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An approach to heterodiarylmethanes via sp^2-sp^3 Suzuki–Miyaura cross-coupling

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ABSTRACT

The synthesis of a range of structurally diverse diarylmethanes via the Suzuki−Miyaura cross-coupling of aryl methane acetates and arylboronic acids is reported, including several challenging examples containing nitrogen, oxygen and sulfur heteroatoms in one or both coupling partners. A single set of optimized conditions was used to generate the diarylmethanes in 52-91% yield.

1. Introduction

Synthetic procedures for the construction of diarylmethanes, especially those containing heterocyclic systems, are highly desirable as (aryl)(heteroaryl)methane skeletons feature in many biologically active compounds. These include drugs with a range of indications such as diabetes and HIV (Figure 1).[1] Heterocyclic compounds are of key importance to the pharmaceutical industry due to their ability to interact with biological systems through polar interactions. Unfortunately, it is these heterocycles that inhibit many of the very useful metal/ligand-catalyzed cross-coupling reactions through their interactions with the catalyst[2] and/or unfavorable electronic properties.[3] The Suzuki−Miyaura cross-coupling reaction has been used to construct diarylmethanes in recent years, primarily using benzylic halides.[4] Such electrophilic partners, however, can be unstable in the presence of nucleophilic heterocyclic systems. Moreover, the rates of oxidative insertion of transition metals into alkyl halide bonds and subsequent reductive elimination to form the cross-coupled product from the catalyst, are relatively slow. In light of these shortcomings, alternative benzylic electrophiles such as phosphates,[5] carbonates[6] and acetates[7] have received some attention. Arylmethane acetates offer several advantages over other electrophiles. Firstly, the compounds are stable both in solution and as isolated solids/oils at room temperature and are often commercially available. Secondly, they are simple and inexpensive to prepare. Thirdly, as synthetic intermediates for pharmaceuticals, they are likely to have low potential for genotoxicity in contrast to $ArCH_2X$ (where X = halide) which is a structurally-alerting functional group that is known to be involved in reactions with DNA.[8] Preliminary screening experiments in our laboratories identified benzylic acetates as superior electrophiles over several others, reinforcing the significance of earlier work by Kuwano and co-workers.[7]

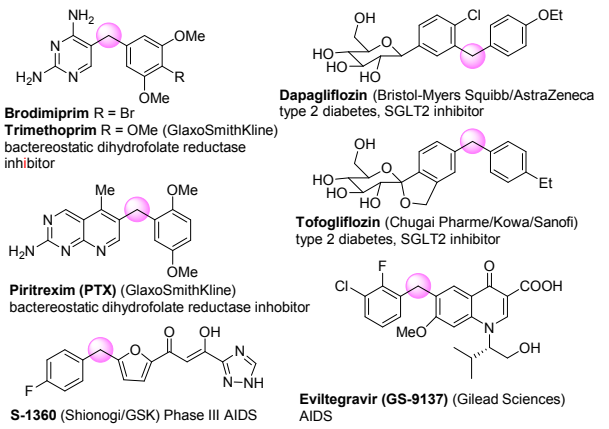


Figure 1. Pharmacologically active examples of compounds containing diarylmethane systems.

A one pot preparation of diaryl methanes via diborylmethane has also been reported via an intermediate coupling of aryl bromides with benzylic boronates.[9] However, the structural diversity in the products reported has been quite limited. Indeed, few examples of Suzuki−Miyaura cross-couplings where both the arylmethane

electrophile and arylboronic acid contain heteroatoms, have been reported.[10] Those that contain nitrogen-based heterocycles have typically been electronically deactivated or N-protected, presumably due to the potent electrophilic nature of the benzylic chlorides employed. Recently, a nickel-catalyzed direct C-H coupling of heteroarenes to benzylic carbonates has appeared in the literature; but these couplings are limited to the activated position of the heterocycle.[11] Herein, we report the synthesis of a range of diarylmethanes via the Suzuki−Miyaura cross-coupling of acetates and boronic acids, including several examples containing heteroatoms in one or both coupling partners.

2. Results and discussion

Reaction conditions were screened for the cross-coupling of pyridin-3-ylmethyl acetate (**1a**) and naphthalen-1-ylboronic acid (**2a**) (Figure 2). The choice of ligand ~~and solvent~~ was varied whilst the catalyst [$Pd(OAc)_2$], base (K_2CO_3), solvent (10:1 *i*PrOH:H_2O) and reaction temperature (80 °C) were kept constant. The highest assay yields (85-98%) were obtained in the presence of X-Phos, S-Phos, RuPhos, dppf, dippf and dppb.

