 3.20 mol) in a 1:1 mixture of acetic acid and water (2000 mL) was added a solution of KI (531 g, 3.20 mol) in water (2000 mL) at 5−10 °C over 30 min. After being stirred at 20 °C for 1 h, an additional amount of water (1500 mL) was added over 30 min. The product was collected by filtration and washed with water to give crude 2-fluoro-3-methyl-4-aminophenyl iodide (**20**) as a light brown solid.

The crude **20** was dissolved in THF (3000 mL), and *N*-methylmorpholine (420 mL, 3.84 mol) was added. To the resulting solution was added isobutyryl chloride (375 g, 3.52 mol) at 0−10 °C over 1 h. The resulting mixture was quenched with the addition of water (8000 mL) over 1 h. The solids were collected by filtration and washed with water. The crude solid was slurried with a 1:1 mixture of MTBE and heptane (5000 mL) for 2 h. The product was collected by filtration and dried in an oven to give **18** as a white solid (760 g, 86%). mp 166−167 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) 9.42 (s, 1H), 7.60 (t, $J$ = 8.0 Hz, 1H), 7.07 (d, $J$ = 8.4 Hz, 1H), 2.67 (m, 1H), 2.12 (d, $J$ = 2.4 Hz, 3H), 1.12 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) 175.3, 161.1 (d, $J$ = 238.0 Hz), 138.6 (d, $J$ = 6.0 Hz), 135.1 (d, $J$ = 4.0 Hz), 122.8 (d, $J$ = 3.0 Hz), 120.3 (d, $J$ = 20.0 Hz), 76.8 (d, $J$ = 27.0 Hz), 34.3, 19.5, 10.3 (d, $J$ = 4.0 Hz); HRMS calcd for $C_{11}H_{13}FINO$ $[M + H]^+$: 322.0098, Found: 322.0112.

**2-Fluoro-3-methyl-4-(acetyl)aminophenyl Iodide (9).** Compound **9** was prepared in 89% yield according to the procedure for **18**: mp 132−134 °C; $^1$H NMR (400 MHz, MeOD-$d_4$) 7.59 (t, $J$ = 8.0 Hz, 1H), 7.04 (d, $J$ = 8.4 Hz, 1H), 2.18 (s, 3H); $^{13}$C NMR (400 MHz, MeOD-$d_4$) 172.2, 161.5 (d, $J$ = 239.0 Hz), 139.2 (d, $J$ = 6.0 Hz), 137.0 (d, $J$ = 3.0 Hz), 124.1 (d, $J$ = 4.0 Hz), 122.4 (d, $J$ = 20.0 Hz), 78.0 (d, $J$ = 28.0 Hz), 23.1, 10.6 (d, $J$ = 4.0 Hz); HRMS calcd for $C_9H_9FINO$ $[M + H]^+$: 293.9785, Found: 293.9801.

**2-Fluoro-3-methyl-4-aminophenyl Iodide TsOH Salt (21).** A solution of the crude **20** (500 g, 2.00 mol) obtained as described above in MTBE (3000 mL) was added to a suspension of *p*-toluenesulfonic acid monohydrate (380 g, 2.00 mol) in MTBE (1000 mL) over 30 min. After being stirred at room temperature for 1 h, the solid was collected by filtration and dried in an oven to give **21** (794 g, 90%). mp 180 °C (decomposed); $^1$H NMR (400 MHz, MeOD-$d_4$) 7.75 (t, $J$ = 8.0 Hz, 1H), 7.66 (ABq, $J$ = 8.0 Hz, 2H), 7.22 (ABq, $J$ = 8.0 Hz, 2H),


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7.03 (d, $J$ = 8.4 Hz, 1H), 2.38 (s, 3H), 2.31 (d, $J$ = 2.0 Hz, 3H); $^{13}$C NMR (400 MHz, MeOD-$d_4$) 161.8 (d, $J$ = 241.0 Hz), 143.3, 141.9, 138.7 (d, $J$ = 3.0 Hz), 133.1 (d, $J$ = 5.0 Hz), 129.9, 126.9, 121.9 (d, $J$ = 23.0 Hz), 121.7 (d, $J$ = 14.0 Hz), 81.9 (d, $J$ = 27.0 Hz), 21.4, 10.0 (d, $J$ = 4.0 Hz); HRMS calculated for $C_7H_7FIN$ $[M + H]^+$: 251.9685, Found: 251.9675.

