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The Expedient Synthesis of 4,2′-Difluoro-5′-(7-trifluoromethylimidazo[1,2-*a*]pyrimidin-3-yl)biphenyl-2-carbonitrile, a GABA α2/3 Agonist

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Abstract:

An expedient regioselective synthesis of a GABA α2/3 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 $GABA_A$ receptors of which the α2/3 subtype has been recognized as having anxiolytic benefit.[1a] Our interest in this field necessitated the development of an expedient synthesis of a potential GABA α2/3 agonist drug candidate **1**.[1b] 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-economy-poor, 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.[2−4] Moreover, our department recently reported[5] 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.[6] 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,[7] 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,[7] 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[8] and 2−5 mol % $Pd(OAc)_2$/2 PPh_3 coupling of **5** to **12** gave the desired[9] 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[10] of **1** decreased. Presumably, initial coupling occurred in the desired 3-position; however, under these conditions isomerization via a Dimroth-type rearrangement[11] (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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(7) By HPLC assay. **5**:**5a** ratio 24:1. **5a** readily rejected by swishing **5** in heptane.

(8) Cs_2CO_3 afforded significantly higher yields than K_3PO_4, Li_2CO_3, Na_2CO_3, or dicyclohexylmethylamine.

(9) Catalyst systems prepared from $Pd(OAc)_2$ were more efficient than those prepared from $Pd(dba)_2$, $Pd_2(dba)_3$, $PdCl_2$, or $Pd(O_2CCF_3)_2$.

(10) HPLC analysis of the reaction mixture against authentic samples of **1** and **13**. Confirmed by ^1H NMR, 400 MHz in $CDCl_3$ signal for **H2** (8.25 ppm) and **H3** (8.70 ppm). Bis-coupled product **14**, LC/MS data, and absence of **H2** and **H3** protons in ^1H NMR spectrum.

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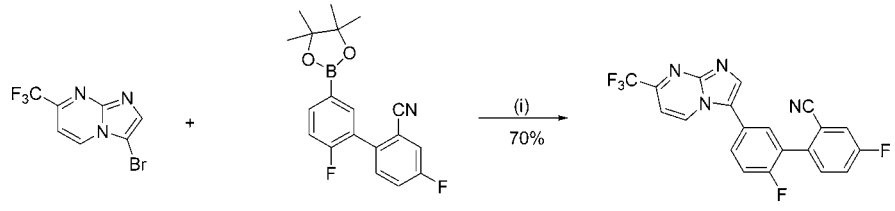
10.1021/op050217j CCC: $33.50

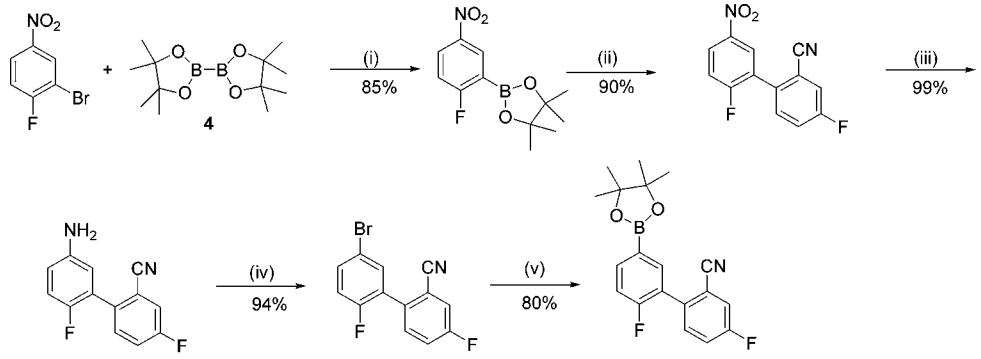
Scheme 1[a]



2 3 1

[a] (i) $Pd(PPh_3)_4$, Na_2CO_3, H_2O, THF, 65 °C.

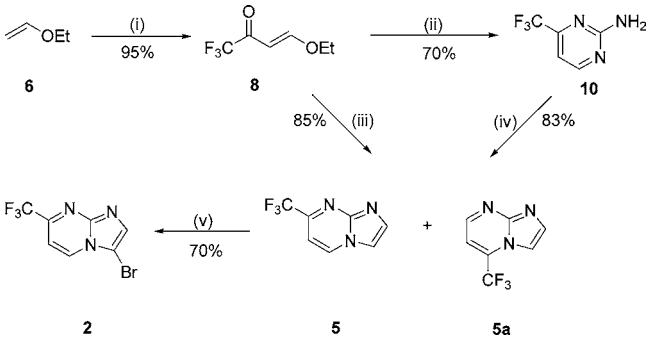
Scheme 2[a]



12 3

[a] Reagents and conditions: (i) $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 90 °C. (ii) 2-Bromo-5-fluorobenzonitrile (**17**), $Pd_2(dba)_3$, P(t-Bu)$_3$, KF, THF, 50 °C. (iii) H_2, PtO_2, EtOH, (iv) $NaNO_2$, CuBr, HBr,1,4-dioxane. (v) diboronpinacolato $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane.

