Trifluoromethyl-substituted pyridyl- and pyrazolylboronic acids and esters: synthesis and Suzuki–Miyaura cross-coupling reactions†

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The synthesis of trifluoromethyl-substituted pyridylboronic acids and pyrazolylboronic esters is described *via* lithiation–boronation protocols (Schemes 1, 3 and 4). A study of their palladium-catalysed cross-couplings with heteroaryl halides is presented. CF_3-substituted aryl/heteroaryl-pyridines are thereby obtained (51–98% yields). Analogous cross-couplings have yielded heteroaryl-3-(trifluoromethyl)pyrazoles (60–85% yields); homocoupling of the pyrazolylboronic esters is suppressed by the addition of potassium formate, although competing protodeboronation is observed. Halogenation of the 4-position of selected pyrazole coupling products allows for further cross-couplings to yield tetra-substituted pyrazolyl derivatives (Scheme 5). X-Ray crystal structures are reported for selected pyridylboronic acids, pyrazolylboronic esters and derived trifluoromethyl-substituted heterobiaryl systems. These multi-ring CF_3-substituted systems are of interest as building blocks for drug discovery and materials chemistry.

Introduction

The presence of a trifluoromethyl moiety can dramatically modify the physical and chemical properties of a compound making it a privileged motif in medicinal and materials chemistry when attempting to tailor a specific activity profile.[1] Trifluoromethyl-substituted heteroaryls, *e.g.* pyridines and pyrazoles, are found in several biologically active compounds,[2] for example, the insecticide Chlorfluazuron is a chitin synthesis inhibitor[3] and Aptivus® is a commercial HIV protease inhibitor.[4] Structures are shown in Chart 1. Pyrazoles bearing a trifluoromethyl group constitute the core structure of pharmaceuticals across a number of therapeutic areas:[5] Celebrex® is a COX-2 inhibitor and non-steroidal anti-inflammatory,[6] whereas SC-560 is a COX-1 inhibitor and shows anti-tumour activity (Chart 1).[7] Razaxaban and derivatives are factor Xa inhibitors used in the treatment of thrombotic diseases.[8]

The traditional methods for the incorporation of a trifluoromethyl group into organic compounds from an inorganic fluorine source[9,10] have been supplemented by more convenient procedures. These include the copper-promoted reductive coupling of aryl iodides with trifluoromethyl iodide,[11] and the in situ generation of trifluoromethylcopper species from (trifluoromethyl)trimethylsilane ("Ruppert–Prakash reagent"[12]) in the presence of copper(I) iodide and potassium fluoride for the preparation of CF_3-substituted benzene and pyridine derivatives.[13] Starting from arenes and heteroarenes functionalised with a CF_3

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† Electronic supplementary information (ESI) available: Synthetic procedures and characterisation data for new compounds, including X-ray molecular structures of compounds **3**, **27**, **30b**, **36** and **51**. CCDC reference numbers 699539–699542 and 699843. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b901024f

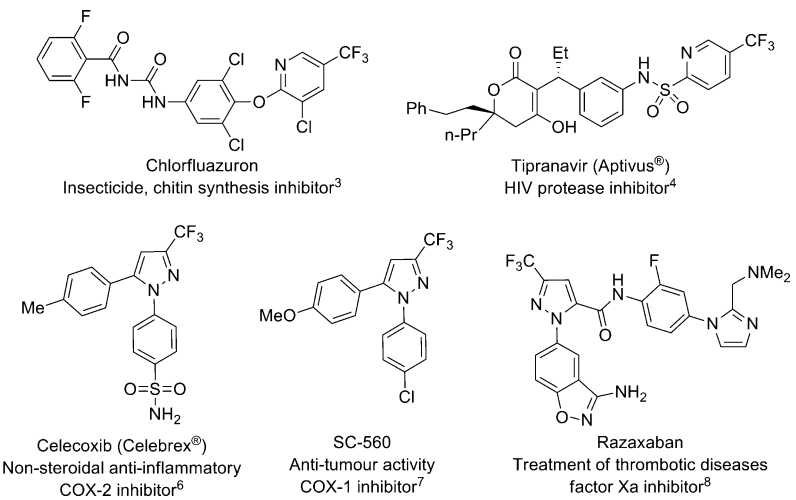


Chart 1 Examples of biologically active trifluoromethyl-substituted pyridines and pyrazoles.

