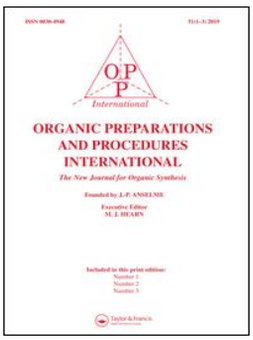

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EXPERIMENTAL PAPER

A Practical Synthesis of the Key Intermediate for Fluxapyroxad

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Fluxapyroxad (Figure 1), a broad-spectrum pyrazole-carboxamide fungicide, is commonly employed for the treatment of a large variety of commercial crops. More specifically, the application of *Fluxapyroxad* results in the inhibition of spore germination, germ tube formation, and mycelial growth within the target fungus species.[1–3] Literature reports have indicated that 3',4',5'-trifluoro-[1,1'-biphenyl]-2-amine (**1**) is considered to be a key intermediate in the synthesis of *Fluxapyroxad.* [4–7]

In the past few decades, scientists have made numerous efforts to develop efficient routes to **1**. For example, Zierke and co-workers[8] developed the route presented in Scheme 1, whereby 3,4,5-trifluorophenylzinc bromide was initially prepared by treating 3,4,5-trifluorobromobenzene with Mg and $ZnCl_2$, and **1** was subsequently obtained following Negishi coupling of the appropriate aromatic chloride with the organozinc reagent. This was achieved through the use of 0.5 mol% [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr) as the catalyst, whereby a turnover number (TON) of 184 was achieved.

Unfortunately, the high cost of PEPPSI-IPr renders this route unsuitable for larger-scale applications, and protection/deprotection of the amine moiety required a lengthy sequential operation. In addition, Heinrich *et al.*[9] reported the preparation of **1** from 3,4,5-trifluorophenylhydrazine as a radical source for the coupling reaction (Scheme 2).

However, the commercially unavailability of 3,4,5-trifluorophenylhydrazine, the use of MnO_2, and the requirement for an excess of aniline (20 equiv.) may result in serious pollution and expense upon scale-up of this route. Moreover, an undesired *para*-substituted byproduct was also obtained in 16% yield, thereby requiring the use of column chromatography to facilitate its removal. In recent years, it has also been suggested that the biaryl structure could be constructed via a Suzuki-Miyaura reaction,[10–13] which would provide a promising approach to the preparation of **1** from aryl boric acid and *o*-haloaniline (Scheme 3).[14–15] However, the requirement for large quantities of

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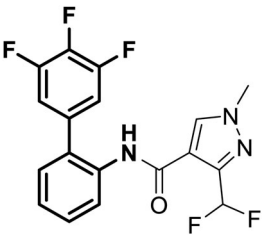
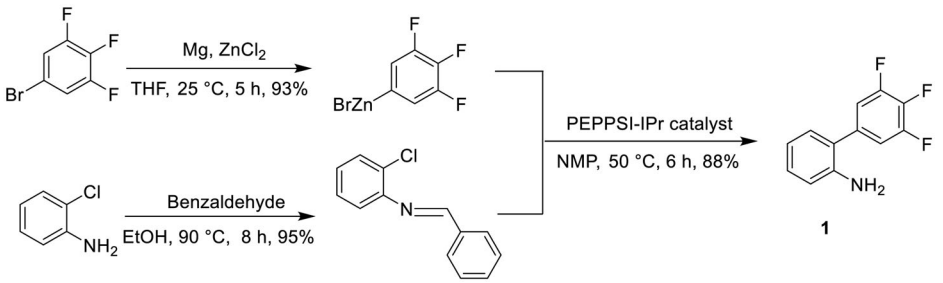


Figure 1. Structure of fluxapyroxad.



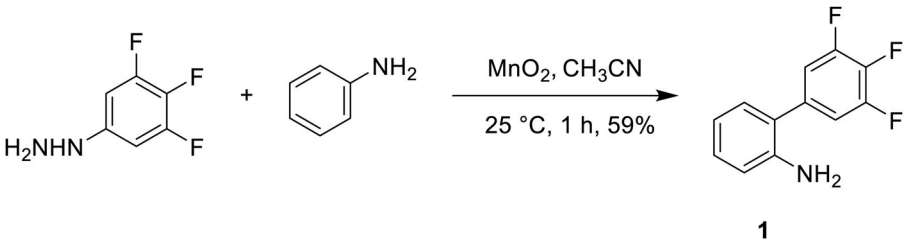
Scheme 1. Synthesis of compound **1** based on a Negishi coupling reaction.[7]

Pd-catalysts to achieve poor TONs (e.g., 3 mol% $Pd(PPh_3)_2Cl_2$ (TON = 28), or 5 mol% $Pd(PPh_3)_4$ (TON = 18.4)) rendered this process too expensive.

