Palladium-Catalyzed Cross Coupling of Benzylammonium Salts with Boronic Acids under Mild Conditions

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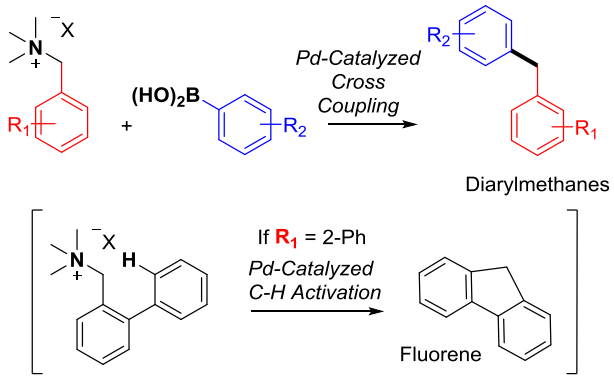

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Abstract Herein we describe a full account of the development of the palladium-catalyzed cross-coupling of benzylammonium salts with boronic acids. A range of different benzylamine-derived quaternary ammonium salts can be coupled successfully with boronic acids under relatively mild conditions. Our optimization has identified ligands that are able to chemoselectively cross-couple at the ammonium in the presence of chlorides. We demonstrate that intramolecular palladium-catalyzed C-H activation is also a viable pathway for the putative benzyl-Pd(II) intermediate obtained upon oxidative addition and have optimized this to obtain fluorene in good yield.

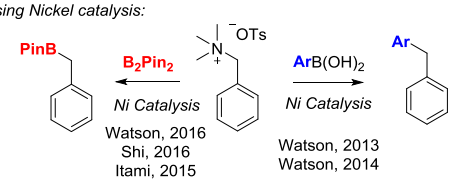
Key words cross-coupling, ammonium salts, palladium catalysis, diarylmethanes, fluorenes

Quaternary ammonium functionality occurs commonly in a wide range of compounds for many applications.[1] It is most frequently employed to promote aqueous solubility or to interact with an anionic partner through ion pairing. It is less often utilized as a reactive functional group, but is nevertheless known to engage in a number of useful reaction types, most prominently in Hofmann elimination[2] and sigmatropic rearrangements such as the Stevens and Sommelet-Hauser[3] rearrangements.[4] Quaternary ammonium salts have also been investigated to a lesser extent in the context of transition metal-catalyzed cross coupling, where they would represent a useful functional handle for oxidative addition due to their ease of accessibility by simple methylation of amines. Whilst the cross-coupling of aniline-derived ammonium salts has been quite well-explored,[5] until recently there are have been far fewer methods applicable to benzylaniline-derived ammonium salts. The diarylmethanes that would result from such couplings are a commonly encountered motif in pharmaceuticals and natural products. Very recently a number of elegant nickel-catalyzed cross couplings of benzylamine-derived ammonium salts have been reported with aryl boronic acids to give diarylmethanes,[5g, 6] with B_2Pin_2 to give benzylic boronates,[5i, 7] and with CO_2 to give carboxylic acids[8] (Scheme 1, a). Notably, Watson and co-workers were able to carry out these couplings stereospecifically from chiral ammonium salts, which proceeded with inversion of configuration.[6, 7b] Until our recent work, to the best of our knowledge only a single example of palladium-catalyzed cross coupling of benzylamine-derived ammonium salts had been reported, that is in a Heck-type reaction with alkenes (Scheme 1, b).[9] We recently reported the ion-pair directed C-H borylation of benzylamine-derived quaternary ammonium salts, which delivered high levels of *meta* selectivity using a novel anionic bipyridine ligand.[10] To probe the elaboration of the ammonium salt products of our borylation reaction, we wished to cross-couple benzylamine-derived ammonium salts with multiple functional handles, including chlorides. Watson and co-workers noted that with their Ni-catalyzed method, cross coupling occurred at both the ammonium group and chloride functionality.[6] Accordingly, we sought an alternative method and showed an example of palladium catalyzed coupling of the benzyl ammonium functionality with boronic acids, which allowed us to cross-couple in the presence of the chloride (Scheme 1, c). In this present paper we disclose a full account of our studies on this reaction (Scheme 1, d).[11] We also disclose the palladium-catalyzed C-H activation of an *ortho*-phenyl substituted ammonium salt to form fluorene, which we discovered during the course of these studies (Scheme 1, e).

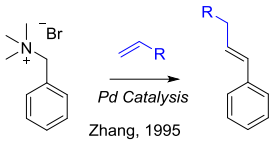
Scheme 1.

Previous Work on Cross Coupling of Quaternized Benzylamines:

(a) Using Nickel catalysis:

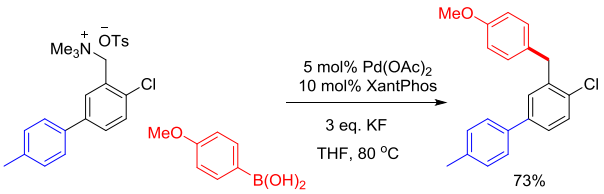


(b) Single example using Palladium catalysis:



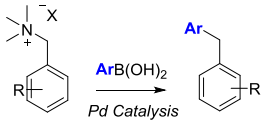
Our previous work:

(c) Example of palladium-catalyzed coupling with boronic acids (ref 10):

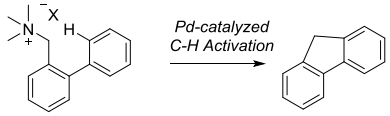


This work:

(d) Full description of optimisation and scope of cross-coupling reaction

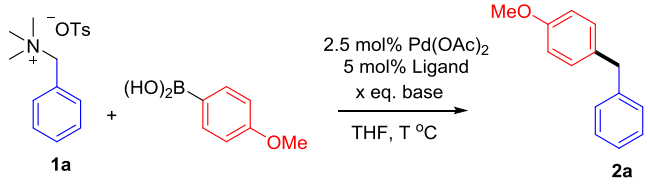


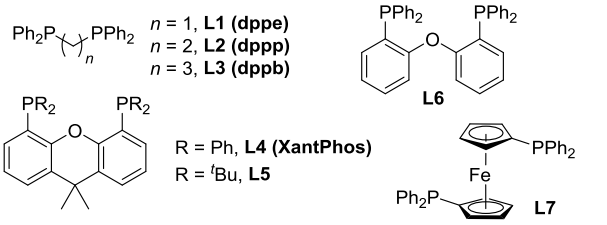
(e) Example of C-H activation of ortho-aryl benzyl ammonium salt to form a fluorene:



We chose benzyltrimethylammonium tosylate **1a** as our initial optimisation substrate and evaluated a number of ligands using KF as base at 60 °C. Of the ligands surveyed, we found that L4 (Xantphos), L6 and XPhos gave the highest yields of product (Table 1, entries 1-12). We subsequently tested L4 and XPhos at lower temperatures and found that XPhos appeared to be the more reactive, still giving good yields at only 40 °C (entries 13-16). A base screen using XPhos at 50 °C revealed that K_3PO_4 is also a highly effective base (entry 17). Among carbonate bases, only Cs_2CO_3 was viable (entries 18-20) and CsF proved to be similar to KF (entry 22).

