# The Expedient Synthesis of 4,2'-Difluoro-5'-(7-trifluoromethylimidazo[1,2-a]pyrimidin-3-yl)biphenyl-2-carbonitrile, a GABA $\alpha$ 2/3 Agonist

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#### **Abstract:**

An expedient regioselective synthesis of a GABA  $\alpha 2/3$  agonist 1 is described. The key step is an efficient regioselective palladium-catalyzed coupling of 7-trifluoromethylimidazo[1,2-*a*]pyrimidine (5) to 5'-chloro-4,2'-difluorobiphenyl-2-carbonitrile (15). The efficiency of this step was affected by the choice of solvent, ligand, and tetrabutylammonium salt additive.

## Introduction

General anxiety disorder is a disease that is estimated to affect over 40 million patients in the U.S.A. Gamma amino butyric acid (GABA) is the major inhibitory neurotransmitter in the CNS where it binds to GABA<sub>A</sub> receptors of which the  $\alpha 2/3$  subtype has been recognized as having anxiolytic benefit.<sup>1a</sup> Our interest in this field necessitated the development of an expedient synthesis of a potential GABA  $\alpha 2/3$  agonist drug candidate **1**.<sup>1b</sup> The synthesis was finalized (Scheme 1) by coupling intermediates **2** and **3** in 70% overall yield.

Preparation of **3** (Scheme 2) was relatively laborious and required the use of commercially expensive, atom-economypoor, bis(pinacolato)diboron reagent (**4**). More favourably, **2** was relatively straightforward to prepare (Scheme 3), with electrophilic bromination of **5** occurring regioselectively to afford **2** in good yield. Although, this route was amenable to preparing gram quantities of **1**, it was unsuitable for our needs in preparing kilogram amounts to support drug trials. The efficient palladium-catalyzed arylation of azole compounds such as imidazoles, thiazoles, and oxazoles with aryl iodides and aryl bromides has been reported.<sup>2–4</sup> Moreover, our department recently reported<sup>5</sup> the palladium-catalyzed regioselective arylation of imidazo[1,2-*a*]pyrimidine with arylbromides. Consequently, in our retrosynthetic analysis we sought to make use of this observation in developing an expedient synthesis of **1**.

## **Results and Discussion**

The reaction between ethyl vinyl ether (**6**) and trifluoroacetic anhydride (**7**) gave trifluoromethyl ketone **8** (Scheme 3) in 95% yield.<sup>6</sup> Owing to degradation on storage, it was used immediately after preparation and condensed with commercially available 2-aminoimidazole hemisulfate (**9**) to give **5**, with high regioselectivity,<sup>7</sup> in 85% yield. Alternatively, **5** could be prepared from the reaction of 2-amino-4-trifluoropyrimidine (**10**) with bromoacetaldehyde diethyl acetal (**11**), with similar regioselectivity,<sup>7</sup> in 83% yield. With efficient syntheses of **5** in hand, the palladium-catalyzed coupling of **5** to the biaryl bromide **12** was investigated.

In polar aprotic solvents such as DMF, DMAc, and NMP with  $Cs_2CO_3$  as the base<sup>8</sup> and 2–5 mol % Pd(OAc)<sub>2</sub>/2 PPh<sub>3</sub> coupling of **5** to **12** gave the desired<sup>9</sup> compound **1** (Scheme 4). However, during the course of the reaction formation of the regioisomer **13**, formation of the bis-coupled product **14** occurred, while the concentration<sup>10</sup> of **1** decreased. Presumably, initial coupling occurred in the desired 3-position; however, under these conditions isomerization via a Dimroth-type rearrangement<sup>11</sup> (Scheme 5) occurred to give the regioisomer **13** that in turn coupled to give **14**.

No reaction was observed in either refluxing THF or 2-methyltetrahydrofuran; however, to our satisfaction, when the reaction was performed in 1,4-dioxane at 90 °C, coupling occurred, with minimal formation of **13**, to give **1** in 80–85% yield. Although it was gratifying to obtain **1** in high yield, the preparation of **12** was inefficient for our purposes. With the recent advances in ligand design efficient Heck

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<sup>(7)</sup> By HPLC assay. 5:5a ratio 24:1. 5a readily rejected by swishing 5 in heptane.