A small amount of **22** was isolated by flash chromatography on silica gel: mp 89−91 °C; $^1$H NMR (600 MHz, DMSO-$d_6$) 7.45 (dd, $J$ = 8.0, 8.4 Hz, 1H), 6.30 (t, $J$ = 8.4 Hz, 1H), 2.09 (d, $J$ = 2.0 Hz, 3H); $^{13}$C NMR (600 MHz, DMSO-$d_6$) 161.0 (d, $J$ = 237.8 Hz), 147.6 (d, $J$ = 7.5 Hz), 136.0 (d, $J$ = 10.2 Hz), 108.5 (d, $J$ = 19.7 Hz), 105.1 (d, $J$ = 24.5 Hz), 77.2 (d, $J$ = 2.0 Hz), 9.7 (d, $J$ = 5.6 Hz); HRMS calculated for $C_7H_7FIN$ $[M + H]^+$: 251.9685, Found: 251.9685.

A small amount of **23** was isolated by flash chromatography on silica gel: mp 92−94 °C; $^1$H NMR (400 MHz, $CDCl_3$) 7.81 (dd, $J$ = 0.4, 6.4 Hz, 1H), 2.15 (m, 3H); $^{13}$C NMR (400 MHz, $CDCl_3$) 160.0 (d, $J$ = 239.0 Hz), 146.7 (d, $J$ = 6.0 Hz), 143.4 (d, $J$ = 3.0 Hz), 109.9 (d, $J$ = 22.0 Hz), 78.2 (d, $J$ = 3.0 Hz), 66.7 (d, $J$ = 29.0 Hz), 10.7 (d, $J$ = 5.0 Hz); HRMS calcd for $C_7H_6FI_2N$ $[M + H]^+$: 377.8652, Found: 377.8652.

**2-Fluoro-3-methyl-4-aminobenzoic Acid (3).** To a solution of **18** (655 g, 2.04 mol) in THF (2500 mL) was added 1.0 M $p$-tolylmagnesium bromide (2090 g, 2.20 mol) in THF at −10 to 0 °C over 30 min. Isopropylmagnesium chloride (2.0 M, 1070 g, 2.20 mol) in THF was then added over 20 min at the same temperature. After 10 min, gas $CO_2$ (300 g, 6.82 mol) was bubbled into the reaction mixture for 20 min at −10 to 15 °C. The reaction mixture was then quenched with 2 N HCl (2300 mL) and extracted with toluene (1500 mL). The organic phase was washed with water (2500 mL) and extracted with 2 N NaOH (2000 mL × 2). The combined extracts were heated to 80 °C with the addition of NaOH (400 g, 10.0 mol) for 8 h and cooled to 0−5 °C. To the mixture was added concentrated HCl (1130 mL) over 1 h. The slurry was filtered, and the filter cake was washed with water to give **3** (294 g, 85%) as a white solid. mp 196−198 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) 7.48 (t, $J$ = 8.0 Hz, 1H), 6.46 (d, $J$ = 9.0 Hz, 1H), 1.97 (s, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) 165.5 (d, $J$ = 3.6 Hz), 161.1 (d, $J$ = 251.4 Hz), 153.1 (d, $J$ = 8.5 Hz), 130.1 (d, $J$ = 3.4 Hz), 108.7 (d, $J$ = 1.6 Hz), 106.9 (d, $J$ = 19.1 Hz), 105.0 (d, $J$ = 11.4 Hz), 8.2 (d, $J$ = 7.4 Hz); HRMS calcd for $C_8H_8FNO_2$ $[M + H]^+$: 170.0611, Found: 170.0617.

A small amount of **18a** was isolated by crystallization from a mixture of IPA/water: mp >200 °C (decomposed); $^1$H NMR (400 MHz, DMSO-$d_6$) 9.52 (s, 1H), 7.66 (t, $J$ = 8.4 Hz, 1H), 7.41 (d, $J$ = 8.8 Hz, 1H), 2.72 (m, 1H), 2.11 (d, $J$ = 2.4 Hz, 3H), 1.12 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) 175.6, 165.0 (d, $J$ = 3.0 Hz), 159.6 (d, $J$ = 253.0 Hz), 142.1 (d, $J$ = 7.0 Hz), 128.6 (d, $J$ = 2.0 Hz), 119.7 (d, $J$ = 3 0.0 Hz), 119.4 (d, $J$ = 18.0 Hz), 115.0 (d, $J$ = 2.0 Hz), 34.4, 19.4, 9.6 (d, $J$ = 6.0 Hz); HRMS calcd for $C_{12}H_{14}FNO_3$ $[M + H]^+$: 240.1030, Found: 240.1033. A small amount of **18b** was isolated by flash chromatography on silica gel: mp 129−130 °C; $^1$H NMR (400 MHz, MeOD-$d_4$) 7.17 (m, 1H), 7.11 (d, $J$ = 8.0 Hz, 1H), 6.96 (t, $J$ = 8.4 Hz, 1H), 2.71 (m, 1H), 2.14 (d, $J$ = 2.0 Hz, 3H), 1.24 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (400 MHz, MeOD-$d_4$) 179.1, 162.8 (d, $J$ = 241.0 Hz), 138.8 (d, $J$ = 6.0 Hz), 127.7 (d, $J$ = 10.0 Hz), 123.0 (d, $J$ = 3 0.0 Hz), 122.3 (d, $J$ = 18.0 Hz), 113.8 (d, $J$ = 13.0 Hz), 36.5, 20.0, 9.9 (d, $J$ = 5.0 Hz); HRMS calcd for $C_{11}H_{14}FNO$ $[M + H]^+$: 196.1132, Found: 196.1140.