Table 1. Optimization of the cross-coupling reaction on substrate **1a**



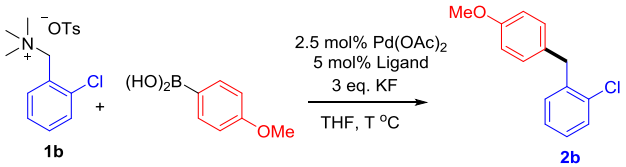


Entry	Ligand	Base	Temp (°C)	Yield **2a** (%)[a]
1	L1	KF	60	0
2	L2	KF	60	10
3	L3	KF	60	63
4	L4	KF	60	92
5	L5	KF	60	0
6	L6	KF	60	93
7	L7	KF	60	33
8	XPhos	KF	60	88
9	SPhos	KF	60	85
10	PPh_3	KF	60	29
11	P(*o*Tol)$_3$	KF	60	0
12	(S)-BINAP	KF	60	18
13	L4	KF	50	87
14	L4	KF	40	47
15	XPhos	KF	50	98 (82)
16	XPhos	KF	40	93
17	XPhos	K_3PO_4	50	94 (82)
18	XPhos	K_2CO_3	50	0
19	XPhos	Na_2CO_3	50	27
20	XPhos	Cs_2CO_3	50	97
21	XPhos	CsOAc	50	33
22	XPhos	CsF	50	93

[a]Determined by ^{1}H-NMR analysis with reference to an internal standard. Isolated yield given in parenthesis for selected experiments.

At this point, we also conducted an investigation into the effect of ligands on the cross coupling of 2-chloro ammonium salt **1b** as we wished to establish a protocol in which chloro-containing substrates could be selectively cross coupled at the ammonium moiety (Table 2). The ability to accomplish this would offer some complementarity to the Ni-catalyzed coupling methods in which chloride-containing substrates are incompatible.[6] Our survey revealed that XPhos gives very low yields of the desired product (entry 8), with the majority of coupling occurring at the chloride. However, L4 (XantPhos), which had been the second most active ligand in optimisation on **1a,** gave no coupling at the chloride and an excellent yield of desired product **2b** (entry 4). In this case heating to 60 °C was found to be necessary (entry 11). This emphasises how important appropriate ligand choice is to accomplish chemoselectivity in more complex substrates.

Table 2. Optimization of the cross-coupling reaction on chloride-containing substrate **1b**



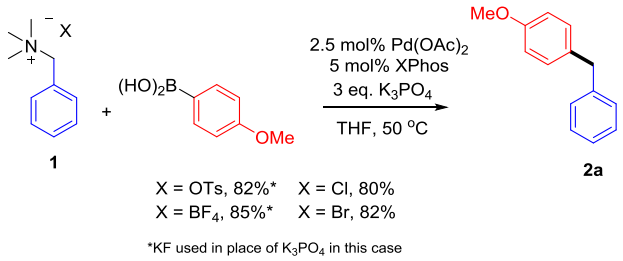
Entry	Ligand	Temp (°C)	Yield **2b** (%)[a]

1	L1	60	23
2	L2	60	28
3	L3	60	87
4	L4	60	93 (90)
5	L5	60	0
6	L6	60	86
7	L7	60	55
8	XPhos	60	4
9	SPhos	60	19
10	(S)-BINAP	60	5
11	L4	50	28

[a]Determined by ^{1}H-NMR analysis with reference to an internal standard. Isolated yield given in parenthesis for selected experiments.

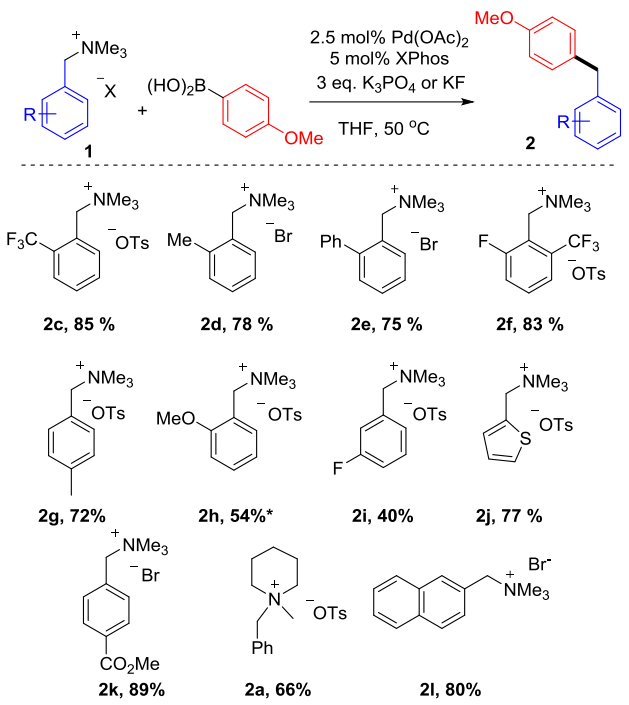
With optimized conditions in hand on the ammonium tosylate salt **1a**, we sought to examine tolerance of the counterion of the ammonium salt and were pleased to find it was general, with common counteranions such as halides and tetrafluoroborate all being compatible (Scheme 2).

Scheme 2. Evaluation of counteranion of ammonium salt.



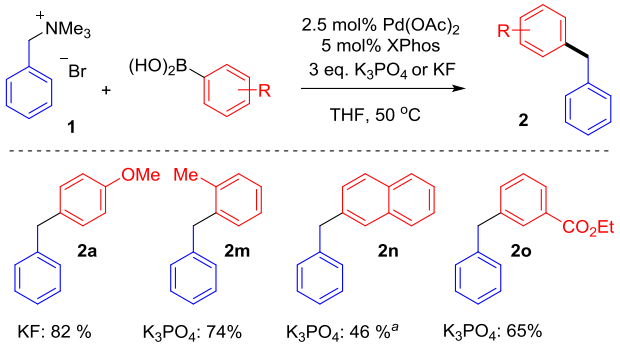
We next examined the scope of the coupling with respect to the benzylammonium salt component and investigated a range of different substituted aromatic and heteroaromatic salts (Scheme 3, starting materials shown in table for clarity). For a selection of examples, we found that *ortho*, *meta* and *para* substitution is tolerated. Also, a heterocyclic thiophene ammonium salt could be coupled in good yield. In the cases of the *ortho*-substituted compounds we often found that the bromide salts gave better yields than the corresponding tosylates, suggesting potentially higher reactivity. We also show that the ammonium salt does not have to be a trimethylammonium, as a piperidine variant reacts smoothly. In cases such as **2i** where the yield was low, the mass balance typically comprised unreacted starting material.

Scheme 3. Scope ammonium salt in coupling reaction



We next demonstrated that a representative selection of boronic acids are compatible in the cross-coupling with benzyltrimethylammonium bromide (Scheme 4). We found that a 4-pyridylboronic acid gave no conversion under these conditions but have not carried out extensive optimisation on this substrate at this stage.