Scheme 3[a]



2 5 5a

[a] Reagents and conditions: (i) $(CF_3CO)_2O$ (**7**), pyridine, CH_2Cl_2. (ii) guanidine hydrochloride, EtOH, NaOH. (iii) 2-aminoimidazole hemisulfate (**9**), NaOMe, EtOH. (iv) bromoacetaldehyde diethyl acetal (**11**), conc HBr, EtOH, reflux. (v) Br_2, KBr, NaOAc, MeOH, 0−5 °C.

couplings to aryl chlorides[12] 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[13] of commercially available 4-chlorofluorobenzene (**18**) by lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in THF at −75 °C with in situ quenching of the anion with $B[O(i\text{-}Pr)]_3$,[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.

Table 1. **Comparison of yields for coupling[a] 5 to 15, with various ligands and Bu_4NX**

entry	ligand/ Bu_4NX	yield[d] (%)	entry	ligand/ Bu_4NX	yield[d] (%)
1[b]	**21**	<1	2	**22**[b]	<1
3[b]	$Cl_2Ni(PPh_3)_2$	<1	4	**23**[b]	3
5[b]	**24**	3	6	**25**	4
7[c]	$Pd[(t\text{-}Bu)_3P]_2$	10	8[c]	P(*t*-Bu)$_3$	20
9	**26**	22	10[c]	**19**	20
11[b]	**20**	25	12[c]	**19**/Bu_4NCl	26
13[c]	**19**/Bu_4NI	36	14[c]	**19**/Bu_4NBr	50
15[c]	**20**/Bu_4NBr	63	16[c]	**20**/Bu_4NCl	75
17[c]	**20**/Bu_4NHSO_4	88	18[c]	**20**/Bu_4NOAc	85

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[15] conditions. For ligand biphenyl-di-*tert*-butylphosphine (**19**), yields increased upon the addition of tetrabutylammonium salts (Table 1, entries 12−14). Interestingly, no reaction was observed when Me_4NBr or Et_3BnNBr were used as additives. More synthetically useful yields

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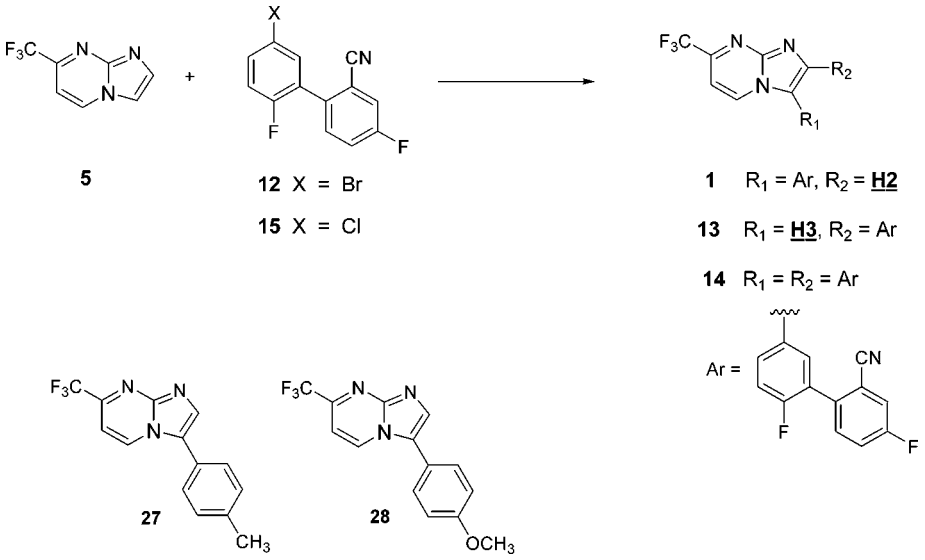
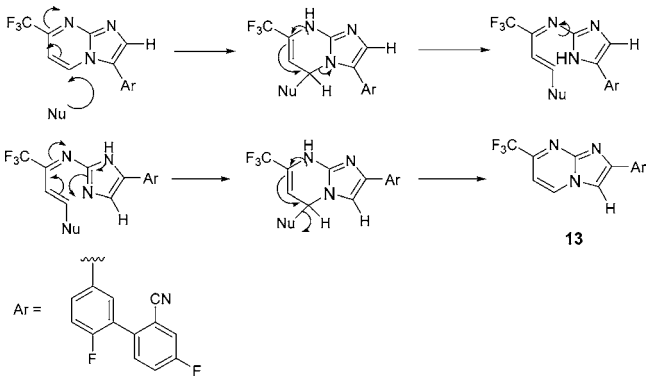
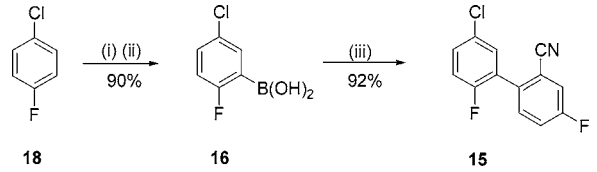
Scheme 4



Scheme 5



Scheme 6[a]



[a] Reagents and conditions: (i) LiTMP, − 75 °C, THF, B[O(*i*-Pr)]$_3$. (ii) 2 N HCl. (iii) 2-Bromo-5-fluorobenzonitrile (**17**), Pd[P(*t*-Bu)$_3$]$_2$, KF, THF 0 to 20 °C.