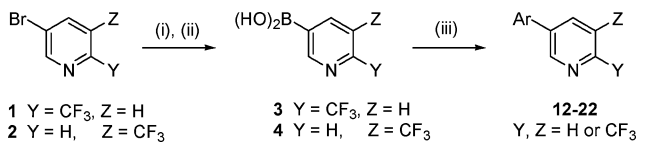
group, Schlosser *et al.* have utilised "regioexhaustive substitution" to prepare a variety of organometallic intermediates; on trapping with electrophiles these yield new fluorinated building blocks.[14]

The palladium-catalysed Suzuki–Miyaura cross-coupling of aryl/heteroarylboronic acids (or esters) with aryl/heteroaryl halides is widely used for the preparation of biaryl and heterobiaryl systems,[15] especially within the pharmaceutical industry.[16] With the increased availability of CF_3-substituted aryl/heteroaryl halides[17] and phenylboronic acid derivatives bearing CF_3 groups,[18] the Suzuki–Miyaura cross-coupling is being utilised in the preparation of aryl/heteroaryl scaffolds with trifluoromethyl functionalities.[19] Pyridylboronic acids and esters substituted with a variety of functional groups, *e.g.* alkoxy,[20] halides,[21] amides[21g] and cyano[22] are well known. In contrast, there are fewer reports of pyrazolylboronic acids in the literature.[23] It is also notable that CF_3-substituted heteroarylboronic acids are less well known,[20d,24] although they are very attractive reagents for the preparation of functionalised heterobiaryl systems.

In this article we report the preparation of CF_3-substituted pyridylboronic acids and pyrazolylboronic esters *via* lithiation/boronation of commercial CF_3-substituted starting materials. The Suzuki–Miyaura cross-couplings of these boronic acids and esters with functionalised halo-heteroaryl partners provide new trifluoromethyl-substituted heterobiaryl systems, including tetra-functionalised pyrazoles.

Results and discussion

Lithium-halogen exchange of 5-bromo-2-(trifluoromethyl)pyridine **1** and 5-bromo-3-(trifluoromethyl)pyridine **2**, with *n*-BuLi in THF at −78 °C, addition of triisopropylborate followed by aqueous workup yielded boronic acid derivatives **3** and **4**[25] as air-stable solids in 95% and 94% yields, respectively, on a *ca.* 10 g scale (Scheme 1). The X-ray crystal structure of **3** was obtained.†[26] For the boronic acids **3**, **4** and **26** satisfactory elemental analysis and mass spectrometric data could not be obtained, probably due to the isolation of a mixture of boronic acid and boroxine derivatives.

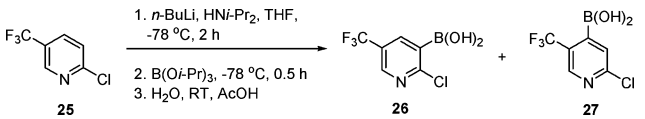


Scheme 1 General route to **12–22**. *Reagents and conditions*: (i) *n*-BuLi, $B(Oi\text{-}Pr)_3$, THF, −78 °C, 3 h; (ii) H_2O, AcOH; (iii) Ar-X, $Pd(PPh_3)_2Cl_2$ (5 mol%), 1,4-dioxane, Na_2CO_3 (1 M), reflux.