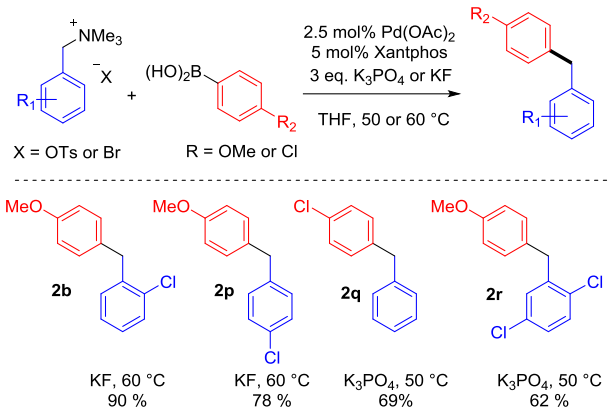
Scheme 4. Selection of boronic acids tested in cross coupling



[a] Comprises an inseparable mixture of 3:1 **2n**: homocoupled boronic acid

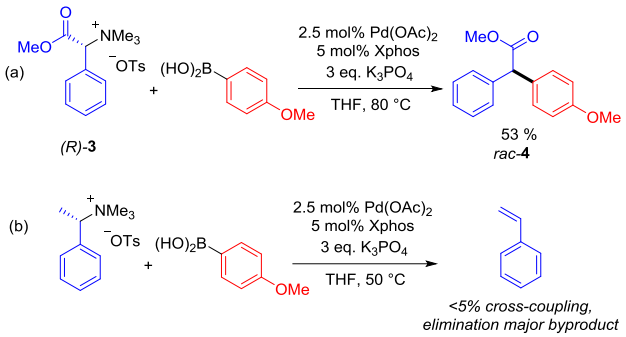
We were keen to examine substrates which contain a chloride on either the ammonium salt or the boronic acid in order to be able to demonstrate orthogonality between the chloride and the ammonium. Based on our previous ligand optimization (Table 2), we selected Xantphos and found that a number of chloride-containing ammonium salts and a chloride-containing boronic acid give good to excellent yields in the coupling, under mild conditions (Scheme 5). This leaves the chloride functionality intact for further cross-coupling.

Scheme 5. Evaluation of chloride-containing substrates using XantPhos as ligand



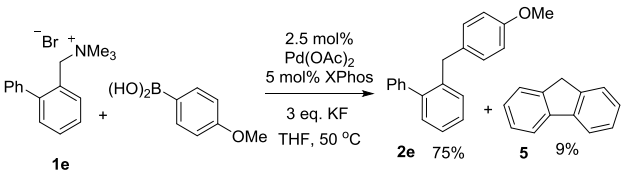
Given the elegant work of Watson and co-workers in which stereospecific coupling was found to occur under Nickel catalysis,[6] we were keen to evaluate whether stereochemical information is retained with our palladium-catalyzed protocol. By using an elevated temperature of 80 °C, we were able to obtain a moderate yield of coupled product **4** (Scheme 6a). However, HPLC analysis showed that this was racemic. The enantiopurity of the starting ammonium salt **3**, obtained by methylation of phenylglycine methyl ester, was confirmed by ^{1}H-NMR analysis after anion exchange with BINPHAT.[12] Therefore we can conclude that the stereochemical information was lost during the course of the cross-coupling process in this particular case. Unfortunately, we were not able to obtain >5% yield of the corresponding α-methyl substrate under our conditions and thus were not able to determine whether this substrate would retain its stereochemical fidelity (Scheme 6b). In this case the major by-product was the result of elimination to the styrene and a range of ligands were tested for this substrate with no success.

Scheme 6. Evaluation of cross-coupling of an α-chiral ammonium salt under our conditions



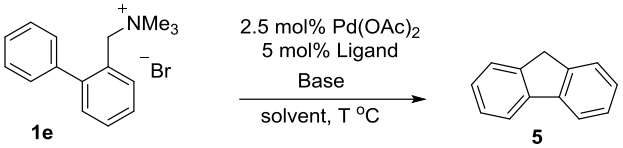
Finally, in our scope studies, we had observed an interesting side product that was produced in 9% yield in the cross-coupling of 2-phenylbenzylammonium salt **1e** (Scheme 7). This was determined to be fluorene (**5**) and most likely arises through C-H activation onto the *ortho*-phenyl ring being competitive with transmetallation with the boronic acid. Indeed, a literature search revealed that 2-phenylbenzyl halides undergo a similar C-H activation process under Pd(II)-catalysis.[13]

Scheme 7. Fluorene side-product observed in coupling of **1e**.



Fluorene derivatives are valuable structural motifs with various applications in chemistry and materials science,[14] and the ability to access them via C-H activation from benzylamine building blocks would be potentially new and useful route to access them. Furthermore, we have shown in our previous work that it is possible to cross-couple at the *ortho* position in the presence of the benzyl ammonium functionality.[10] This leads to the possibility of a tandem cross coupling/C-H activation process for fluorene synthesis. In an effort to increase the yield, we undertook optimization in the absence of the boronic acid (Table 3). Evaluation of bases showed that Cs_2CO_3 is by far the best (entries 1-6), although the yield of fluorene was still only moderate. Reducing the equivalents of base was detrimental (entry 7), as was increasing the temperature to 100 °C (entries 8 and 9). Whilst switching the solvent to dioxane or DME did not significantly improve matters (entries 10-13), it was found that doubling the catalyst/ligand loading was key (entries 14-15) and that the best yield could be achieved at 90 °C with a moderate three equivalents of base (entry 16). Use of DME as solvent together with (S)-BINAP as ligand gave comparable results (entries 17 and 18).[13]

Table 3. Optimization of intramolecular C-H activation to form fluorine (**x**)



Entry	Ligand	Base (eq.)	Temp (°C)	Solvent	Yield **2a** (%)[a]
1	XPhos	KF (5)	80	THF	0
2	XPhos	NMe_3 (5)	80	THF	0
3	XPhos	K_3PO_4 (5)	80	THF	12
4	XPhos	Na_2CO_3 (5)	80	THF	0
5	XPhos	$NaHCO_3$ (5)	80	THF	0
6	XPhos	Cs_2CO_3 (5)	80	THF	50
7	XPhos	Cs_2CO_3 (2)	80	THF	23
8	XPhos	Cs_2CO_3 (2)	100	THF	8
9	XPhos	Cs_2CO_3 (3)	100	THF	21
10	XPhos	Cs_2CO_3 (2)	100	Dioxane	24
11	XPhos	Cs_2CO_3 (3)	100	Dioxane	33
12	XPhos	Cs_2CO_3 (3)	100	DME	1
13	(S)-BINAP	Cs_2CO_3 (2)	100	DME	35
14[b]	XPhos	Cs_2CO_3 (2)	80	THF	46

15[b]	XPhos	Cs_2CO_3 (2)	90	THF	54
16[b]	XPhos	Cs_2CO_3 (3)	90	THF	64 (41)
17[b]	(S)-BINAP	Cs_2CO_3 (2)	90	DME	63 (61)
18[b]	(S)-BINAP	Cs_2CO_3 (3)	90	DME	46

[a]Determined by ^{1}H-NMR analysis with reference to an internal standard. Isolated yield given in parenthesis for selected experiments. [b] 5.0 mol% $Pd(OAc)_2$ and 10% mol% ligand used.

In summary, we have described in detail our studies on the development of the palladium-catalyzed coupling of benzyl ammonium salts and boronic acids under mild conditions. We have shown that a variety of substrates are compatible and that, with appropriate ligand choice, chemoselectivity can be obtained between reaction at the ammonium functionality and reaction at a chloride on the arene. This offers an advantage over the related Ni-catalyzed processes in which chlorides are not tolerated. In addition, we have found that palladium catalyzed C-H activation can occur if an aromatic ring is present at the *ortho* position of the benzylammonium salt, demonstrating another productive pathway for the putative benzyl-Pd(II) intermediate other than transmetallation.