<sup>(8)</sup> Cs<sub>2</sub>CO<sub>3</sub> afforded significantly higher yields than K<sub>3</sub>PO<sub>4</sub>, Li<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, or dicyclohexylmethylamine.

<sup>(9)</sup> Catalyst systems prepared from Pd(OAc)<sub>2</sub> were more efficient than those prepared from Pd(dba)<sub>2</sub>, Pd<sub>2</sub>(dba)<sub>3</sub>, PdCl<sub>2</sub>, or Pd(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>.

<sup>(10)</sup> HPLC analysis of the reaction mixture against authentic samples of 1 and 13. Confirmed by <sup>1</sup>H NMR, 400 MHz in CDCl<sub>3</sub> signal for <u>H2</u> (8.25 ppm) and <u>H3</u> (8.70 ppm). Bis-coupled product 14, LC/MS data, and absence of H2 and H3 protons in <sup>1</sup>H NMR spectrum.

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<sup>a</sup> (i) Pd(PPh<sub>3</sub>)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, THF, 65 °C.

Scheme 2<sup>a</sup>



<sup>a</sup> Reagents and conditions: (i) Pd(dppf)<sub>2</sub>Cl<sub>2</sub>, KOAc, 1,4-dioxane, 90 °C. (ii) 2-Bromo-5-fluorobenzonitrile (17), Pd<sub>2</sub>(dba)<sub>3</sub>, P(t-Bu)<sub>3</sub>, KF, THF, 50 °C. (iii) H<sub>2</sub>, PtO<sub>2</sub>, EtOH, (iv) NaNO<sub>2</sub>, CuBr, HBr,1,4-dioxane. (v) diboronpinacolato Pd(dppf)<sub>2</sub>Cl<sub>2</sub>, KOAc, 1,4-dioxane.

Scheme 3<sup>a</sup>



<sup>a</sup> Reagents and conditions: (i) (CF<sub>3</sub>CO)<sub>2</sub>O (7), pyridine, CH<sub>2</sub>Cl<sub>2</sub>. (ii) guanidine hydrochloride, EtOH, NaOH. (iii) 2-aminoimidazole hemisulfate (9), NaOMe, EtOH. (iv) bromoacetaldehyde diethyl acetal (11), conc HBr, EtOH, reflux. (v) Br2, KBr, NaOAc, MeOH, 0-5 °C.

couplings to aryl chlorides<sup>12</sup> have become possible. The coupling of 5 with the biaryl chloride 15 was an attractive option since 15 could easily be prepared in short order from the coupling of the boronic acid 16 to commercially available 2-bromofluorobenzonitrile (17) to give 15 in 92% yield. The boronic acid 16 itself was readily prepared from ortholithiation<sup>13</sup> of commercially available 4-chlorofluorobenzene (18) by lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in THF

Table 1. Comparison of yields for coupling<sup>a</sup> 5 to 15, with various ligands and Bu<sub>4</sub>NX