Having established the most effective ligands, attention switched to determining the optimal solvent for the reaction. Keeping all other variables constant, the coupling was performed in DMAc, THF, toluene and *i*PrOH in the presence of X-Phos, S-Phos, RuPhos, dppf, dippf and dppb (Table 1). Gratifyingly, the use of *i*PrOH (the solvent used in the original ligand screen) offered considerably higher assay yields (up to 98%) than the other three solvents for all six ligands for coupling **1a** with **2a**. The highest assay yields (98%) resulted from the use of both S-Phos and RuPhos. The latter was selected for further study.

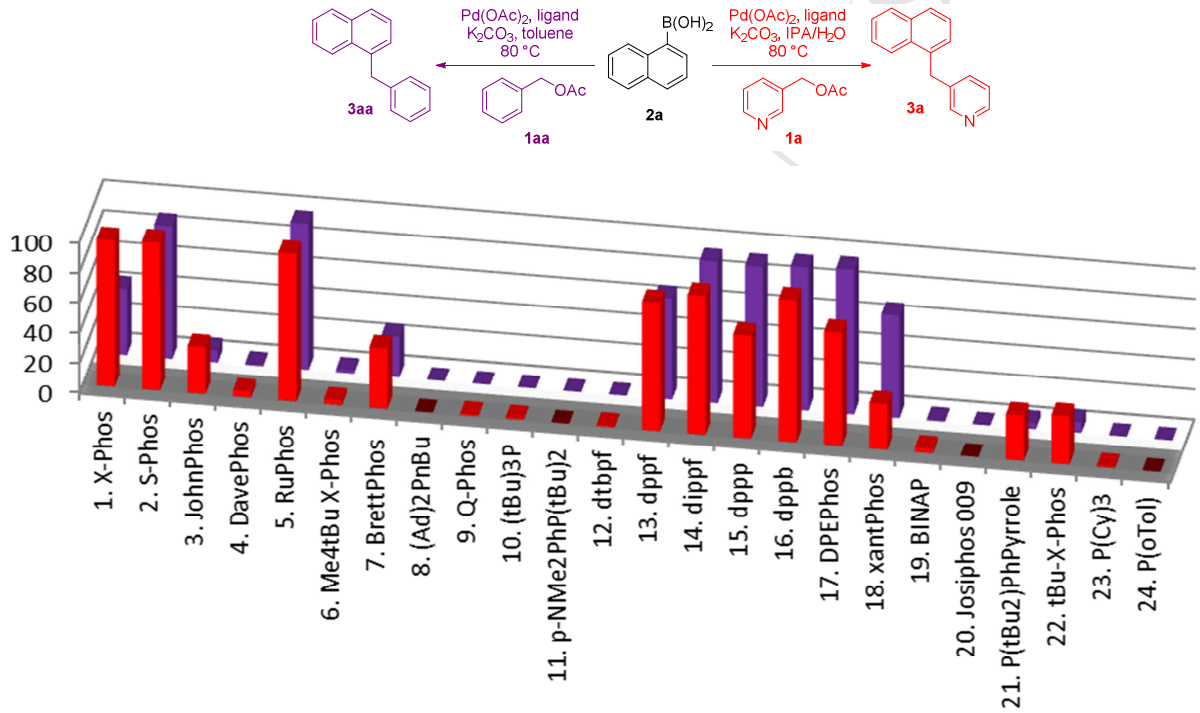


Figure 2. Screen of ligands for the cross-coupling of pyridin-3-ylmethyl acetate (**1a**, red, front) and benzyl acetate (**1aa**, purple, rear) with naphthalen-1-ylboronic acid (**2a)**. Reactions conditions: 0.02 mmol of **1a** or **1aa**, 0.02 mmol of **2a**, 0.06 mmol of K_2CO_3, 5 mol % of $Pd(OAc)_2$ and either 10.5 mol % monodentate ligand or 5.025 mol % bidentate ligand in 5.5 mL/mmol solvent (10:1 *i*PrOH:H_2O for **1a** and toluene for **1aa**) at 80 °C for 48 h. Vertical axis shows % assay yield.