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All reagents were used as supplied from commercial sources without further purification. Cross coupling reactions were carried out in 4 ml 15x45mm crimp top vials, which were purged with Argon. Vials were heated in welled heating blocks. ^{1}H-NMR spectra were recorded on a 600MHz Bruker Avance 600 BBI spectrometer. Chemical shifts are reported in parts per million (ppm) and the spectra are calibrated to the resonance resulting from incomplete deuteration of solvents. ^{13}C NMR spectra were recorded on a 600MHz Bruker Avance 600 BBI spectrometer or 500MHz DCH Cryoprobe spectrometer with complete proton decoupling. Chemical shifts are reported in ppm and calibrated to the solvent resonance resulting from incomplete deuteration. Data are reported as follows: chemical shift in ppm, integration (only for ^{1}H spectra), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or combinations of them; ^{13}C signals are singlets unless otherwise stated), coupling constants J in Hz. ^{19}F NMR spectra were recorded on a 400MHz Avance III HD Smart Probe spectrometer. Analytical thin layer chromatography was performed using precoated Merck glass backed silica gel plates (Silicagel 60 F254). Visualisation was by ultraviolet fluorescence (254nm) and staining the plates with cerium ammonium molybdate (CAM). Flash column chromatography was performed using silica gel 60 (0.040μm to 0.063 μm).

Synthesis of Ammonium Salts

The preparations of **1a**, **1b**, **1c**, **1d**, **1h** and **1i** have been previously reported.[10]

General Procedure A for the Preparation of Ammonium Tosylate Salts

A flask was charged with $NaHCO_3$ which was suspended in either MeOH or MeCN. The specified benzylamine was added, followed by methyl toluenesulfonate. After stirring the reaction at room temperature overnight, the solvent was removed and the precipitate filtered off and washed with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure, redissolved in a minimum amount of CH_2Cl_2 and the product precipitated by addition of Et_2O. The precipitate was collected by filtration and washed with further Et_2O. If further purification was necessary, it is stated accordingly**.**

General Procedure B for the Preparation of Ammonium Bromide Salts

Trimethylamine was added to a solution of a benzylbromide in MeCN and the resulting mixture was stirred at room temperature for 1 h. The volatiles were evaporated and the remaining precipitate was collected by filtration and washed with Et_2O.

1-([1,1'-biphenyl]-2-yl)-N,N,N-trimethylmethanaminium bromide (1e)

Prepared according to General Procedure B with 2-(bromomethyl)-1,1'-biphenyl (0.73 ml, 4 mmol, 1 eq.) and trimethylamine (6 ml, 1M in THF, 6 mmol, 1.5 eq.) in MeCN (4 ml), the white solid of **1e** was obtained (1.169 g, 3.8 mmol, 95 %).

^{1}H NMR (600MHz, d_6-DMSO) *d* 7.74 (dd, J = 7.7, 1.3 Hz, 1H), 7.62 (td, J = 7.5, 1.4 Hz, 1H), 7.57 – 7.44 (m, 4H), 7.47 – 7.37 (m, 4H), 4.68 (s, 2H), 2.76 (s, 9H);

^{13}C NMR (151MHz, d_6-DMSO) *d* 144.55, 139.95, 134.64, 131.48, 130.67, 129.48, 128.87, 127.69, 127.67, 125.35, 64.79, 52.00.

HRMS m/z: $[M]^+$ calc'd for $[C_{17}H_{23}N]^+$ expect 226.1596; found 226.1597.

1-(2-fluoro-6-(trifluoromethyl)phenyl)-N,N,N-trimethylmethanaminium tosylate (1f)

Trimethylamine (1.28 mL, 5.4 mmol, 4.2M in ethanol) was added to a solution of 2-fluoro-6-(trifluoromethyl)benzyl bromide (700 mg, 2.72 mmol) in acetonitrile and stirred for 1 hour at room temperature. The volatiles were evaporated under reduced pressure, the residue dissolved in CH_2Cl_2 and Et_2O was slowly added. The precipitated bromide salt was collected by filtration (840 mg, 2.65 mmol, 98%). This salt (632 mg, 2 mmol) was dissolved in chloroform and AgOTs (837 mmol, 3 mmol) was added. The resulting reaction mixture was stirred for 30 minutes, then filtered through a bed of Celite. The solvent was removed under reduced pressure to afford the tosylate salt **1f** as a white solid (572 mg, 1.4 mmol, 70%).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.68-7.63 (m, 3H), 7.59 (d, J = 7.9 Hz, 1H), 7.43 (t, J = 8.8 Hz, 1H), 7.05 (d, J = 8.0 Hz, 4.81 (s, 2H), 3.29 (s, 9H), 2.25 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 162.5 (d, $^1J_{CF}$ = 254 Hz), 143.8, 139.2, 133.9 (d, $^3J_{CF}$ = 10 Hz), 132.5 (dq, $^3J_{CF}/^2J_{CF}$ = 1, 32 Hz), 128.6, 125.7, 124.2 (dq, $^4J_{CF}/^3J_{CF}$ = 6, 3 Hz), 123.0 (q, $^1J_{CF}$ = 271 Hz), 121.0 (d, $^2J_{CF}$ = 24 Hz), 113.9 (d, $^2J_{CF}$ = 16 Hz), 59.6, 54.2, 21.2.

HRMS m/z: $[M]^+$ calc'd for $[C_{11}H_{14}NF_4]^+$ expect 263.1062; found 263.1056.

N,N,N-trimethyl-1-(p-tolyl)methanaminium tosylate (1g)

To a solution of the corresponding bromide salt (244 mg, 1.0 mmol) in $CHCl_3$ (5 ml) was added AgOTs (418 mg, 1.5 mmol) and the reaction stirred at room temperature for 30 mins. After this time the reaction was filtered through a thin pad of Celite and the solvent evaporated to give the title compound as a white solid (170 mg, 0.51 mmol, 51% yield).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 4.55 (s, 2H), 3.12 (s, 9H), 2.30 (s, 3H), 2.28 (s, 1H);

13C NMR (151MHz, $CDCl_3$) δ 143.6, 140.5, 139.5, 132.9, 129.6, 128.8, 125.8, 124.7, 68.7, 52.1, 21.28, 21.27.

HRMS m/z: $[M]^+$ calc'd for $[C_{11}H_{18}N]^+$ expect 164.1434; found 164.1432.

N,N,N-trimethyl-1-(thiophen-2-yl)methanaminium tosylate (1j)

Prepared according to General Procedure A with thiophen-2-ylmethanamine (0.51 ml, 5.0 mmol, 1 eq.), $NaHCO_3$ (4.2 g, 50 mmol, 10 eq.) and methyl toluenesulfonate (4.7 ml, 25 mmol, 5 eq.) in 10 ml MeOH. This yielded **1j** as a white powder (1.34 g, 4.1 mmol, 82 %).

^{1}H NMR (600 MHz, d_6-DMSO) δ 7.81 (d, *J* = 5.1 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 3.2 Hz, 1H), 7.18 (dd, *J* = 3.7, 5.0 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.81 (s, 2H), 3.05 (s, 9H), 2.28 (s, 3H).

^{13}C NMR (151MHz, d_6-DMSO) 146.0, 138.2, 134.7, 131.1, 129.4, 128.6, 128.3, 125.9, 62.1, 51.9, 21.2.

HRMS m/z: $[M]^+$ calc'd for $[C_8H_{14}NS]^+$ expect 156.0841; found 156.0841.

1-(4-(methoxycarbonyl)phenyl)-N,N,N-trimethylmethanaminium bromide (1k)[15]

Prepared according to General Procedure B with methyl 4-(bromomethyl)benzoate (458 mg, 2 mmol, 1 eq.) and trimethylamine (3 ml, 1M in THF, 3 mmol, 1.5 eq.) in MeCN (8 ml), solid **1k** was obtained (534 mg, 1.9 mmol, 93 %).

^{1}H NMR (600MHz, MeOD-*d*$_4$) *d* 8.19 – 8.14 (m, 2H), 7.75 – 7.70 (m, 2H), 4.65 (s, 2H), 3.94 (s, 3H), 3.16 (s, 9H).