	· · /		DUAINA	(%)
		,	· .	. ,
1	<1	2	$22^b$	<1
l <sub>2</sub> Ni(PPh <sub>3</sub> ) <sub>2</sub>	<1	4	$23^b$	3
4	3	6	25	4
$d[(t-Bu)_3P]_2$	10	$8^c$	$P(t-Bu)_3$	20
6	22	$10^{c}$	19	20
0	25	$12^{c}$	19/Bu <sub>4</sub> NCl	26
9/Bu <sub>4</sub> NI	36	$14^{c}$	19/Bu <sub>4</sub> NBr	50
0/Bu <sub>4</sub> NBr	63	16 <sup>c</sup>	20/Bu <sub>4</sub> NCl	75
0/Bu <sub>4</sub> NHSO <sub>4</sub>	88	$18^{c}$	20/Bu <sub>4</sub> NOAc	85
	d[( <i>t</i> -Bu) <sub>3</sub> P] <sub>2</sub> 6 0 9/Bu <sub>4</sub> NI 0/Bu <sub>4</sub> NBr 0/Bu <sub>4</sub> NHSO <sub>4</sub>	d[( <i>t</i> -Bu) <sub>3</sub> P] <sub>2</sub> 10 <b>6</b> 22 <b>0</b> 25 <b>9</b> /Bu <sub>4</sub> NI 36 <b>0</b> /Bu <sub>4</sub> NBr 63 <b>0</b> /Bu <sub>4</sub> NHSO <sub>4</sub> 88	$\begin{array}{cccccccc} d[(t-Bu)_{3}P]_{2} & 10 & 8^{c} \\ 6 & 22 & 10^{c} \\ 0 & 25 & 12^{c} \\ 9/\mathrm{Bu}_{4}\mathrm{NI} & 36 & 14^{c} \\ 0/\mathrm{Bu}_{4}\mathrm{NBr} & 63 & 16^{c} \\ 0/\mathrm{Bu}_{4}\mathrm{NHSO}_{4} & 88 & 18^{c} \end{array}$	$d[(t-Bu)_3P]_2$ 10 $8^c$ $P(t-Bu)_3$ $6$ 22 $10^c$ $19$ $0$ 25 $12^c$ $19/Bu_4NCl$ $9/Bu_4NI$ 36 $14^c$ $19/Bu_4NBr$ $0/Bu_4NBr$ 63 $16^c$ $20/Bu_4NCl$ $0/Bu_4NHSO_4$ 88 $18^c$ $20/Bu_4NOAc$

at -75 °C with in situ quenching of the anion with  $B[O(i-Pr)]_{3}^{14}$  followed by an acidic work up to afford 16 in 90% yield (Scheme 6). Although, the corresponding 3-bromo-6-fluorobenzeneboronic acid could also be prepared in this fashion in high yield, subsequent coupling to 17 resulted, as one might expect, in a mixture of coupled products.

The initial results (Table 1, entries 1-13) for the coupling of 5 to 15 with ligands 19 to 26 (Figure 1) were disappointing. Encouragingly, more favorable results were obtained under Jeffrey-type<sup>15</sup> conditions. For ligand biphenyl-di-tertbutylphosphine (19), yields increased upon the addition of tetrabutylammonium salts (Table 1, entries 12-14). Interestingly, no reaction was observed when Me<sub>4</sub>NBr or Et<sub>3</sub>BnNBr were used as additives. More synthetically useful yields

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Scheme 5





<sup>*a*</sup> Reagents and conditions: (i) LiTMP, -75 °C, THF, B[O(*i*-Pr)]<sub>3</sub>. (ii) 2 N HCl. (iii) 2-Bromo-5-fluorobenzonitrile (**17**), Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub>, KF, THF 0 to 20 °C.

(Table 1, entries 16-18) were obtained with the ligand X-phos 20 in combination with Bu<sub>4</sub>NHSO<sub>4</sub>, Bu<sub>4</sub>NOAc, or Bu<sub>4</sub>NCl. Indeed the combination of **20** with Bu<sub>4</sub>NHSO<sub>4</sub> was found particularly useful in coupling of 5 to challenging electron-rich aryl chlorides such as 4-chlorotoluene and 4-chloroanisole to give their relevant coupling products 27 and 28 (Scheme 4) in 72 and 77% yields, respectively. It is not clear the exact role Bu<sub>4</sub>NHSO<sub>4</sub> plays when used in conjunction with ligands such as 19 or 20. Little (<2%) reaction was observed in the absence of either ligand, and it seems unlikely that phase transfer catalysis is in play since a beneficial effect was not observed for tetramethylammonium or triethylbenzylammonium salts. More likely, addition of the salt leads to the formation of a stabilized anionic Pd(0) species,<sup>16</sup> thus allowing sufficient turnover of the Heck cycle to drive the reaction to completion before loss of

catalytic activity is observed. In conclusion, a convergent six-step synthesis of our GABA  $\alpha 2/3$  agonist 1 has been developed via the regioselective palladium-catalyzed coupling of 5 to 15 in 80–90% yield. Key to the efficiency of this coupling was the use of 1,4-dioxane as solvent, Cs<sub>2</sub>CO<sub>3</sub> as base, X-phos (20) as the ligand, and addition of 10 mol % Bu<sub>4</sub>NOAc or Bu<sub>4</sub>NHSO<sub>4</sub>. The combination of X-phos (20) and Bu<sub>4</sub>NHSO<sub>4</sub> was found to be useful for the coupling of 5 to challenging electron-rich aryl chlorides such as 4-chlorotoluene and 4-chloroanisole.