Suzuki–Miyaura cross-coupling reactions[15] of **3** and **4** were carried out with (hetero)aryl bromides and chlorides **5–11** under standard conditions [$Pd(PPh_3)_2Cl_2$, (*t*-Bu_3P was added in some cases), 1,4-dioxane, Na_2CO_3, reflux] to yield products **12–22**, respectively. The results presented in Table 1 show that the reactions generally proceed in high yields for both electron-rich (entries 5, 6 and 9) and electron-deficient coupling partners (entries 1–4, 7, 8, 10–12). The efficient reactions of heteroaryl chlorides (entries 3, 4, 10–12) are notable due to their wider availability and lower cost than bromide derivatives. Primary amine, nitro and methoxy functionalities on the coupling partners were tolerated. Initial attempts to couple 2,3-dichloro-5-(trifluoromethyl)pyridine **7**, with two equivalents of boronic acid **3** resulted in high yields of the mono-substituted product **14** (entry 3). An extended reaction time and additional *t*-Bu_3P ligand was required to promote the bis-coupling reaction (entry 12) yielding **22** as the major product (58% yield) alongside **21** (36% yield).

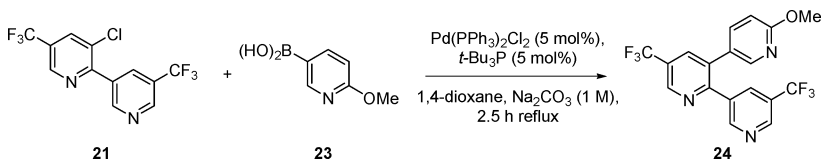
The chloro-bipyridyl derivative **21** was further cross-coupled with 2-methoxy-5-pyridylboronic acid **23**, yielding the tripyridyl derivative **24** in 75% yield (Scheme 2). These reactions suggest the versatility of trifluoromethyl-substituted pyridylboronic acids **3** and **4** for the synthesis of functionalised bi- and tri-(hetero)arenes.

2-Chloro-5-trifluoromethylpyridine **25** is readily available from commercial suppliers and a patent outlines the preparation of 2-chloro-5-(trifluoromethyl)-3-pyridylboronic acid **26** in 25% yield.[24e] By adapting the patent by using triisopropylborate instead of trimethylborate, the directed *ortho*-lithiation and boronation of **25** (Scheme 3) yielded a product whose ^{1}H NMR spectrum matched the data assigned to **26** in the patent. However, the ^{19}F NMR spectrum showed that our product was a mixture of two boronic acid species (δ_F −61.2 and −58.9: *ca.* 1:1.4 ratio) and the two isomers **26** and **27** were isolated in 25% and 42% yields, respectively, by column chromatography. X-ray analysis further confirmed structure **27**.†[26] We conclude, therefore, that both isomers **26** and **27** were also obtained in reference 24e, where the ^{1}H NMR data were wrongly assigned solely to isomer **26**. Methods for the regioselective lithiation of **25** are known.[14c] However, we did not investigate the regioselective boronic acid preparation further after finding that these highly electron-deficient boronic acids did not undergo Suzuki–Miyaura cross-couplings, even with highly reactive 2-iodopyridine, instead they rapidly underwent hydrolytic protodeboronation, with only **25** and unreacted 2-iodopyridine observed by TLC.



Scheme 3 Preparation of **26** and **27**.

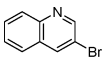
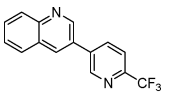
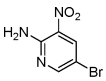
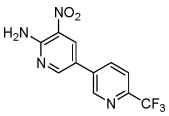
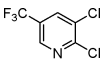
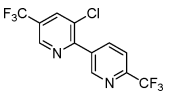
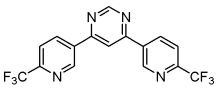
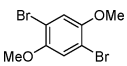
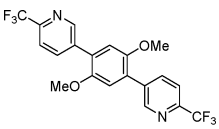
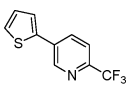
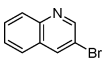
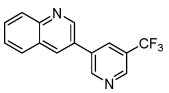
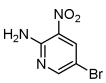
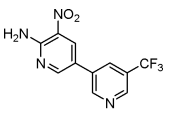
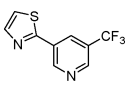
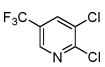
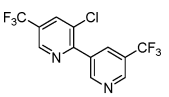
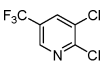
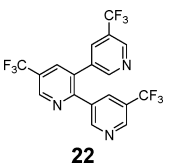
The Cu-catalysed *N*-arylation of 3-(trifluoromethyl)pyrazole with iodobenzene has been reported;[27] following these conditions [Cu_2O, salicylaldoxime, MeCN, Cs_2CO_3, reflux] the *N*-(hetero)arylated pyrazole derivatives **29a–c** were obtained in high



Scheme 2 Synthesis of tripyridyl derivative **24**.