^{13}C NMR (151MHz, MeOD-*d*$_4$) δ 166.2, 133.0, 132.5, 132.1, 129.7, 68.2, 52.0, 51.6

Data in agreement with the literature.[15]

N,N,N-trimethyl-1-(naphthalen-2-yl)methanaminium bromide (1l)[16]

Prepared according to General Procedure B with 2-(bromomethyl)naphthalene (442 mg, 2 mmol, 1 eq.) and trimethylamine (3 ml, 1M in THF, 3 mmol, 1.5 eq.) in MeCN (4 ml), white solid **1l** was obtained (486 mg, 1.7 mmol, 87 %).

^{1}H NMR (600MHz, MeOD-*d*$_4$) *d* 8.15 (s, 1H), 8.06 – 7.95 (m, 3H), 7.66 – 7.58 (m, 3H), 4.73 (s, 2H), 3.18 (s, 9H).

13C NMR (151MHz, MeOD-*d*$_4$) δ 134.0, 133.2, 133.0, 128.7, 128.6, 128.1, 127.5, 127.4, 126.7, 125.0, 69.2, 51.9.

Data in agreement with the literature.[16]

1-(4-chlorophenyl)-N,N,N-trimethylmethanaminium 4-methylbenzenesulfonate (1p)

Prepared according to General Procedure A with 4-chlorobenzylamine (0.48 ml, 4.0 mmol, 1 eq.), $NaHCO_3$ (3.36 g, 40 mmol, 10 eq.) and methyl toluenesulfonate (3.0 ml, 20 mmol, 5 eq.) in 14 ml MeOH. This yielded **1o** as a white powder (1.216 g, 3.4 mmol, 85 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 4.79 (s, 2H), 3.22 (s, 9H), 2.33 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 143.3, 139.8, 136.9, 134.5, 129.3, 128.9, 126.2, 125.7, 67.7, 52.3, 21.3.

HRMS m/z: $[M]^+$ calc'd for $[C_{10}H_{15}NCl]^+$ expect 184.0888; found 184.0886.

1-(2,5-dichlorophenyl)-N,N,N-trimethylmethanaminium methylbenzenesulfonate (1r)

Prepared according to General Procedure A with 2,5-dichlorobenzylamine (1.0 g, 5.7 mmol, 1 eq.), $NaHCO_3$ (4.7 g, 57 mmol, 10 eq.) and methyl toluenesulfonate (4.3 ml, 28.5 mmol, 5 eq.) in 20 ml MeOH. This yielded **1r** as a white powder (2.1 g, 5.4 mmol, 94 %).

^{1}H NMR (600MHz, MeOD-*d*$_4$) δ 7.79 (d, J = 2.3 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 8.5, 2.3 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 4.71 (s, 2H), 3.21 (s, 9H), 2.38 (s, 3H);

^{13}C NMR (151MHz, MeOD-*d*$_4$) δ 144.0, 141.9, 136.6, 136.5, 134.8, 134.0, 133.6, 130.1, 129.3, 127.2, 66.4, 54.0, 21.6.

HRMS m/z: $[M]^+$ calc'd for $[C_{10}H_{14}NCl_2]^+$ expect 218.0498; found 218.0488.

(R)-2-methoxy-N,N,N-trimethyl-2-oxo-1-phenylethan-1-aminium 4-methylbenzenesulfonate (3)

Prepared according to General Procedure A with methyl (R)-2-amino-2-phenylacetate hydrochloride (807 mg, 4.0 mmol, 1 eq.), $NaHCO_3$ (3.36 g, 40 mmol, 10 eq.) and methyl toluenesulfonate (3 ml, 20 mmol, 5 eq.) in 14 ml MeCN. For further purification the crude was dissolved in water (20 ml) and washed with CH_2Cl_2 (3x20 ml) and Et_2O (3x20 ml). Water was removed under reduced pressure, yielding **1p** as an oil (647 mg, 1.7 mmol, 43%). The enantiopurity was controlled by dissolving **1p** (5 mg) and S-BINPHAT (15 mg) in CH_2Cl_2/acetone (2 ml, 1:1) and stirring for 5 min.

After removing the solvent, the taken ^{1}H NMR (600MHz, $CDCl_3$) showed only one ammonium peak, conforming the product's enantiopurity. A portion (533 mg) of the obtained oil were additionally washed twice with Et_2O, decanting the washing off and dissolved in a minimum amount of CH_2Cl_2. A white solid (330 mg) was obtained by addition of Et_2O, collected by filtration and washed with Et_2O.

^{1}H NMR (600MHz, $CDCl_3$) *d* 7.81 – 7.76 (m, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 6.09 (s, 1H), 3.70 (s, 3H), 3.45 (s, 9H), 2.32 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) *d* 167.4, 143.3, 139.6, 131.6, 129.7, 128.8, 126.8, 125.9, 74.6, 53.5, 51.8, 21.4.

HRMS m/z: $[M]^+$ calc'd for $[C_{12}H_{18}NO_2]^+$ expect 208.1338; found 208.1336.

Palladium Catalyzed Cross-Coupling

General procedure for palladium-catalyzed cross-coupling

The desired amount of substrate, boronic acid (3 eq.), base (3 eq.), $Pd(OAc)_2$ (2.5 mol%.) and ligand (5 mol%.) were weighed out as solids, the vial sealed and purged with argon, then solvent added and purged again. The reactions were run at a specified reaction time over night. The crude was filtered through a pad of Celite and washed three times with $CHCl_3$. The solvent was removed under reduced pressure, an internal standard added and the reaction analysed by ^{1}H NMR. For purification, the analysed mixture was concentrated, the product extracted with Et_2O and filtered through dry $MgSO_4$ and further purified by flash column chromatography.

1-benzyl-4-methoxybenzene (2a)[17]

Following general procedure using **1a** (OTs) (78 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), Xphos (4.8 mg, $1x10^{-2}$ mmol), in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2a** (33 mg, 0.16 mmol, 82 %).

^{1}H NMR (600MHz, CDCl3) δ 7.30 (t, J = 7.6 Hz, 2H), 7.24 – 7.17 (m, 3H), 7.13 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.94 (s, 2H), 3.80 (s, 3H); **^{13}C NMR** (151MHz, CDCl3) δ 158.0, 141.7, 133.3, 129.9, 128.9, 128.5, 126.1, 114.0, 55.3, 41.1.

Data in agreement with literature.[17]

1-chloro-2-(4-methoxybenzyl)benzene (2b)[18]

Following general procedure using 1-(2-chlorophenyl)-N,N,N-trimethylmethanaminium tosylate (36 mg, 0.1 mmol), (4-methoxyphenyl)boronic acid (46 mg, 0.3 mmol), KF (17 mg, 0.3 mmol), $Pd(OAc)_2$ (0.6 mg, 2.5 $x10^{-3}$ mmol), Xantphos (2.9 mg, $5x10^{-3}$ mmol) in THF (0.2 ml) at 60 °C. Purification by silica gel chromatography (25% to 40% CH_2Cl_2/petroleum ether) gave **2b** (21 mg, 0.09 mmol, 90 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.37 (dd, J = 7.5, 1.7 Hz, 1H), 7.23 – 7.10 (m, 5H), 6.87 – 6.81 (m, 2H), 4.05 (s, 2H), 3.79 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 158.2, 139.2, 134.2, 131.6, 131.0, 130.0, 129.6, 127.6, 126.9, 114.0, 55.3, 38.4.