Figure 1. Ligands employed in coupling 5 to 15.

## Experimental

**General.** For <sup>19</sup>F NMR (H decoupled)  $\delta$  values were measured against CFCl<sub>3</sub> as reference. The HPLC assay for the determination of concentration and final purity of **1** was performed with an YMC ODS AQ 5  $\mu$  (250 mm × 4.6 mm)

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column at 25 °C, and compounds were detected at 215 nm. Separation was achieved by employing a gradient elution (90% A for 5 min, then to 10% A over 15 min, and then held at 10% A for a further 15 min) of two mobile phases A and B at a flow rate of 1.0 mL min<sup>-1</sup>. Phase A consisted of 0.1% phosphoric acid in water, and phase B consisted of acetonitrile. Melting points were uncorrected.

Preparation of 7-Trifluoromethylimidazo[1,2-a]pyramidine (5). Method A. To a stirred mixture of 9 (1.7 g, 12.7 mmol) and NaOMe (1.4 g, 13.1 mmol) in ethanol (17 mL) at 0 °C was added 8 (2.5 g, 15.2 mmol). The mixture stirred for 1 h, and then was heated at reflux temperature for 2 h. The mixture cooled to ambient temperature and was filtered. The filter cake was washed with ethanol (40 mL), and the organic filtrates were combined and volatiles evaporated in vacuo. The residue was suspended in heptane (30 mL) and stirred at ambient temperature for 16 h. The suspension was filtered and the solid washed with heptane (5 mL) and dried to afford 4 (2.0 g, 10.8 mmol) in 85% yield. Mp 163–164 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>Cl) δ 7.24 (1H, d, J = 7.2 Hz), 7.77 (1H, d, J = 1.2 Hz), 8.03 (1H, d, J = 1.2 Hz), 8.72 (1H, d, J = 7.2 Hz). <sup>19</sup>F NMR (376 MHz, CD<sub>3</sub>Cl)  $\delta$  -68.78 (s). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>Cl)  $\delta$  147.0  $(q, {}^{2}J_{CF} = 36.9 \text{ Hz}), 138.3, 135.0, 120.5 (q, J = 275.5 \text{ Hz})$ 112.1, 104.8 (q, J = 2.4 Hz). HRMS calcd for (M<sup>•+</sup> + H) 188.0430, found 188.0437.

*Method B.* To a stirred suspension of **10** (101.8 g, 624.3 mmol) and **11** (120.0 mL, 773.6 mmol) in ethanol (600 mL) was added concd HBr (50 mL). The mixture was heated at reflux temperature for 3 h and then cooled to ambient temperatue and stirred for a further 16 h. The mixture cooled to 0 °C, and 50% NaOH was added slowly (50 mL) followed by water (200 mL). The mixture was extracted with isopropyl acetate (2 × 300 mL); the organic extracts were combined and volatiles evaporated in vacuo. The residue was suspended in heptane (600 mL) and stirred for 2 h at ambient temperature. The suspension was filtered, and the solids were washed with heptane (50 mL) and dried in vacuo to give **4** (97.0 g, 518.4 mmol) in 83% yield.