	X-Phos	**S-Phos**	**RuPhos**	**dppf**	**dippf**	**dppb**
***i*PrOH**	97	98	98	85	92	94
DMAc	46	7	68	15	20	0
THF	18	6	34	4	23	51
Toluene	4	3	7	64	44	35

Table 1. Screen of ligands and solvents for the cross-coupling of pyridin-3-ylmethyl acetate **1a** and naphthalen-1-ylboronic acid **2a**. Reactions conditions: **1a** and **2a** (1 equiv each), K_2CO_3, (3 equiv), $Pd(OAc)_2$ (5 mol %), monodentate ligand (10.5 mol %) or bidentate ligand (5.025 mol %), solvent:H_2O (10:1, 0.18 M), 80 °C, 48 h; % assay yield is indicated.

Interestingly, a screen for the cross-coupling of simple benzyl acetate (**1aa**) with **2a** showed good results with a wider range of ligands and solvents (see Supporting Information), thus verifying the increased difficulty encountered in the presence of a heterocyclic system. In contrast to the coupling of **1a**, this screen revealed the best results for the coupling of **1aa** were obtained in toluene for the higher performing ligands while only modest results were obtained in *i*PrOH. A further screen of bases with several successful ligands at various catalyst loadings showed good results for the coupling of **1a** with **2a** can be obtained with RuPhos using a variety of bases at catalyst loadings as low as 1 mol % (Table 2). Even weak bases such as KF and $KHCO_3$ gave excellent results, which would allow coupling of base labile substrates under mild conditions.

Table 2. Screen of bases at various catalyst loadings with several ligands in cross coupling of **1a** with **2a**.[a]

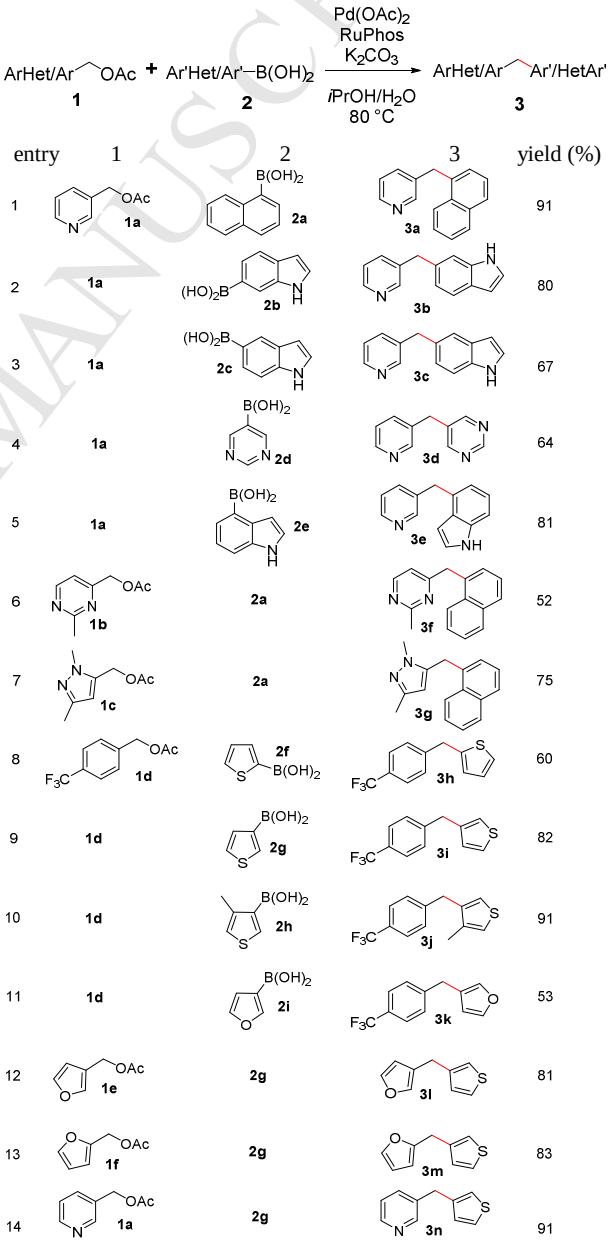
	mol% Pd	K_2CO_3	K_3PO_4	KF	$KHCO_3$	Na_2CO_3	Cy_2NMe
RuPhos	5	98	98	98	98	98	98
RuPhos	2	98	98	98	98	98	98
RuPhos	1	98	98	98	98	98	90
S-Phos	5	98	98	98	98	98	98
S-Phos	2	98	98	98	98	98	95
S-Phos	1	91	91	92	96	86	61
dippf	5	92	93	93	93	93	90
dippf	2	83	83	83	83	82	70
dippf	1	70	66	71	74	71	51

[a] Reactions conditions: 0.02 mmol of **1a**, 0.02 mmol of **2a**, 0.06 mmol of base, 2.1 equiv monodentate ligand or 1.05 equiv mol % bidentate ligand relative to $Pd(OAc)_2$ in 10:1 *i*PrOH:H_2O (5.5 mL/mmol**)** at 80 °C for 48 h; % assay yield is indicated.