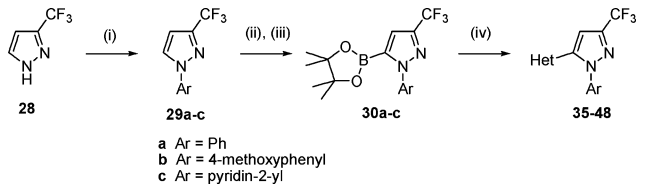
Table 1 Palladium-catalysed cross-coupling reactions of **3** and **4**[a]

3 or **4** + Ar–X $\xrightarrow{\text{(i)}}$ **12–22**

Entry	Boronic acid	Time (h)	Ar-X	Product	Yield (%)[b]
1	**3**	22	 **5**	 **12**	94
2	**3**	17	 **6**	 **13**	75
3	**3**[c]	4	 **7**	 **14**	92
4	**3**[d]	21[f]	 **8**	 **15**	81
5	**3**[d]	1	 **9**	 **16**	77
6	**3**	3	 **10**	 **17**	93
7	**4**	22	 **5**	 **18**	98
8	**4**	17	 **6**	 **19**	78
9	**4**	20.5[f]	 **11**	 **20**	51
10	**4**[e]	3	 **7**	 **21**	75
11		28.5			83
12	**4**[d]	55[g]	 **7**	 **22**	58[h]

[a] *Reagents and conditions*: entries 1–3, 5–11, (i) $Pd(PPh_3)_2Cl_2$ (5 mol%), 1,4-dioxane, Na_2CO_3 1 M, reflux; entries 4, 12, (i) $Pd(PPh_3)_2Cl_2$ (5 mol%)/*t*-Bu_3P (5 mol%), 1,4-dioxane, Na_2CO_3 1 M, reflux. [b] Isolated yield. [c] 2 equiv. boronic acid. [d] 2.1 equiv. boronic acid. [e] 1 equiv. boronic acid. [f] TLC indicated reaction was complete in 2 h. [g] After 28 h reflux a further 5 mol% $Pd(PPh_3)_2Cl_2$ was added and the reaction was left at reflux for a further 27 h. [h] 36% of **21** was isolated as the minor product.

yields (94–98%) (Scheme 4). It is known that regioselective arylation occurs when a trifluoromethyl substituent is at C-3, and this was confirmed for **29a–c** by the coupling constants of the hydrogen atoms on the pyrazole ring.[28] Lithiation of 1-substituted pyrazoles with *n*-BuLi occurs at the C-5 position when this is unsubstituted;[29] accordingly, treating **29a–c** with *n*-BuLi followed by 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and acidic workup yielded the pinacol ester derivatives **30a–c** in 92%, 98% and 84% yields, respectively. The X-ray crystal structure of **30b** was obtained.†[26]



Scheme 4 General route to **35–48**. *Reagents and conditions*: (i) Ar-I, Cu_2O (5 mol%), salicylaldoxime (20 mol%), Cs_2CO_3, MeCN, reflux, 18 h; (ii) *n*-BuLi, THF, −78 °C, 0.5 h; (iii) 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, −78 °C, 1.5 h; warm to RT over 1 h, AcOH; (iv) Het-Br, Pd(dppf)Cl_2·DCM (10 mol%), 1,4-dioxane, K_3PO_4, HCOOK, 80 °C.