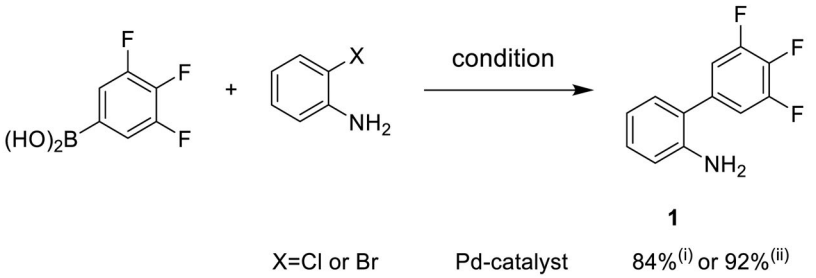
Thus, we herein report an improved synthesis of **1**. More specifically, the commercially available (3,4,5-trifluorophenyl)boronic acid (**2**) was selected as the starting material, and a new and pragmatic route employing a Suzuki-Miyaura coupling/hydrolysis/Hofmann degradation reaction was developed to generate the key intermediate compound **1** in 99.79% purity and 93% overall yield (Scheme 4). Importantly, the critical Suzuki-Miyaura coupling reaction was catalyzed by 0.02 mol% $Pd(PPh_3)_4$ to give a high TON of 4900. In this procedure, 3',4',5'-trifluoro-[1,1'-biphenyl]-2-carbonitrile (**3**) was synthesized by the reaction of 1.3 equiv of (3,4,5-trifluorophenyl) boronic acid (**2**) with *o*-chlorobenzonitrile (**4**) in toluene/water using NaOH at 85 °C (Scheme 4).

To determine the optimal conditions for this transformation, a range of bidentate bisphosphine ligands were investigated, including dppp, dppf, and $PCy_3{\cdot}HBF_4$.[16] When 1 mol% $Pd(PPh_3)_4$ was employed for the purpose of this reaction, excellent yields of **3** were obtained (Table 1, entries 2–4); this is likely due to the electron density on phosphorus facilitating the oxidative insertion of palladium into the Ar-Cl bond.[17–21] Finally, the target product was achieved in high yield using 0.02 mol% $Pd(PPh_3)_4$ and 0.04 mol% $PCy_3{\cdot}HBF_4$ (Table 1, entries 5–9).

Subsequently, the treatment of **3** with H_2SO_4 in toluene over 24 h at 80 °C yielded 3',4',5'-trifluoro-[1,1'-biphenyl]-2-formamide (**5**) in 98% yield. Finally, 3',4',5'-trifluoro-[1,1'-biphenyl]-2-amine (**1**) was prepared by the Hofmann degradation reaction of **5**, whereby the reaction proceeded smoothly using NaClO (7.5 wt%) in ethanol at 0–5 °C over 2 h, followed by stirring at 50 °C for an additional 2 h.



Scheme 2. Synthesis of compound **1** based on a radical coupling process.[8]



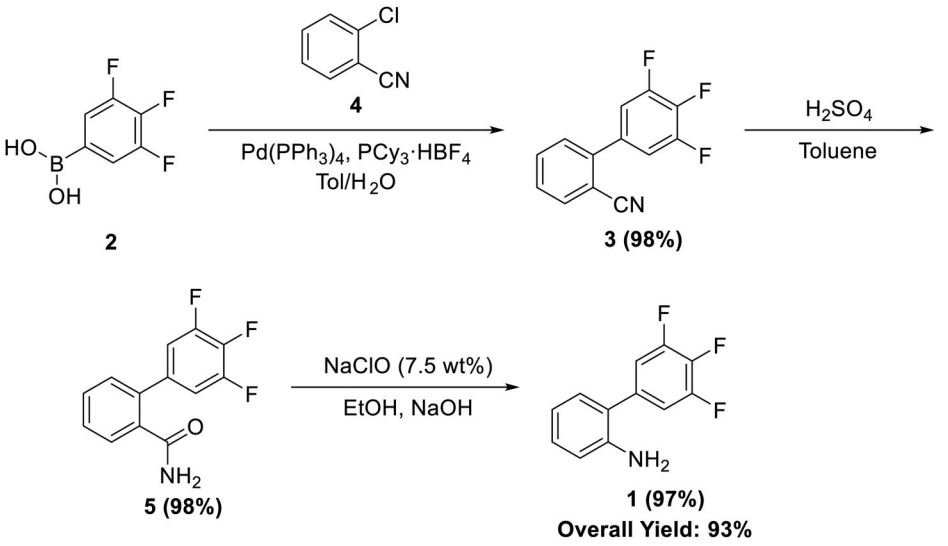
(i) $(PPh_3)_2PdCl_2$ (3 mol%), K_2CO_3, dioxane, H_2O, 70 °C, 3 h. (ii) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3, THF, H_2O, 70 °C, 16 h.