Having achieved success with a nitrogen heteroatom in the methyl acetate portion, we decided to explore the feasibility of coupling pyridinylmethyl acetate **1a** with *N*-heteroarylboronic acids **2b-e** (Table 3). Couplings of **1a** with 1*H*-indolylboronic acids **2b**, **2c** and **2e** were found to proceed in moderate to good yield (67-81% isolated yields, entries 1-3) whilst a 64% yield was obtained from coupling pyrimidinylboronic acid **2d** with **1a** (entry 4).

Next, the effect of varying the *N*-heteroaryl(methyl) acetate coupling partner was explored in conjunction with naphthaleneboronic acid **2a**. The original test substrates (**1a** and **2a**) were coupled and the product isolated in 91% yield. A more modest yield (52%) was obtained from the coupling of (2-methylpyrimidin-4-yl)methyl acetate (**1b**) and **2a** whilst the use of (1,3-dimethyl-1*H*-pyrazol-5-yl)methyl acetate (**1c**) led to a 75% yield of cross-coupled product (entries 6,7). The tolerability of these reaction conditions to boronic acids containing heteroatoms other than nitrogen was investigated next using 4-(trifluoromethyl)benzyl acetate (**1d**) as the control substrate. Pleasingly, the use of both thienyl (**2f-h**) and furanyl (**2i**) boronic acids was successful with cross-coupled products **3h-k** generated in 53-91% yield (Entries 8-11).

Table 3. Cross coupling of various heteroaryl and aryl(methyl) acetates[b] with heteroaryl and arylboronic acids.[c]

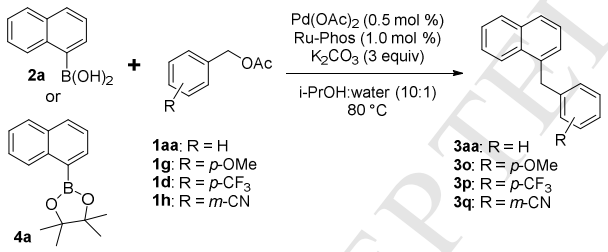


[b]Methane acetate preparation: aryl methanol alcohol (1.0 equiv) in dichloromethane (15 mL), triethylamine (1.3 equiv) and acetic anhydride (1.1 equiv) at 0 °C for 16 h. Products were isolated as oils after aqueous work-up. [c]Cross-coupling conditions: substrate **1** (1.1 equiv), substrate **2** (1.0 equiv), $Pd(OAc)_2$ (2 mol %), RuPhos (4 mol %), K_2CO_3 (2.5 equiv), 10:1 *i*PrOH:H_2O, 80 °C, under N_2 atmosphere.

The potential of the standard reaction conditions to generate products with differing heteroatoms in each heterocycle was assessed using thiophen-3-ylboronic acid **2g** as the control substrate. Furanyl(methyl) acetates **1e** and **1f** and pyridinyl methane acetate **1a** were selected as the coupling partners. All three reactions were successful with **3l-n** isolated in good to excellent yield (entries 12-14).

To broaden the scope of this coupling to include boronic acid esters, naphthaleneboronic acid pinacol ester **4a** was coupled with several benzylic esters (Table 4). Good results were obtained in coupling **1a** with **4a** (91% assay yield, 86% isolated yield); whereas, inferior results were obtained in coupling **1aa** with **2a** (20% assay yield, 17% isolated yield). Further investigation demonstrated that yields were considerably affected by choice of boron species. Electron-rich benzylic acetates **1aa** and **1 g** offered poor cross-coupling efficiency, presumably due to slow oxidative addition, with both compounds still present at the end of the reactions. However, this difference was less pronounced in the case of electron-poor benzylic acetates **1d** and **1h** with diarylmethane products obtained in similar yield for both. Therefore, as a practical recommendation, we suggest exploring the use of boronic esters in addition to acids when utilizing our coupling conditions.