**2-Fluoro-3-methyl-4-(acetyl)aminobenzoic Acid (9a).** Compound **9a** was prepared in 62% yield according to the procedure for **18a**: mp 228−229 °C; $^1$H NMR (400 MHz, MeOD-$d_4$) 7.76 (t, $J$ = 8.0 Hz, 1H), 7.43 (d, $J$ = 8.8 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H); $^{13}$C NMR (400 MHz, MeOD-$d_4$) 172.2, 167.4 (d, $J$ = 4.0 Hz), 161.9 (d, $J$ = 255.0 Hz), 143.1 (d, $J$ = 7.0 Hz), 130.2 (d, $J$ = 3.0 Hz), 121.5 (d, $J$ = 19.0 Hz), 121.0, 116.9 (d, $J$ = 11.0 Hz), 23.3, 9.8 (d, $J$ = 6.0 Hz); HRMS calcd for $C_{10}H_{10}FNO_3$ $[M + H]^+$: 212.0717, Found: 212.0726. Compound **9b** was isolated in 34% yield: mp 114−116 °C; $^1$H NMR (400 MHz, MeOD-$d_4$) 7.17 (m, 2H), 6.95 (m, 1H), 2.17 (s, 3H), 2.15 (d, $J$ = 5.0 Hz, 3H); $^{13}$C NMR (400 MHz, MeOD-$d_4$) 172.3, 162.8 (d, $J$ = 241.0 Hz), 138.8 (d, $J$ = 6.0 Hz), 127.7 (d, $J$ = 10.0 Hz), 122.7 (d, $J$ = 3.0 Hz), 121.8 (d, $J$ = 18.0 Hz), 113.7 (d, $J$ = 23.0 Hz), 23.0, 9.8 (d, $J$ = 5.0 Hz); HRMS calcd for $C_9H_{10}FNO$ $[M + H]^+$: 168.0819, Found: 168.0827.

**4-{2-[4-Chloro-2-(3-fluoro-5-trifluoromethylbenzoyl)-phenoxy]acetylamino}-2-fluoro-3-methylbenzoic Acid (1).** To a mixture of **15** (920 g, 2.44 mol) and DMF (3.0 mL, 39 mmol) in acetonitrile (6.75 L) was added oxalyl chloride (358 g, 2.76 mol). The resulting mixture was stirred at 30 °C for 3 h and concentrated to ∼2.5 L. This solution of acid chloride **8** was used directly without isolation. This solution was added to a suspension of **3** (393 g, 2.33 mol) and $K_3PO_4$ (1000 g, 4.57 mol) in acetonitrile (4.3 L) at 0−5 °C over 30 min. After being stirred at room temperature for 10 h, the mixture was quenched by addition of 6% HCl (5.5 L) over 1 h. The resulting slurry was filtered, and the cake was washed with water to give **1** as an off-white solid after drying in an oven (1080 g, 86%). mp >200 °C (decomposed); $^1$H NMR (500 MHz, DMSO-$d_6$) 9.54 (s, 1H), 7.96 (d, $J$ = 7.0 Hz, 1H), 7.88 (s, 1H), 7.87 (d, $J$ = 8.5 Hz, 1H), 7.65 (m, 2H), 7.54 (s, 1H), 7.41 (d, $J$ = 8.5 Hz, 1H), 7.24 (d, $J$ = 8.5 Hz, 1H), 4.81 (s, 2H), 2.02 (s, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) 191.6, 165.9, 164.9, 164.8, 161.9 (d, $J$ = 247.5 Hz), 159.6 (d, $J$ = 253.4 Hz), 154.3, 140.8 (d, $J$ = 6.8 Hz), 139.9 (d, $J$ = 6.8 Hz), 132.7, 131.3 (dq, $J$ = 7.9, 33.0 Hz), 129.3, 128.7 (d, $J$ = 2.4 Hz), 128.1, 125.3, 122.8 (q, $J$ = 270.1 Hz), 121.7 (m), 120.3 (d, $J$ = 22.1 Hz), 118.9 (m), 117.4 (m), 115.4 (d, $J$ = 11.6 Hz), 115.3, 67.1, 9.3 (d, $J$ = 6.3 Hz); HRMS calcd for $C_{24}H_{15}ClF_5NO_5$ $[M + H]^+$: 528.0631, Found: 528.0642.