Suzuki–Miyaura cross-couplings of **30a**,**b** using the conditions reported by Harrity *et al.* for the coupling of pyrazolylboronic ester derivatives [Pd(dppf)Cl_2·DCM, 1,4-dioxane, K_3PO_4, 85 °C][23d] yielded the desired cross-coupled products alongside products resulting from homo-coupling of the boronic ester and hydrolytic protodeboronation (Table 2, entries 2 and 4). To improve the yields of the cross-coupled products we suppressed the homo-coupling by addition of potassium formate.[30] However, protodeboronation could not be completely eliminated. On changing the base to KOAc no homo-coupling was observed; however, protodeboronation still occurred (entries 10 and 13). When **30b** was subjected to the Suzuki–Miyaura conditions [Pd(dppf)Cl_2·DCM, 1,4-dioxane, 80 °C] in the absence of a coupling partner and in the presence of K_3PO_4, the product resulting from the homo-coupling of the boronic ester was detected; however, with KOAc only protodeboronated product **29b** was observed. Protodeboronation of **30b** occurred in 1,4-dioxane only in the presence of base at elevated temperatures (no catalyst or coupling partner present). A range of conditions for the cross-coupling of **30b** with 3-bromo-5-methoxypyridine were screened;[31] however, the conditions [Pd(dppf)Cl_2·DCM, 1,4-dioxane, K_3PO_4, HCOOK, 80 °C], resulted in the highest conversion to the coupling product. The results are collated in Table 2; for **30a** and **b** the reactions proceeded in moderate to high yields (60–82%) with a variety of heteroaryl bromides as coupling partners, including those bearing nitro and primary amine substituents, yielding compounds **35–46**. The coupling reactions of **30c** were less successful (Table 2, entries 17 and 18). The major product was the protodeboronated product **29c**: yields of coupling products **47** and **48** were 16% and 30%, respectively. These results are consistent with the combined electron withdrawing effects of the *N*-pyridyl and trifluoromethyl substituents increasing the instability of the C–B bond and thus making it prone to hydrolytic deboronation under basic conditions.[32]

Table 2 Palladium-catalysed cross-coupling reactions of **30a–c**[a]

30a–c + Het-Br $\xrightarrow{(i)}$ **35–48**

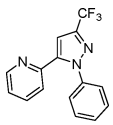
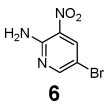
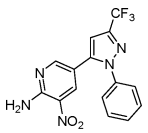
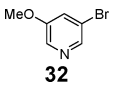
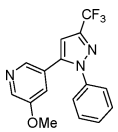
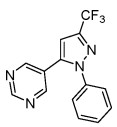
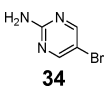
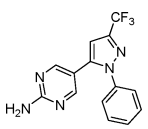
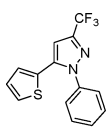
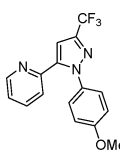
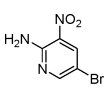
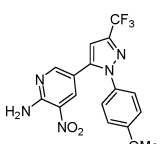
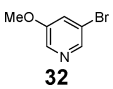
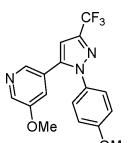
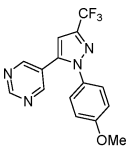
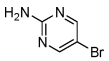
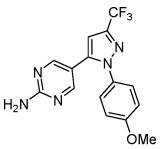
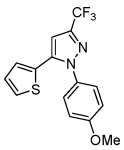
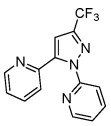
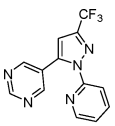
Entry	Boronic ester	Time (h)	Het-Br	Product	Yield (%)[b]
1[c]	**30a**	4.5	 **31**	 **35**	77
2		43			59
3	**30a**	4	 **6**	 **36**	82
4[c]		26.5			66
5	**30a**	4	 **32**	 **37**	80
6	**30a**	3	 **33**	 **38**	74
7	**30a**	5	 **34**	 **39**	67
8	**30a**	5	 **10**	 **40**	81
9	**30b**	5.5	 **31**	 **41**	63
10[d]		17.5			49
11	**30b**	5	 **6**	 **42**	79
12	**30b**	5	 **32**	 **43**	82
13[d]		17.5			42