Table 4. Boronic acid vs. pinacol boronate.[d]



Entry	Benzylic acetate	Coupling partner	Yield, %
1	**1a**	**4a**	86[e] (**3a**)
2	**1aa**	**2a**	17[f] (**3aa**)
3	**1aa**	**4a**	55 (**3aa**)
4	**1g**	**2a**	13 (**3o**)
5	**1g**	**4a**	23 (**3o**)
6	**1d**	**2a**	66 (**3p**)
7	**1d**	**4a**	70 (**3p**)
8	**1h**	**2a**	72 (**3q**)
9	**1h**	**4a**	80 (**3q**)

[d] Reactions conditions: substrate **1** (1.1 equiv), substrate **2a** or **4a** (1.2 equiv), $Pd(OAc)_2$ (0.5 mol %), RuPhos (1 mol %), K_2CO_3 (3.5 equiv), 10:1 *i*PrOH:H_2O, 80 °C, under N_2 atmosphere; 0.02 mmol; % isolated yield is indicated. [e]Assay yield was 91%. [f]Assay yield was 20%.

3. Conclusion

In conclusion, a single set of conditions has been developed to facilitate the synthesis of a range of structurally diverse diarylmethanes. Such compounds are highly desirable as many biologically active substances contain (aryl)(heteroaryl)methane skeletons. The Suzuki−Miyaura cross-coupling of heteroaryl/arylmethane acetates and heteroaryl/arylboronic acids generated 14 heterocyclic products in 52-91% yield. Notably, diarylmethanes bearing heteroatoms on both coupling partners were successfully prepared, expanding access to these valuable building blocks.

4. Experimental section

4.1 General remarks

All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by HPLC. HPLC analyses were performed using an Ascentis Express C18, 2.7 µm, 150 × 4.60 mm column, and a mobile phase consisting of acetonitrile and 0.1% aqueous phosphoric acid. Melting points were obtained using Stuart Scientific Melting Point Apparatus SMP3. NMR spectra were recorded on a Bruker AVANCE DPX or DRX 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) spectrometer. ^{1}H NMR data are reported as follows: chemical shifts are reported in ppm with the solvent resonance resulting from incomplete deuteration as the internal standard ($CDCl_3$: 7.26; CD_2Cl_2: 5.35), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or combinations thereof), coupling constants, and integration. ^{13}C NMR data are reported as follows: chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.16; $^{13}CD_2Cl_2$: 53.43); and then where applicable the multiplicity (d = doublet), coupling constant, and integration. High resolution mass spectra were obtained by LCMS using a Waters QToF Premier system, and a mobile phase consisting of 0.1% aqueous formic acid and 0.1% formic acid in acetonitrile.

4.2 Acetate formation: General synthetic method

Aryl methanol alcohol (6 mmol) in dichloromethane (15 ml) was cooled to 0 °C. Triethylamine (7.8 mmol) and acetic anhydride (6.6 mmol) were added dropwise sequentially, keeping T < 1 °C. The solution was aged at room temperature for 1-16 h, samples were taken at different time intervals and analysed by HPLC, and the reaction was quenched with 10%

aqueous NH_4Cl (4 ml) when HPLC indicated reaction completion. The aqueous layer was discarded and the organics were washed with water (4 ml) and then dried over Na_2SO_4. The solvent was removed in vacuo, affording the product.

Pyridin-3-ylmethyl acetate (**1a**). Yellow oil; yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.57 (d, J = 4.8 Hz, 1H), 7.69 (dd, J = 7.6, 1.2 Hz, 1H), 7.30 (dd, J = 7.6, 4.8 Hz, 1H), 5.12 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 170.7, 149.6, 149.5, 136.1, 131.3, 123.5, 63.7, 20.9; HRMS (ESI+) calculated for $C_8H_9NO_2$ 176.0534, found 176.0532. Spectroscopic data consistent with literature.[12]

2-Methylpyrimidin-4-yl)methyl acetate (**1b**). Amber colored solid; yield 96%; mp 61-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 5.1 Hz, 1H), 7.15 (dd, J = 5.1, 0.8 Hz, 1H), 5.16 (s, 2H), 2.74 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 167.9, 164.9, 157.3, 114.9, 65.4, 25.9, 20.8; HRMS (ESI+) calculated for $C_8H_{10}N_2O_2$ 167.0821, found 167.0824.