Preparation of 3-Chloro-6-fluorobenzeneboronic Acid (16). To a stirred solution of 2,2,6,6-tetramethylpiperidine (18.6 mL, 110.2 mmol) in dry THF (200 mL) at -50 °C, under an atmosphere of nitrogen, was added hexyllithium 2.3 M in hexane (47.8 mL, 109.9 mmol) slowly over 30 min and was stirred for a further 45 min at -50 °C. The solution was then chilled to -75 °C, and trisopropylborate (25.8 mL, 111.8 mmol) was added slowly over 30 min. The solution stirred at -75 °C for 15 min, and 18 (11.0 mL, 103.3 mmol) was added dropwise; stirring continued at -75 °C for 5 h. Glacial acetic acid (40 mL) was then added and the resulting slurry warmed to ambient temperature. The mixture was partitioned between water (950 mL) and isopropyl acetate (150 mL). The two layers were separated, and the aqueous phase was extracted with isopropyl acetate (100 mL). The organic solutions were combined and volatiles evaporated in vacuo to residue that was recrystallized from isopropyl acetate/hexane and gave 16 (16.1 g, 92.7 mmol) in 90% yield. Mp 206–207.5 °C. <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO)

δ 7.1 (1H, t, J = 8.8 Hz), 7.43 (1H, ddd, J = 2.8, 4.8, 8.8 Hz), 7.48 (1H, dd, J = 2.8, 4.8 Hz), 8.37 (2H, br). <sup>19</sup>F NMR (379 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) δ -107.5. <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>Cl) δ 164.4 (d, J = 244.9 Hz), 135.4 (d, J = 10.4 Hz), 135.0 (d, J = 8.8 Hz), 131.7 (d, J = 3.2 Hz), 125.5 (br), 117.5 (d, J = 26.5 Hz).

Preparation of 5-Chloro-4,2'-difluorobiphenyl-2carbonitrile (15). To a mixture of 16 (19.3 g, 110.6 mmol), 17 (20.0 g, 100.0 mmol), and potassium fluoride (15.5 g, 264.5 mmol) in THF (500 mL) at ambient temperature under an atmosphere of nitrogen was added bis(tri-tert-butylphosphino)palladium (0.14 g, 0.3 mmol). The mixture stirred for 5 h. Isopropyl acetate (400 mL) was added and the mixture filtered through SiO<sub>2</sub>. The filter cake washed with isopropyl acetate (3  $\times$  100 mL). The combined filtrate was evaporated in vacuo and the residue suspended in heptane (200 mL). The suspension stirred at ambient temperature for 30 min, and the solid was collected, washed with heptane (100 mL), and dried and gave 15 (23.0 g, 92.4 mmol) in 92% yield. Mp = 105.5-106.5 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.20 (1H, t, J = 7.2 Hz), 7.39 (1H, dd, J = 2.4, 6.4 Hz), 7.41-7.53 (4H, m). <sup>19</sup>F NMR (376 MHz, CD<sub>2</sub>Cl<sub>2</sub>) -112.0, -118.7. <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  161.9 (d, J = 251.4 Hz), 158.1 (d, J = 248.2 Hz), 134.4 (d, J = 3.2 Hz), 132.9 (dd, J = 1.6, 8.8 Hz), 131.0 (d, J = 3.2 Hz), 130.9 (d, J = 8.0Hz), 129.4 (d, J = 4.0 Hz), 126.6 (d, J = 16.9 Hz), 120.6 (d, J = 21.7 Hz), 120.1 (d, J = 24.9 Hz), 117.6 (d, J = 24.1 Hz)Hz), 116.5 (d, J = 3.2 Hz), 114.3 (d, J = 9.6 Hz). Anal. Calcd for C<sub>13</sub>H<sub>6</sub>ClFN: C, 62.54; H, 2.43; N, 5.61; Cl, 14.20; F, 15.22. Found: C, 62.33; H, 2.32; N, 5.48; Cl, 14.20; F, 15.41.