Scheme 3. Synthesis of compound **1** based on the Suzuki-Miyaura coupling reaction.[14–15]

In summary, we herein reported a cost-efficient and practical synthetic process for the key intermediate (**1**) of *Fluxapyroxad* using the commercially available (3,4,5-trifluorophenyl) boronic acid (**2**) as the starting material. This was achieved over three steps, which included Suzuki-Miyaura reaction/hydrolysis/Hofmann degradation sequence to afford the final product **1** in 93% yield and 99.79% purity. Furthermore, the Szuki-miyaura coupling reaction was successfully applied in efficiently constructing compound **3** using 0.02 mol% $Pd(PPh_3)_4$, which significantly reduced the cost.

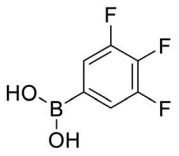
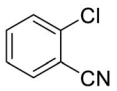
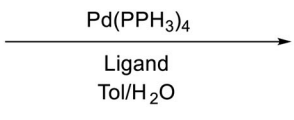
Experimental section

All solvents and reagents were purchased from commercial sources and used without further purification unless otherwise indicated. The progress of the reaction was monitored by TLC [stationary phase: silica gel, solvent: hexane/ethyl acetate (10/1)], and visualized under UV light (254 and 365 nm). Melting points (mp) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Brüker spectrometer at 600 and 150 MHz, respectively. The chemical shifts are reported as δ ppm using tetramethylsilane (TMS) as internal standard. ESI-MS analyses were performed on a Trace DSQ mass spectrometer. The HPLC analysis data are reported in area %, not adjusted to weight. High-resolution mass spectrometry (HRMS) was carried out using an Agilent 6210 TOF LC-MS. Elemental analyses (EA) were acquired on a Malvern 3000 instrument.



Scheme 4. Improved scheme for the synthesis of key intermediate **1**.

Table 1. Optimization of the Suzuki-Miyaura cross-coupling reaction.[a]

Entry	$Pd(PPh_3)_4$ (mol%)	Ligand	Yield[b](%)
	 + 		
	2	**4**	**3**
1	1	–	75
2	1	dppp	97
3	1	dppf	95
4	1	$PCy_3{\cdot}HBF_4$	99
5	0.04	$PCy_3{\cdot}HBF_4$	99
6	0.03	$PCy_3{\cdot}HBF_4$	98
7	0.02	$PCy_3{\cdot}HBF_4$	98
8	0.01	$PCy_3{\cdot}HBF_4$	93
9	0.009	$PCy_3{\cdot}HBF_4$	85

[a]Reaction conditions: **2** (0.455 mol), **4** (0.35 mol), NaOH (0.7 mol), TBAB (0.0525 mol), catalyst: ligand (n: n) = 1: 2 for 12 h in Tol/H_2O = 4/1 with N_2, 85 °C.
[b]Isolated yield of **3**.

3′,4′,5′-Trifluoro-[1,1′-biphenyl]-2-carbonitrile (3)

A 10 L, three-necked, round-bottomed flask containing *o*-chlorobenzonitrile **4** (275.8 g, 2 mol) was equipped with a rubber septum. Toluene (4 L) and H_2O (1 L) were introduced to the flask. The reaction flask was charged with tetrabutylammonium bromide (96.6 g, 0.3 mol), sodium hydroxide (160.5 g, 4 mol), (3,4,5-trifluorophenyl) boronic acid **2** (457.6 g, 2.6 mol), $Pd(PPh_3)_4$ (462 mg), and $PCy_3{\cdot}HBF_4$ (294 mg). The mixture was stirred until reaching complete dissolution, and then heated at reflux (85 °C) for 12 h. After this time, the aqueous layer was extracted with toluene (3 × 250 mL). The

combined organic fraction was dried over anhydrous magnesium sulfate, filtered, and the solvent was then concentrated under reduced pressure. The resulting yellow residue was recrystallized from ethanol and then filtered to afford pure 3',4',5'-trifluoro-[1,1'-biphenyl]-2-carbonitrile **3** as a white solid (456.7 g, 98%), mp 125-127 °C, with 98.07% purity by HPLC. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.79 (d, $J = 7.8$ Hz, 1H), 7.68 (t, $J = 7.8$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 7.19 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.47, 149.97, 142.25, 141.48, 138.95, 133.93, 133.15, 129.85, 128.70, 117.82, 113.31, 111.3; MS-ESI: 256 $[M + Na]^+$. HRMS (ESI): Calcd for $C_{13}H_6F_3N$: 234.0529, Found: 234.0525.