Data in agreement with literature.[18]

1-(4-methoxybenzyl)-2-(trifluoromethyl)benzene (2c)[19]

Following general procedure using **1c** (OTs) (78 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$mmol), Xphos (4.8 mg, $1x10^{-2}$ mmol), in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2c** (45 mg, 0.17 mmol, 85 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.67 (dd, J = 7.9, 1.3 Hz, 1H), 7.43 (td, J = 7.6, 1.3 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.11 – 7.06 (m, 2H), 6.89 – 6.83 (m, 2H), 4.14 (s, 2H), 3.80 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 158.1, 140.0, 131.8, 131.7, 131.5, 130.1, 128.5 (q, $^2J_{CF}$ = 29.7 Hz), 126.0, 125.7 (q, $^3J_{CF}$ = 5.8 Hz), 124.5 (q, $^1J_{CF}$ = 273.9 Hz), 113.9, 55.2, 36.8 (q, $^4J_{CF}$ = 2.2 Hz);

^{19}F NMR (376 MHz, $CDCl_3$) δ -59.6.

Data in agreement with literature.[19]

1-(4-methoxybenzyl)-2-methylbenzene (2d)[17]

Following general procedure using **1d** (Br) (49 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3} mmol), Xphos (4.8mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2d** (33 mg, 0.16 mmol, 78 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 3H), 7.12 – 7.02 (m, 3H), 6.85 – 6.80 (m, 2H), 3.93 (s, 2H), 3.79 (s, 3H), 2.25 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 157.8, 139.3, 136.5, 132.4, 130.2, 129.7, 129.6, 126.3, 125.9, 113.7, 55.2, 38.5, 19.6.

Data in agreement with literature.[17]

2-(4-methoxybenzyl)-1,1'-biphenyl (2e)[20]

Following general procedure using **1e** (Br) (61 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2e** (41 mg, 0.15 mmol, 75 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.37 – 7.31 (m, 1H), 7.34 – 7.24 (m, 5H), 7.22 (dd, J = 6.7, 1.8 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.80 – 6.74 (m, 2H), 3.91 (s, 2H), 3.78 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) *δ* 157.7, 142.1, 141.6, 138.6, 133.5, 130.1, 130.0, 129.7, 129.2, 128.0, 127.4, 126.8, 126.0, 113.5, 55.2, 38.1.

Data in agreement with literature.[20]

1-fluoro-2-(4-methoxybenzyl)-3-(trifluoromethyl)benzene (2f)

Following general procedure using **1f** (OTs) (82 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), KF (35 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (20% CH_2Cl_2/petroleum ether) gave **2f** (47 mg, 0.17 mmol, 83 %).

^{1}H NMR (600MHz, $CDCl_3$) *δ* 7.50 (d, J = 7.8 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.29 – 7.22 (m, 1H), 7.07 (d, J = 8.3 Hz, 2H), 6.84 – 6.78 (m, 2H), 4.14 (s, 2H), 3.77 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 162.1 (d, $^1J_{CF}$ = 248 Hz), 158.1, 131.1, 130.9 (dq, $^3J_{CF}$/$^2J_{CF}$ = 4, 30 Hz), 129.2, 128.2 (d, $^3J_{CF}$ = 9 Hz), 127.3 (d, $^2J_{CF}$ = 17.6 Hz), 123.9 (dq, $^4J_{CF}$/$^1J_{CF}$ = 4, 274 Hz), 121.9 (dq, $^4J_{CF}$/$^3J_{CF}$ = 4, 6 Hz), 119.3 (d, $^2J_{CF}$ = 23 Hz), 113.8, 55.3, 30.6 (dq, $^3J_{CF}$/$^4J_{CF}$ = 4, 2 Hz);

^{19}F NMR (376 MHz, $CDCl_3$) δ -58.8, -112.3.

HRMS m/z: $[M]^+$ calc'd for $[C_{15}H_{12}F_4O]^+$ expect 284.0824; found 284.0823.

1-methoxy-4-(4-methylbenzyl)benzene (2g)[17]

Following general procedure using **1g** (OTs) (67 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3}mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (25% CH_2Cl_2/petroleum ether) gave **2g** (31 mg, 0.14 mmol, 72 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 6H), 6.87 – 6.81 (m, 2H), 3.90 (s, 2H), 3.79 (s, 3H), 2.33 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 158.0, 138.6, 135.5, 133.6, 129.9, 129.2, 128.8, 113.9, 55.3, 40.7, 21.1.

Data in agreement with literature.[17]

1-methoxy-2-(4-methoxybenzyl)benzene (2h)[6]

Following general procedure using **1h** (OTs) (70 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 80 °C. Purification by silica gel chromatography (first run with 25% up to 40% CH_2Cl_2/petroleum ether, second run with 10% Et_2O/petroleum ether) gave **2h** (25 mg, 0.11 mmol, 54 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.19 (td, J = 7.8, 1.8 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.06 (dd, J = 7.2, 1.7 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.85 – 6.79 (m, 2H), 3.92 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 157.8, 157.4, 133.2, 130.2, 130.2, 130.0, 127.4, 120.5, 113.8, 110.5, 55.4, 55.3, 35.0.

Data in agreement with literature.[6]

1-fluoro-3-(4-methoxybenzyl)benzene (2i)[17]

Following general procedure using **1i** (OTs) (68 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), Pd(OAc)2 (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (25% CH_2Cl_2/petroleum ether) gave **2i** (17 mg, 0.08 mmol, 40 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.23 (td, J = 7.9, 6.0 Hz, 1H), 7.13 – 7.08 (m, 2H), 6.98 – 6.93 (m, 1H), 6.91 – 6.82 (m, 4H), 3.92 (s, 2H), 3.79 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 163.1 (d, $^1J_{CF}$ = 245.5 Hz), 158.2, 144.3 (d, $^3J_{CF}$ = 7.2 Hz), 132.5, 130.0, 129.9 (d, $^3J_{CF}$ = 8.3 Hz), 124.5 (d, $^4J_{CF}$ = 2.8 Hz), 115.7 (d, $^2J_{CF}$ = 21.1 Hz), 114.1, 113.0 (d, $^2J_{CF}$ = 21.1 Hz), 55.4, 40.88 (d, $^4J_{CF}$ = 1.8 Hz).

Data in agreement with literature.[17]

2-(4-methoxybenzyl)thiophene (2j)[17]

Following general procedure using **1j** (OTs) (66 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2}mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (25% up to 40% CH_2Cl_2/petroleum ether) gave **2j** (31 mg, 0.15 mmol, 77 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 7.15 (dd, J = 5.1, 1.2 Hz, 1H), 6.93 (dd, J = 5.1, 3.4 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.80 (dq, J = 3.4, 1.1 Hz, 1H), 4.12 (s, 2H), 3.81 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 158.3, 144.8, 132.7, 129.7, 126.9, 124.9, 123.9, 114.0, 55.3, 35.3.

Data in agreement with literature.[17]

Methyl 4-(4-methoxybenzyl)benzoate (2k)[21]

Following general procedure using **1k** (Br) (58 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), Pd(OAc)2 (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (4% up to 8% EtOAc/petroleum ether) gave **2n** (46 mg, 0.18 mmol, 89 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.97 (s, 2H), 3.90 (s, 3H), 3.79 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 167.2, 158.3, 147.1, 132.3, 130.0, 129.9, 128.9, 128.1, 114.1, 55.4, 52.1, 41.1.