(1,3-Dimethyl-1H-pyrazol-5-yl)methyl acetate (**1c**). Yellow oil; yield 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 1H), 5.05 (s, 2H), 3.81 (s, 3H), 2.23 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 147.4, 137.2, 107.1, 56.0, 36.2, 20.8, 13.3; HRMS (ESI+) calculated for $C_8H_{12}N_2O_2$ 169.0977, found 169.0974. Spectroscopic data consistent with literature.[13]

4-Trifluoromethanebenzyl acetate (**1d**). Colorless oil; yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 2.18 (s, 2H), 2.15 (d, 3H). Spectroscopic data consistent with literature.[14]

Furan-3-ylmethyl acetate (**1e**). Dark yellow oil; yield 100%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J = 1.6, 0.8 Hz, 1H), 7.42 (m, 1H), 6.44 (m, 1H), 4.99 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 143.4, 141.6, 120.4, 110.6, 57.7, 21.0. Spectroscopic data consistent with literature.[15]

4-Methoxybenzyl acetate (**1g**). Colorless oil; yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.06 (s, 2H), 3.83 (s, 3H), 2.10 (s, 3H). Spectroscopic data consistent with literature.[16]

3-Cyanobenzyl acetate (**1h**). Colorless oil; yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.61 (m, 2H), 7.49 (m, 1H), 5.14 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 137.6, 132.3, 131.8, 131.5, 129.4, 118.5, 112.8, 64.8, 20.9; HRMS (ESI+) calculated for $C_{10}H_{10}O_2N$ 176.0712, found 176.0711. Spectroscopic data consistent with literature.[17]

4.3 Suzuki reaction: General synthetic method

Boronic acid (6 mmol), acetate (7.2 mmol), $Pd(OAc)_2$ (0.12 mmol) and RuPhos (0.24 mmol) in 2-propanol (10 ml) and water (1 ml) were stirred for 5 minutes under N_2 atmosphere. K_2CO_3 (15 mmol) was added and the suspension was sparged sub-surface with N_2 for 5 minutes. The suspension was heated to 80 °C for 1-48 h, samples were taken at different time intervals and analysed by HPLC, and the reaction was cooled to room temperature when HPLC indicated reaction completion. Water (2.5 ml) and MTBE (2.5 ml) were added and the aqueous layer was removed. The organic layer was washed sequentially with brine and saturated aqueous NH_4Cl. The organics were dried over Na_2SO_4 and the solvent was removed in vacuo. Product was purified by column chromatography (heptane/MTBE).

3-(Naphthalen-1-ylmethyl)pyridine (**3a**). Pink solid, yield 91%; mp 52-53 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.47 (d, J = 4.0 Hz, 1H), 7.92 (m, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.47 (m, 4H), 7.32 (d, J = 7.2 Hz, 1H), 7.19 (dd, J = 8.0, 5.2 Hz, 1H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 147.5, 136.2 (2C), 135.2, 134.0, 131.8, 128.9, 127.7, 127.4, 126.3, 125.8, 125.6, 123.9, 123.5, 36.2; HRMS (ESI+) calculated for $C_{16}H_{13}N$ 220.1126, found 220.1124. Spectroscopic data consistent with literature.[18]

1-Benzylnaphthalene (**3aa**). White solid, yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 1H), 7.90 (m, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.47 (m, 3H), 7.28 (m, 6H), 4.49 (s, 2H). Spectroscopic data consistent with literature.[19]

6-(Pyridin-3-ylmethyl)-1H-indole (**3b**). Off-white solid; yield 80%; mp 87-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (br s, 1H), 8.56 (m, 1H), 8.47 (dd, J = 4.8, 1.6 Hz, 1H), 7.6 (d, J = 8.2 Hz, 1H), 7.52 (m, 1H), 7.19 (m, 3H), 6.99 (dd, J = 7.8, 1.6 Hz, 1H), 6.54 (m, 1H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 147.1, 137.6, 136.8, 136.3, 133.6, 126.5, 124.4, 123.6, 121.2, 120.9, 111.2, 102.3, 39.3; HRMS (ESI+) calculated for $C_{14}H_{12}N_2$ 209.1079, found 209.1073.