Anal. Calcd for $C_{13}H_6F_3N$: C, 66.96; H, 2.59. Found: C, 66.81; H, 2.59.

HPLC Conditions— Column: Welch Xtimate C18 (250 mm × 4.6 mm, 5 μm); Detection: 210 nm; Flow rate: 1.0 mL/min; Temperature: rt; Run time: 10 min; Mobile phase: acetonitrile/water = 75/25, t_R: 5.735 min, purity: 98.07%.

3',4',5'-Trifluoro-[1,1'-biphenyl]-2-carboxamide (5)

Into a 10 L three-necked round-bottomed flask were introduced 3',4',5'-trifluoro-[1,1'-biphenyl]-2-carbonitrile **3** (233.3 g, 1 mol), toluene (160 mL), and concentrated sulfuric acid (H_2SO_4, 163.4 mL, 302.3 g, 3 mol). The resulting mixture was stirred at 80 °C for 24 h and then quenched by the addition of cold H_2O (500 mL). Ethyl acetate (500 mL) was then added followed by a solution of sodium hydroxide (240.3 g, 6 mmol) in H_2O (500 g) at 25–30 °C. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The combined organic fraction was dried over anhydrous magnesium sulfate, filtered, and the solvent was then concentrated *in vacuo*. 3',4',5'-Trifluoro-[1,1'-biphenyl]-2-carboxamide **5** (245.8 g, 98%) was obtained following crystallization from ethanol, mp 139-141 °C, with 99.42% purity by HPLC. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.65 (dd, $J = 7.8$, 1.2 Hz 1H), 7.51 (td, $J = 7.8$, 1.2 Hz, 1H), 7.45 (td, $J = 7.8$, 1.2 Hz, 1H), 7.33 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.07 (m, 2H), 5.74 (s, 1H), 5.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.92, 152.28, 149.78, 140.82, 138.31, 137.06, 136.18, 134.89, 130.70, 130.20, 128.41, 112.95. MS (ESI): 250 $[M - H]^+$. HRMS (ESI): Calcd for $C_{13}H_8F_3NO$: 252.0630, Found: 252.0631.

Anal. Calcd for $C_{13}H_8F_3NO$: C, 62.16; H, 3.21. Found: C, 62.12; H, 3.29.

HPLC Conditions— Column: Welch Ultimate XB-Phenyl (250 mm × 4.6 mm, 5 μm); Detection: 210 nm; Flow rate: 1.0 mL/min; Temperature: rt; Run time: 15 min; Mobile phase: acetonitrile/water = 40/60, t_R: 4.510 min, purity: 99.42%.

3',4',5'-Trifluoro-[1,1'-biphenyl]-2-amine (1)

Into a 10 L three-necked round-bottomed flask were introduced ethanol (2.5 L), sodium hydroxide grains (160.2 g, 4 mol) and 3',4',5'-trifluoro-[1,1'-biphenyl]-2-carboxamide **5** (251.3 g, 1 mol). After stirring for 5 min, NaClO (7.5%) (1.5 L, 1.5 mol) was added, and the mixture was stirred for a futher 2 h at 0-5 °C. The reaction was then warmed to 50 °C for 2 h after which time it was allowed to cool, and extractions with dichloromethane (3 × 500 mL) were carried out. The organic fraction was dried over anhydrous magnesium sulfate, filtered and the solvent was recovered by distillation to give the

desired 3',4',5'-trifluoro-[1,1'-biphenyl]-2-amine **1** (216.3 g, 97%), mp 56-57 °C, lit[14] mp 57-58 °C, 99.79% purity by HPLC. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.19 (m, 1H), 7.15–7.08 (m, 2H), 7.07 (dd, $J = 7.6$, 1.5 Hz, 1H), 6.83 (td, $J = 7.5$, 1.1 Hz, 1H), 6.77 (dd, $J = 8.0$, 0.9 Hz, 1H), 3.76 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.28, 150.62, 143.35, 139.87, 138.20, 135.75, 130.28, 129.59, 124.53, 119.03, 116.12, 113.35. MS-ESI: 224 $[M + H]^+$.

HPLC Conditions— Column: Welch Welchrom-C_{18} (250 mm × 4.6 mm, 5 μm); Detection: 226 nm; Flow rate: 1.0 mL/min; Temperature: rt; Run time: 15 min; Mobile phase: acetonitrile/water = 80/20, t_R: 5.382 min, purity: 99.79%.

Copies of the complete NMR, MS, HRMS, EA and HPLC data were submitted for review and are available from the corresponding author upon request.

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