Data in agreement with the literature.[21]

2-(4-Methoxybenzyl)naphthalene (2l)[6]

Following general procedure using 1l (56 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, 5x10^{-3} mmol), Xphos (4.8 mg, 1x10^{-2} mmol) in THF (0.4 ml) at 50 °C. Analysis of crude ^{1}H NMR showed 82 % yield,

purification by silica gel chromatography (25 % CH_2Cl_2/petroleum) gave 2l (40 mg, 0.16 mmol, 80 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 3H), 7.67 – 7.63 (m, 1H), 7.46 (dqd, J = 8.2, 6.8, 1.5 Hz, 2H), 7.34 (dd, J = 8.4, 1.8 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.91 – 6.85 (m, 2H), 4.12 (s, 2H), 3.81 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.15, 139.19, 133.74, 133.21, 132.18, 130.09, 128.17, 127.74, 127.71, 127.67, 127.03, 126.07, 125.42, 114.04, 55.38, 41.34.

Data in agreement with the literature.[6]

1-benzyl-2-methylbenzene (2m)[22]

Following general procedure using **1a** (OTs) (64 mg, 0.2 mmol), (2-methylphenyl)boronic acid (82 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), Xphos (4.8 mg, $1x10^{-2}$mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (1% up to 3% EtOAc/petroleum ether) gave **2m** (containing ~5% homocoupled boronic acid impurity) as a colourless oil (27 mg, 74%).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.22 – 7.09 (m, 7H), 4.00 (s, 2H), 2.26 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 140.5, 139.0, 136.7, 130.4, 130.0, 128.8, 128.5, 126.5, 126.1, 126.0, 39.5, 19.82.

Data in agreement with literature.[22]

2-benzylnaphthalene (2n)

Following general procedure using **1a** (OTs) (64 mg, 0.2 mmol), naphthalen-2-ylboronic acid (103 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), Xphos (4.8 mg, $1x10^{-2}$ mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (2% up to 5% EtOAc/petroleum ether) gave a mixture of **2n** and the homocoupled boronic acid in a 3:1 ratio**.** (28 mg, 0.12 mmol, both homo and cross coupled products, 46%).

2l: ^{1}H NMR (600MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 3H), 7.65 (d, J = 1.8 Hz, 1H), 7.45 (ddd, J = 8.2, 6.8, 1.5 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.28 – 7.20 (m, 3H), 4.16 (s, 2H);

^{13}C NMR (151MHz, $CDCl_3$) δ 141.1, 138.7, 133.7, 132.2, 129.1, 128.6, 128.2, 127.7, 127.7, 127.6, 127.2, 126.2, 126.1, 125.4, 42.2.

Data in agreement with literature.[6]

Homocoupled impurity: ^{1}H NMR (600MHz, $CDCl_3$) δ 8.19 (d, J = 1.7 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 7.4 Hz, 2H), 7.91 (dd, J = 8.4, 1.8 Hz, 4H), 7.53 (dqd, J = 8.2, 6.9, 1.4 Hz, 4H); **^{13}C NMR** (151MHz, $CDCl_3$) δ 138.5, 133.8, 132.8, 128.6, 128.3, 127.8, 126.5, 126.2, 126.1, 125.8.

Data in agreement with literature.[23]

Ethyl 3-benzylbenzoate (2o)[24]

Following general procedure using **1a** (OTs) (64 mg, 0.2 mmol), 3-ethoxycarbonylphenylboronic acid (116 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), XPhos (4.8 mg, $1x10^{-2}$ mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (5% EtOAC in petroleum ether then a further purification with 30% to 50% CH_2Cl_2/petroleum ether) yielded **2o** as a colourless oil (31 mg, 0.13 mmol, 65%).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.91 (dt, J = 6.9, 1.4 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.24 – 7.20 (m, 3H), 4.38 (q, J = 7.2 Hz, 2H), 4.05 (s, 2H), 1.40 (t, J = 7.2 Hz, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 166.7, 141.4, 140.5, 133.4, 130.7, 130.0, 128.9, 128.6, 128.5, 127.4, 126.3, 60.9, 41.7, 14.3.

Data in agreement with literature.[24]

1-chloro-4-(4-methoxybenzyl)benzene (2p)[25]

Following general procedure using **1p** (OTs) (36 mg, 0.1 mmol), (4-methoxyphenyl)boronic acid (46 mg, 0.3 mmol), KF (17 mg, 0.3 mmol), $Pd(OAc)_2$ (0.6 mg, $2.5x10^{-3}$ mmol), Xantphos (2.9 mg, $5x10^{-3}$ mmol) in THF (0.2 ml) at 60 °C. Purification by silica gel chromatography (25% CH_2Cl_2/petroleum ether) gave **2p** (18 mg, 0.08 mmol, 78 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 7.13 – 7.05 (m, 4H), 6.86 – 6.81 (m, 2H), 3.89 (s, 2H), 3.79 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 158.2, 140.1, 132.7, 131.9, 130.2, 129.9, 128.6, 114.1, 55.4, 40.4.

Data in agreement with literature.[25]

1-benzyl-4-chlorobenzene (2q)[26]

Following general procedure using 1a (Br) (46 mg, 0.2 mmol), (4-chlorophenyl)boronic acid (78 mg, 0.5 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), Xantphos (5.8 mg, $1x10^{-2}$ mmol) in THF (0.4 ml) at 50 °C. Analysis of crude ^{1}H NMR showed 94% yield, purification by silica gel chromatography (1% CH_2Cl_2/hexane) gave **2q** (28 mg, 0.14 mmol, 69%).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.31 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 3.97 (s, 2H);

^{13}C NMR (151MHz, $CDCl_3$) δ 140.5, 139.6, 131.9, 130.2, 128.8, 128.6, 128.5, 126.3, 41.2.

Data in agreement the literature.[26]

1,4-dichloro-2-(4-methoxybenzyl)benzene (2r)

Following general procedure using **1r** (OTs) (78 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), Xantphos (5.8 mg, $1x10^{-2}$ mmol) in THF (0.4 ml) at 50 °C. Purification by silica gel chromatography (25% CH_2Cl_2/petroleum ether) gave **2r** (33 mg, 0.12 mmol, 62 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 1H), 7.16 – 7.08 (m, 4H), 6.89 – 6.83 (m, 2H), 4.00 (s, 2H), 3.80 (s, 3H);

^{13}C NMR (151MHz, $CDCl_3$) δ 158.4, 141.0, 132.7, 132.4, 130.7, 130.6, 130.6, 130.1, 127.7, 114.2, 55.3, 38.3.

HRMS m/z: [M] calc'd for [$C_{14}H_{12}Cl_2O$] expect 266.0265; found 266.0253.

Methyl 2-(4-methoxyphenyl)-2-phenylacetate (4)[27]

Following general procedure using **3** (76 mg, 0.2 mmol), (4-methoxyphenyl)boronic acid (91 mg, 0.6 mmol), K_3PO_4 (127 mg, 0.6 mmol), $Pd(OAc)_2$ (1.1 mg, $5x10^{-3}$ mmol), Xphos (4.8 mg, $1x10^{-2}$ mmol) in THF (0.4 ml) at 80 °C. Purification by silica gel chromatography (3% up to 5% EtOAc/petroleum ether) gave **5** (27 mg, 0.11 mmol, 53%). Chiral HPLC analysis (Chiralcel OD Column, 1 ml/min, 0.5% *i*PrOH/hexane, t_R = 18.64 min and 19.95 min) of the product showed a racemic mixture was obtained.

^{1}H NMR (600MHz, CDCl3) δ 7.36 – 7.27 (m, 4H), 7.30 – 7.21 (m, 3H), 6.89 – 6.83 (m, 2H), 4.99 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H);

^{13}C NMR (151MHz, CDCl3) δ 173.3, 158.9, 139.1, 130.8, 129.8, 128.7, 128.5, 127.3, 114.1, 56.3, 55.3, 52.4.