A small amount of **25** was isolated by prep HPLC: $^1$H NMR (500 MHz, MeOD-$d_4$) 7.80 (t, $J$ = 8.0 Hz, 1H), 7.70 (s, 1H), 7.59 (d, $J$ = 8.0 Hz, 1H), 7.50 (d, $J$ = 8.5 Hz, 1H), 7.47 (d, $J$ = 8.0 Hz, 1H), 7.43 (dd, $J$ = 2.0, 8.5 Hz, 1H), 7.17 (d, $J$ = 8.5 Hz, 1H), 7.03 (d, $J$ = 2.0 Hz, 1H), 5.29 (s, 1H), 2.27 (d, $J$ = 2.0 Hz, 3H); $^{13}$C NMR (400 MHz, MeOD-$d_4$) 167.4, 167.1, 163.9 (d, $J$ = 245.5 Hz), 161.9 (d, $J$ = 254.9 Hz), 159.4, 148.7 (d, $J$ = 7.3 Hz), 142.0 (d, $J$ = 6.8 Hz), 134.6 (dq, $J$ = 8.0, 33.0 Hz), 132.2, 130.4 (d, $J$ = 2.0 Hz), 128.4, 125.8, 124.8 (q, $J$ = 270 Hz), 122.6 (d, $J$ = 19.0 Hz), 121.6 (d, $J$ = 4.0 Hz), 121.4 (d, $J$ = 4.0 Hz), 120.7 (d, $J$ = 4.0 Hz), 119.0 (d, $J$ = 23.0 Hz), 117.6 (d, $J$ = 11.0 Hz), 113.7, 113.2 (dd, $J$ = 4.0, 25.0 Hz), 94.1, 83.7, 9.9 (d, $J$ = 7.0 Hz); HRMS calcd for $C_{24}H_{13}F_5ClNO_4$ $[M + H_2O + NH_4]^+$: 545.0897, Found: 545.0916.

A small amount of **26** was isolated by prep HPLC: $^1$H NMR (500 MHz, DMSO-$d_6$) 8.51 (s, 1H), 7.86 (d, $J$ = 8.0 Hz, 1H), 7.67 (dd, $J$ = 2.0, 8.5 Hz, 1H), 7.56 (d, $J$ = 2.0 Hz, 1H), 7.56−7.50 (m, 1H), 7.51 (d, $J$ = 8.5 Hz, 1H), 7.45 (s, 1H), 7.35 (d, $J$ = 8.5 Hz, 1H), 6.68 (d, $J$ = 8.5 Hz, 1H), 1.74 (s, 3H); $^{13}$C NMR (500 MHz, DMSO-$d_6$) 193.0, 164.9 (d, $J$ = 3.1 Hz), 161.5 (d, $J$ = 247.4 Hz), 160.2 (d, $J$ = 246.0 Hz), 147.0


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(d, $J$ = 7.4 Hz), 140.8, 140.7 (d, $J$ = 6.8 Hz), 133.7, 131.0, 130.9 (dq, $J$ = 7.9, 33.0 Hz), 129.8 (d, $J$ = 2.8 Hz), 128.5, 126.3, 124.4, 122.7 (dq, $J$ = 2.6, 270.1 Hz), 120.9 (m), 119.3 (d, $J$ = 22.5), 116.3 (dd, $J$ = 3.1, 25.2 Hz), 113.6 (d, $J$ = 19.0 Hz), 111.1, 110.8 (d, $J$ = 11.2 Hz), 8.5 (d, $J$ = 11.8 Hz); HRMS calcd for $C_{22}H_{13}F_5ClNO_3$ $[M + H]^+$: 470.0582, Found: 470.0582.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1H/^{13}C$ NMR spectra for **1**−**3**, **7**, **9**, **9a**−**b**, **14**−**16**, **17**, **17a**−**b**, **18**, **18a**−**b**, and **21**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(10) The trideuterium-acetamide of **9** was subjected to the successive addition of *p*-tolMgCl (10 min) and *i*PrMgCl (20 min) followed by MeOH quench. After saponification with aqueous NaOH, a mixture of 2-methyl-3-fluoroaniline (**19**) (81%) and the 4-deuterium analogue of **19** (19%) was obtained which evidenced the internal quench of the resulting magnesium species by the active acetyl protons.

(11) A gelatinous mixture was formed once the analogues trimethylacetamide and benzamide of **17**, both lacking acidic $\alpha$-protons, were treated with *p*-tolMgCl in THF. The insufficient stirring of the mixture was considered to be not scalable.

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