5-(Pyridin-3-ylmethyl)-1H-indole (**3c**). Off-white solid; yield 67%; mp 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (m, 2H), 8.47 (dd, J = 4.7, 1.6 Hz, 1H), 7.53 (ddd, J = 7.8, 2.3, 1.6 Hz, 1H), 7.47 (m, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.21 (m, 2H), 7.01 (dd, J = 8.2, 1.6 Hz, 1H), 6.52 (m, 1H), 4.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 147.0, 138.0, 136.8, 134.7, 131.0, 128.2, 124.8, 123.5, 123.1, 120.6, 111.3, 102.3, 39.2; HRMS (ESI+) calculated for $C_{14}H_{12}N_2$ 209.1079, found 209.1073.

5-(Pyridin-3-ylmethyl)pyrimidine (**3d**). Colorless oil; yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.59 (s, 2H), 8.52 (d, J = 2.8 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.26 (dd, J = 8.0, 4.7 Hz, 1H), 3.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 157.0 (2C), 149.8, 148.4, 136.3, 122.9, 133.1, 123.8, 33.7; HRMS (ESI+) calculated for $C_{10}H_9N_3$ 172.0875, found 172.0868.

4-(Pyridin-3-ylmethyl)-1H-indole (**3e**). Green solid; yield 81%; mp 138-140 °C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 8.64 (br s, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.46 (dd, J = 4.7, 1.6 Hz, 1H), 7.56 (m, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.18 (m, 3H), 6.92 (dd, J = 7.4, 0.8 Hz, 1H), 6.51 (m, 1H), 4.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 147.0, 136.8, 136.7, 135.9, 131.5, 127.3, 124.2, 123.5, 122.1, 120.1, 109.9, 100.8, 36.7; HRMS (ESI+) calculated for $C_{14}H_{12}N_2$ 209.1079, found 209.1070.

2-Methyl-4-(naphthalen-1-ylmethyl)pyrimidine (**3f**). Colorless oil; yield 52%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 5.1 Hz, 1H), 7.90 (m, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.46 (m, 4H), 6.67 (d, J = 5.2 Hz, 1H), 4.56 (s, 2H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 167.7, 156.8, 134.0, 133.2, 132.0, 128.8, 128.1 (2C), 126.4, 125.9, 125.6, 124.2, 117.1, 41.8, 26.0; HRMS (ESI+) calculated for $C_{16}H_{13}N$ 235.1239, found 235.1239.

1,3-Dimethyl-5-(naphthalen-1-ylmethyl)-1H-pyrazole (**3g**). Pink solid; yield 91%; mp 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 1H), 7.91 (m, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.54 (m, 2H), 7.42 (m, 1H), 7.14 (d, J = 7.1 Hz, 1H), 5.70 (s, 1H). 4.37 (s, 2H), 3.76 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 141.5, 122.9, 133.5, 131.7, 128.8, 127.6, 126.3, 126.2, 125.8, 125.6, 123.5, 106.0, 36.0, 29.2, 13.4; HRMS (ESI+) calculated for $C_{16}H_{16}N_2$ 237.1392, found 237.1382.

2-(4-(Trifluoromethyl)benzyl)thiophene (**3h**). Colorless oil; yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.20 (dd, J = 5.1, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.84 (ddd, J = 3.5, 2.0, 1.2 Hz, 1H), 4.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 142.5, 128.89 (2C), 128.87 (d, J = 32 Hz, 2C), 127.0, 125.6, 125.5 (d, J = 3.8 Hz, 2C), 124.4, 124.3 (d, J = 270 Hz, 2C), 35.8; HRMS (ESI+) calculated for $C_{12}H_9F_3S$ 243.0455, found 243.0444.

3-(4-(Trifluoromethyl)benzyl)thiophene (**3i**). Colorless oil; yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 2H), 7.38-7.31 (m, 3H), 6.98 (s, 1H), 6.94 (d, J = 5.2 Hz, 1H), 4.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 140.3, 129.1 (2C), 128.6 (d, J = 33 Hz, 2C), 127.2 (d, J = 220 Hz, 1C), 125.7, 125.4 (d, J = 4 Hz, 2C), 123.0, 121.7, 36.3; HRMS (ESI+) calculated for $C_{12}H_9F_3S$ 243.0455, found 243.0446.

3-Methyl-4-(4-(trifluoromethyl)benzyl)thiophene (**3j**). Colorless oil; yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.2 Hz, 2H), 7.30 (dd, J = 8.6, 0.8 Hz, 2H), 6.97 (m, 1H), 6.86 (d, J = 3.5 Hz, 1H), 3.97 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 139.4, 136.8, 129.0 (2C), 128.5 (d, J = 32 Hz, 1C), 125.3 (d, J = 4 Hz, 2C), 124.3 (d, J = 270 Hz, 1C), 122.6, 121.8, 35.2, 14.5; HRMS (ESI+) calculated for $C_{13}H_{11}F_3S$ 257.0612, found 257.0605.