Data in agreement with literature.[27]

Fluorene (5)[28]

Following general procedure (excluding boronic acid) using **1e** (61 mg, 0.2 mmol, 1 eq.), Cs_2CO_3 (196 mg, 0.6 mmol, 2 eq.), $Pd(OAc)_2$ (2.2 mg, $1x10^{-2}$ mmol, 5 mol%), Xphos (9.6 mg, $2x10^{-2}$ mmol, 10 mol%) in THF (0.4 ml) at 90 °C. Purification by silica gel chromatography (2% CH_2Cl_2/petroleum ether) gave **5** (14 mg, 0.08 mmol, 41 %).

^{1}H NMR (600MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 7.4 Hz, 2H), 7.39 (td, J = 7.4, 1.0 Hz, 2H), 7.32 (td, J = 7.4, 1.1 Hz, 2H), 3.92 (s, 2H);

^{13}C NMR (151MHz, $CDCl_3$) δ 143.3, 141.8, 126.8, 126.8, 125.1, 120.0, 37.0. Data in agreement with literature.[28]

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References

(1) Zhang, C.; Cui, F.; Zeng, G.-m.; Jiang, M.; Yang, Z.-z.; Yu, Z.-g.; Zhu, M.-y.; Shen, L.-q. *Science of The Total Environment* **2015,** *518–519*, 352.

(2) Cope, A. C.; Trumbull, E. R., Olefins from Amines: The Hofmann Elimination Reaction and Amine Oxide Pyrolysis. In *Organic Reactions*, ed.; John Wiley & Sons, Inc.: 2004.

(3) (a) Tayama, E.; Kimura, H. *Angew. Chem. Int. Ed.* **2007,** *46*, 8869; (b) Biswas, B.; Singleton, D. A. *J. Am. Chem. Soc.* **2015,** *137*, 14244.

(4) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2009,** *38*, 1027; (b) Pine, S. H., The Base-Promoted Rearrangements of Quaternary Ammonium Salts. In *Organic Reactions*, ed.; John Wiley & Sons, Inc.: 2004.

(5) (a) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003,** *125*, 6046; (b) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010,** *12*, 4388; (c) Xie, L.-G.; Wang, Z.-X. *Angew. Chem. Int. Ed.* **2011,** *50*, 4901; (d) Zhang, X.-Q.; Wang, Z.-X. *J. Org. Chem.* **2012,** *77*, 3658; (e) Guo, W.-J.; Wang, Z.-X. *Tetrahedron* **2013,** *69*, 9580; (f) Zhang, X.-Q.; Wang, Z.-X. *Org. Biomol. Chem.* **2014,** *12*, 1448; (g) Zhang, H.; Hagihara, S.; Itami, K. *Chem. Eur J.* **2015,** *21*, 16796; (h) Zhu, F.; Tao, J.-L.; Wang, Z.-X. *Org. Lett.* **2015,** *17*, 4926; (i) Hu, J.; Sun, H.; Cai, W.; Pu, X.; Zhang, Y.; Shi, Z. *J. Org. Chem.* **2016,** *81*, 14.

(6) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013,** *135*, 280.

(7) (a) Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P. *Tetrahedron* **2014,** *70*, 4257; (b) Basch, C. H.; Cobb, K. M.; Watson, M. P. *Org. Lett.* **2016,** *18*, 136.

(8) Moragas, T.; Gaydou, M.; Martin, R. *Angew. Chem. Int. Ed.* **2016,** *55*, 5053.

(9) Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1995**, 245.

(10) Davis, H. J.; Mihai, M. T.; Phipps, R. J. *J. Am. Chem. Soc.* **2016,** *138*, 12759.

(11) During the preparation of this manuscript, Zhao and co-workers reported a similar cross coupling reaction: Wang, T.; Yang, S.; Xu, S.; Han, C.; Guo, G.; Zhao, J. *RSC Adv.* **2017**, *7*, 15805. Disappointingly, our own previous contribution was not acknowledged, despite our paper being referenced in another context. A notable advantage of our protocol is that ligand optimisation allows the reactions to be carried out at 50 °C rather than 100 °C.

(12) Lacour, J.; Vial, L.; Herse, C. *Org. Lett.* **2002,** *4*, 1351.

(13) (a) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008,** *130*, 16158; (b) Hwang, S. J.; Kim, H. J.; Chang, S. *Org. Lett.* **2009,** *11*, 4588.

(14) (a) Amatatsu, Y. *The Journal of Physical Chemistry A* **2011,** *115*, 13611; (b) Conyard, J.; Addison, K.; Heisler, I. A.; Cnossen, A.; Browne, W. R.; Feringa, B. L.; Meech, S. R. *Nat Chem* **2012,** *4*, 547; (c) Knaapila, M.; Bright, D. W.; Nehls, B. S.; Garamus, V. M.; Almásy, L.; Schweins, R.; Scherf, U.; Monkman, A. P. *Macromolecules* **2011,** *44*, 6453; (d) Thangthong, A. m.; Prachumrak, N.; Namuangruk, S.; Jungsuttiwong, S.; Keawin, T.; Sudyoadsuk, T.; Promarak, V. *Eur. J. Org. Chem.* **2012,** *2012*, 5263; (e) Fleckenstein, C. A.; Plenio, H. *Chem. Eur J.* **2007,** *13*, 2701.

(15) Loe-Mie, F.; Marchand, G.; Berthier, J.; Sarrut, N.; Pucheault, M.; Blanchard-Desce, M.; Vinet, F.; Vaultier, M. *Angew. Chem. Int. Ed.* **2010,** *49*, 424.

(16) Liu, Y.; Fang, R.; Tan, X.; Wang, Z.; Zhang, X. *Chem. Eur J.* **2012,** *18*, 15650.

(17) Zhang, J.; Lu, G.; Xu, J.; Sun, H.; Shen, Q. *Org. Lett.* **2016,** *18*, 2860.

(18) Quinio, P.; Benischke, A. D.; Moyeux, A.; Cahiez, G.; Knochel, P. *Synlett* **2015,** *26*, 514.

(19) Endo, K.; Ishioka, T.; Ohkubo, T.; Shibata, T. *J. Org. Chem.* **2012,** *77*, 7223.

(20) Kuwano, R.; Yokogi, M. *Chem. Commun.* **2005**, 5899.

(21) Rao, M. L. N.; Dhanorkar, R. J. *RSC Adv.* **2014,** *4*, 13134.

(22) Zhang, P.; Xu, J.; Gao, Y.; Li, X.; Tang, G.; Zhao, Y. *Synlett* **2014,** *25*, 2928.

(23) Nakamura, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015,** *17*, 6142.

(24) Pal, S.; Chowdhury, S.; Rozwadowski, E.; Auffrant, A.; Gosmini, C. *Adv. Synth. Catal.* **2016,** *358*, 2431.

(25) Huang, R.; Zhang, X.; Pan, J.; Li, J.; Shen, H.; Ling, X.; Xiong, Y. *Tetrahedron* **2015,** *71*, 1540.

(26) Schäfer, G.; Bode, J. W. *Angew. Chem. Int. Ed.* **2011,** *50*, 10913.

(27) Ghorai, J.; Anbarasan, P. *J. Org. Chem.* **2015,** *80*, 3455.

(28) Shi, G.; Chen, D.; Jiang, H.; Zhang, Y.; Zhang, Y. *Org. Lett.* **2016,** *18*, 2958.