Table 2 *(Contd.)*

30a–c + Het-Br $\xrightarrow{(i)}$ **35–48**

Entry	Boronic ester	Time (h)	Het-Br	Product	Yield (%)[b]
14	**30b**	3	 **33**	 **44**	60
15	**30b**	5	 **34**	 **45**	72
16	**30b**	5	 **10**	 **46**	85
17	**30c**	4.5	 **31**	 **47**	16
18	**30c**	4.5	 **33**	 **48**	30

[a] *Reagents and conditions*: (i) $Pd(dppf)Cl_2$·DCM (10 mol%), 1,4-dioxane, K_3PO_4, HCOOK, 80 °C. [b] Isolated yield. [c] Without HCOOK. [d] Without HCOOK and using KOAc as base.

The pyrazolyl coupling products **35** and **36** were further elaborated by preparing their 4-bromo derivatives and subsequently cross-coupling with another heteroarylboronic acid to yield 1,4,5-[tri(hetero)aryl]-3-(trifluoromethyl)pyrazole derivatives (Scheme 5). The reaction of **35** and **36** with bromine in acetic acid at 100 °C resulted in regioselective electrophilic bromination at C-4 of the pyrazole ring yielding **49** and **50** in 66% and 86% yields, respectively. In a further Suzuki–Miyaura cross-coupling reaction, **49** and **50** gave the fully functionalised pyrazole derivatives **51** and **52** in 80% and 30%[33] yields, respectively. The X-ray structure of **51** was obtained.†[26]

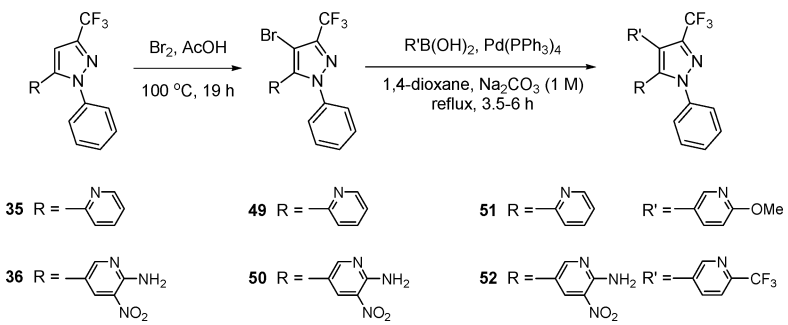
Conclusions

In conclusion, we have described the preparation of CF_3-substituted pyridylboronic acids which are stable to storage under ambient conditions. These species readily undergo Suzuki–Miyaura cross-coupling reactions to yield heteroaryl-(trifluoromethyl)pyridines in good to excellent yields. However, if further electron-withdrawing substituents are introduced on the pyridyl ring the boronic acid derivatives are unstable to protolytic deboronation. 3-(Trifluoromethyl)-pyrazolylboronic esters have been synthesised through an expedient procedure. These species undergo palladium-catalysed cross-coupling reactions to provide heteroaryl-(trifluoromethyl)pyrazoles in synthetically viable yields, although in some cases competing protodeboronation was observed. With the trifluoromethyl-substituent having the appeal of tailoring activity profiles, these functionalised CF_3-substituted heterocycles are of potential utility as new pharmacophores and scaffolds for drug discovery. Furthermore, they offer scope for further synthetic transformations as highlighted by selected examples within this work.

Experimental

Representative procedure for the synthesis of 3 and 4: 5-(Trifluoromethyl)-3-pyridylboronic acid (4)

n-Butyllithium (2.5 M in hexane, 19.5 cm^3, 49 mmol) was added to a mixture of 3-bromo-5-(trifluoromethyl)pyridine **2** (10.0 g, 44 mmol) and triisopropylborate (12.3 cm^3, 53 mmol) in anhydrous THF (80 cm^3) at −78 °C under argon. The reaction was stirred at −78 °C for 3.5 h before warming gradually to −10 °C when the reaction was quenched with deionised water (80 cm^3). The organic solvent was removed in vacuo. The resulting aqueous phase was treated with $NaOH_{(s)}$ to obtain pH 10, then washed with diethyl ether (1 × 80 cm^3) and acidified to pH 5 using acetic acid. The solution was extracted with EtOAc (1 × 250 cm^3) and evaporated to dryness *in vacuo* to yield **4** as an off-white solid (7.91 g, 94%): mp 300.8 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 9.43 (1H, s), 9.23 (1H, s), 9.11 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6, DCl) δ 151.6, 145.7 (1C, q, J = 3 Hz), 142.2 (1C, q, J