3-(4-(Trifluoromethyl)benzyl)furan (**3k**). Colorless oil; yield 53%; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.59 (d, J = 8.1 Hz, 2H), 7.40 (m, 3H), 7.29 (d, J = 1.5 Hz, 1H), 6.28 (s, 1H), 3.87 (s, 2H). Spectroscopic data was consistent with literature.[20]

3-(Thiophen-3-ylmethyl)furan (**3l**). Colorless oil; yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 1H), 7.28 (m, 2H), 6.98 (m, 2H), 6.31 (d, J = 2.0 Hz, 1H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 140.8, 139.5, 128.3, 125.6, 123.8, 121.0, 25.8; HRMS (ESI+) calculated for C_9H_8OS 165.0374, found 165.0386.

2-(Thiophen-3-ylmethyl)furan (**3m**). Colorless oil; yield 83%; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.38 (dd, J = 2.0, 0.8 Hz, 1H), 7.31 (dd, J = 5.1, 3.1 Hz, 1H), 7.08 (m, 1H), 7.02 (dd, J = 5.1, 1.2 Hz, 1H), 6.35 (dd, J = 3.1, 2.0 Hz, 1H), 6.09 (m, 1H), 4.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 141.4, 138.5, 128.3, 125.6, 121.5, 110.3, 105.9, 29.0; HRMS (ESI+) calculated for C_9H_8OS 165.0374, found 165.0370. Spectroscopic data consistent with literature.[21]

3-(Thiophen-3-ylmethyl)pyridine (**3n**). Colorless oil; yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 1.6 Hz, 1H), 8.49 (dd, J = 4.7, 1.6 Hz, 1H), 7.51 (m, 1H), 7.29 (dd, J = 4.9, 2.9 Hz, 1H), 7.24 (ddd, J = 7.8, 4.7, 0.8 Hz, 1H), 6.95 (m, 1H), 6.91 (dd, J = 4.9, 1.4 Hz, 1H), 4.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 147.7, 140.1, 136.2, 136.0, 128.2, 126.2, 123.5, 121.7, 33.7; HRMS (ESI+) calculated for $C_{10}H_9NS$ 176.0534, found 176.0532.

1-(4-Methoxybenzyl)naphthalene (**3o**). White solid; yield 23%; ^{1}H NMR (400 MHz, $CDCl_3$): 8.04 (m, 1H), 7.89 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.46 (m, 3H), 7.30 (m, 1H), 7.15 (m, 2H), 6.85 (m, 2H), 4.42 (s, 2H), 3.80 (s, 3H). Spectroscopic data consistent with literature.[22]

1-(4-Trifluoromethanebenzyl)naphthalene (**3p**). White solid, yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.50 (m, 5H), 7.32 (m, 3H), 4.52 (s, 2H). Spectroscopic data consistent with literature.[23]

3-(Naphthalene-1-ylmethyl)benzonitrile (**3q**). Colorless oil; yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.84 (m, 3H), 7.53-7.45 (m, 6H), 7.39-7.32 (m, 2H), 4.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 134.9, 134.1, 133.2, 132.1, 131.8, 130.0, 129.3, 128.9, 127.9, 127.7, 126.4, 125.9, 125.6, 123.9, 119.0, 112.5, 38.6; HRMS (ESI+) calculated for $C_{18}H_{13}N$ 244.1126, found 244.1116.

Naphthalene-1-boronic acid pinacol ester (**4a**). Naphthalene-1-boronic acid (60 mmol) and pinacol (60 mmol) in THF (50 ml) were aged for 3 days at room temperature. Solvent was removed in vacuo. Purification by column chromatography (hexane/EtOAc) afforded the desired product as a white solid; yield 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 8.8 Hz, 1H), 8.10 (dd, J = 1.2, 6.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 1.2, 8.8 Hz, 1H), 7.56 (ddd, J = 1.6, 6.8, 10.0 Hz, 1H), 7.49 (dd, J = 7.2, 8.0 Hz, 2H), 1.45 (s, 12H). Spectroscopic data consistent with literature.[24]

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Supplementary material

Procedures for ligand, solvent and base screens. Detailed screening results. NMR spectra for all new compounds.