(Table 1, entries 16−18) were obtained with the ligand X-phos **20** in combination with Bu_4NHSO_4, Bu_4NOAc, or Bu_4NCl. Indeed the combination of **20** with Bu_4NHSO_4 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_4NHSO_4 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,[16] 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 α2/3 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_2CO_3 as base, X-phos (**20**) as the ligand, and addition of 10 mol % Bu_4NOAc or Bu_4NHSO_4. The combination of X-phos (**20**) and Bu_4NHSO_4 was found to be useful for the coupling of **5** to challenging electron-rich aryl chlorides such as 4-chlorotoluene and 4-chloroanisole.

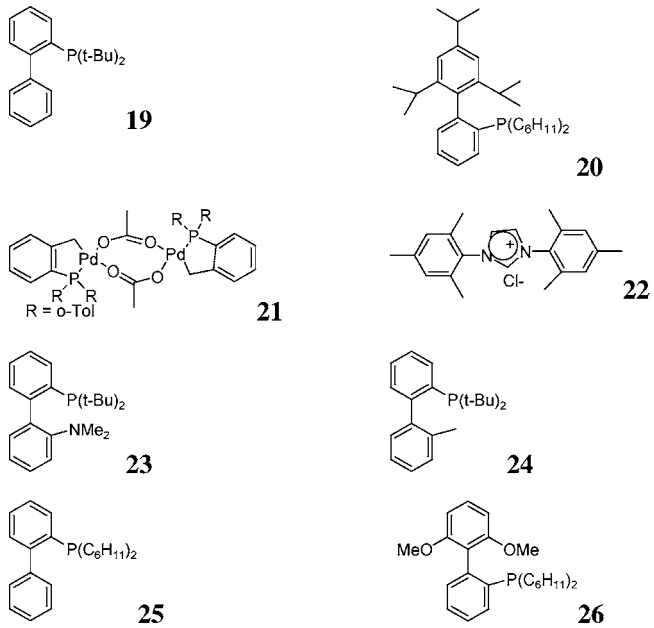


Figure 1. **Ligands employed in coupling 5 to 15.**

Experimental

General. For ^{19}F NMR (H decoupled) δ values were measured against $CFCl_3$ as reference. The HPLC assay for the determination of concentration and final purity of **1** was performed with an YMC ODS AQ 5 μ (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^{-1}. 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. ^{1}H NMR (400 MHz, CD_3Cl) 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). ^{19}F NMR (376 MHz, CD_3Cl) δ −68.78 (s). ^{13}C NMR (100 MHz, CD_3Cl) δ 147.0 (q, $^2J_{CF}$ = 36.9 Hz), 138.3, 135.0, 120.5 (q, J = 275.5 Hz) 112.1, 104.8 (q, J = 2.4 Hz). HRMS calcd for ($M^{\bullet+}$ + 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. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) 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). ^{19}F NMR (379 MHz, $(CD_3)_2SO$) δ −107.5. ^{13}C NMR (100 MHz, CD_3Cl) 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-2-carbonitrile (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_2. The filter cake washed with isopropyl acetate (3 × 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. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.20 (1H, t, J = 7.2 Hz), 7.39 (1H, dd, J = 2.4, 6.4 Hz), 7.41−7.53 (4H, m). ^{19}F NMR (376 MHz, CD_2Cl_2) −112.0, −118.7. ^{13}C NMR (100 MHz, CD_2Cl_2) δ 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 = 8.0 Hz), 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), 116.5 (d, J = 3.2 Hz), 114.3 (d, J = 9.6 Hz). Anal. Calcd for $C_{13}H_6ClFN$: 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-trifluoromethyl-imidazo[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_4NHSO_4 (0.9 g, 2.7 mmol), Cs_2CO_3 (13.1 g, 40.1 mmol), XPhos (1.4 g, 2.9 mmol), and $Pd(OAc)_2$ (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. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 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). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 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 = 25.7 Hz), 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-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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.7. HRMS calcd for (M + H) 278.0899, found 278.0911. Anal. Calcd for $C_{14}H_{10}F_3N$: 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*]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. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.4. HRMS calcd for (M + H) 294.0848, found 294.0854. Anal. Calcd for $C_{14}H_{10}F_3NO$: 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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