Scheme 5 Derivatisation of coupling products **35** and **36**.

= 4 Hz), 126.9 (1C, q, J = 35 Hz), 122.7 (1C, q, J = 273 Hz) (*C*-B not observed); ^{11}B NMR (128 MHz, DMSO-d_6, DCl) δ 27.8; ^{19}F NMR (188 MHz, DMSO-d_6, DCl) δ –61.0.

Representative procedure for the synthesis of 30a-c: 3-(Trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-phenyl-1*H*-pyrazole (30a)

n-Butyllithium (2.5 M in hexane, 1.4 cm^3, 3.5 mmol) was added dropwise to a solution of **29a** (617 mg, 2.9 mmol) in anhydrous THF (20 cm^3) at −78 °C under argon. The reaction mixture was stirred for 45 min at −78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.62 cm^3, 3.1 mmol) was added dropwise to the reaction mixture at −78 °C and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.18 cm^3, 3.2 mmol) was added. The mixture was filtered through a celite pad, which was washed with EtOAc (100 cm^3). The organic solvent was removed *in vacuo* and the crude product distilled to remove any unreacted starting material and boron-containing species. The remaining pale-brown solid was **30a** (906 mg, 92%); mp 77.7–79.3 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.65–7.62 (2H, m), 7.54–7.48 (3H, m), 7.19 (1H, s), 1.29 (12H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 143.8 (1C, q, J = 38 Hz), 141.6, 129.54, 129.53, 125.9, 122.8 (1C, q, J = 266 Hz), 115.8 (1C, q, J = 2 Hz), 85.7, 25.0; ^{11}B NMR (128 MHz, acetone-d_6) δ 27.9; ^{19}F NMR (188 MHz, acetone-d_6) δ –62.5; MS (EI) m/z 337.8 ([M(**30a**)]$^+$, 80%), 211.9 ([M(**29a**)]$^+$, 60%). Anal. Calcd. for $C_{16}H_{18}BF_3N_2O_2$: C, 56.83; H, 5.37; N, 8.28. Found: C, 56.72; H, 5.37; N, 8.07%.

Typical procedure for the Suzuki–Miyaura cross-coupling reactions of 3 and 4 in Table 1

The boronic acid **3** or **4** (1.0–2.1 equiv.) the arylhalide (1.0 equiv.) and $Pd(PPh_3)_2Cl_2$ (*ca.* 5 mol%), [for conditions b; *t*-Bu_3P (*ca.* 5 mol%)] were sequentially added to degassed 1,4-dioxane (7 cm^3) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 2 equiv.) was added and the reaction mixture was heated under argon at reflux for the time stated. The mixture was transferred to a separating funnel, ethyl acetate was added and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column followed on some occasions by recrystallisation or Kügelrohr distillation.

Typical procedure for the Suzuki–Miyaura cross-coupling reactions of 30a–c in Table 2

The boronic esters **30a-c** (1.1 equiv.) the arylhalide (1.0 equiv.), $Pd(dppf)Cl_2$·DCM (*ca.* 10 mol%), K_3PO_4 (3.0 equiv.) and HCOOK (46 mol% with respect to the boronic ester) were sequentially added to degassed 1,4-dioxane (7 cm^3) and the mixture was heated under argon at 80 °C for the time stated. The mixture was filtered through a celite pad, which was rinsed with EtOAc. The organic solvent was removed *in vacuo* and the resulting mixture was purified by chromatography on a silica gel column followed on some occasions by recrystallisation.

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