Preparation of 4,2'-Difluoro-5'-(7-trifluoromethylimidazo[1,2-a]pyrimidin-3-yl)-biphenyl-2-carbonitrile (1). Under an atmosphere of nitrogen a well-stirred, degassed mixture of 5 (5.0 g, 26.7 mmol), 15 (6.7 g, 26.7 mmol), Bu<sub>4</sub>NHSO<sub>4</sub> (0.9 g, 2.7 mmol), Cs<sub>2</sub>CO<sub>3</sub> (13.1 g, 40.1 mmol), XPhos (1.4 g, 2.9 mmol), and Pd(OAc)<sub>2</sub> (0.3 g, 1.3 mmol) in 1,4-dioxane (140 mL) was heated at 90 °C for 8 h. The mixture cooled to ambient temperature, and 1 was isolated by quenching into water. The solid formed was isolated by filtration and washed with water (100 mL) and gave 1 (11.6 g, 80 wt % pure, 23.2 mmol) in 87% yield. Pure material was obtained by recrystallization from ethanol (95%). Mp = 189 °C. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.29 (1H, d, J = 7.2 Hz), 7.43-7.49 (2H, m), 7.56 (1H, dd, J = 2.4, 8.0 Hz), 7.60-7.70 (3H, m), 8.09 (1H, s), 8.99 (1H, d, J = 7.2 Hz). <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  162.1 (d, J = 221.7 Hz), 159.5 (d, J = 218.4 Hz), 147.1, 146.4 (q, J = 36.9 Hz), 136.8, 134.6 (d, J = 4.0 Hz), 133.3 (dd, J = 2.4, 8.8 Hz), 133.2, 131.4 (d, J = 8.8 Hz), 130.9 (d, J = 3.2 Hz), 126.2 (d, J = 16.1 Hz), 124.3 (d, J = 4.0 Hz), 124.1, 120.7 (q, J)= 274.7 Hz), 120.6 (d, J = 21.7 Hz), 120.3 (d, J = 25.7Hz), 117.9 (d, J = 23.3 Hz), 117.3 (d, J = 3.2 Hz), 114.0 (d, J = 9.6 Hz), 105.1 (q, J = 1.6 Hz). HRMS calcd for (M + H) 401.0820, found 401.0825.

**4-Methyl-(7-trifluoromethyl-imidazo[1,2-***a***]pyrimidin-<b>3-yl)benzene (27).** This compound was obtained in 72% yield from the reaction of **5** with 4-chlorotoluene. Pale-yellow solid: mp 192–193 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.47 (3H, s), 7.21 (1H, d, J = 7.2 Hz), 7.38–7.40 (2H, m), 7.43–7.46 (2H, m), 8.05 (1H, s), 8.80 (1H, d, J = 7.2 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  146.1, 145.2 (q, J = 36.9 Hz), 139.7, 136.4, 132.4, 130.4, 128.0, 125.7, 124.5, 120.6 (q, J = 275.5 Hz), 104.8 (q, J = 2.4 Hz), 21.4. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –68.7. HRMS calcd for (M + H) 278.0899, found 278.0911. Anal. Calcd for C<sub>14</sub>H<sub>10</sub>F<sub>3</sub>N: C, 60.65; H, 3.64; N, 15.16; F, 20.55. Found: C, 60.65; H, 3.64; N, 15.11; F, 21.03.

**4-Methoxy-(7-trifluoromethyl-imidazo[1,2-***a***]<b>pyrimidin-3-yl)benzene (28).** This compound was obtained in 77% yield from the reaction of **5** with 4-chloroanisole. Yellow solid: mp 173.5–174.0 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.90 (3H, s), 7.07–7.11 (2H, m), 7.21 (1H, d, J = 7.2 Hz), 7.46–7.49 (2H, m), 8.01 (1H, s), 8.76 (1H, d, J = 7.2 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  160.4, 146.7, 145.9 (q, J = 36.9 Hz), 136.1, 132.3, 129.5, 125.5, 121.1 (q, J = 275.5 Hz), 119.5, 115.1, 104.7 (q, J = 2.4 Hz), 55.5. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  –68.4. HRMS calcd for (M + H) 294.0848, found 294.0854. Anal. Calcd for C<sub>14</sub>H<sub>10</sub>F<sub>3</sub>NO: C, 57.34; H, 3.44; N, 14.33; F, 19.71. Found: C, 57.29; H, 3.27; N, 14.25; F, 19.71.

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### **Supporting Information Available**

Copies of NMR data for compounds 1, 5, 15, 16, 27 and 28. This material is available free of charge via the Internet at http://pubs.acs.org.

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