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Aryldiazonium Tetrafluoroborate salts as Green and Efficient Coupling Partners for the Suzuki-Miyaura Reaction: From Optimisation to Mole Scale.

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ABSTRACT: The use of aryldiazonium tetrafluoroborate salts as coupling partners in the Suzuki-Miyaura reaction was investigated from a process chemistry perspective including safety evaluation, solvent and catalyst screening and multi-variate factor optimization. Optimised conditions were applied to a range of substrates to evaluate the scope and limitations of the reaction and one example was carried out on mole-scale to demonstrate the practicality and scalability of the process.

INTRODUCTION

Cross-coupling reactions are central to organic synthesis, particularly in Industry, and this importance was recognised by the award of the Nobel Prize for Chemistry in 2010. For industrial applications, price is one of the most important factors in route design¹ and recent years has seen increased focus in reducing the cost of cross-coupling procedures by investigating cheaper palladium sources and the provision of alternative coupling partners.²

Palladium on carbon is the cheapest form in which to source this precious and versatile transition metal. In fine chemical synthesis palladium on carbon is mainly used for hydrogenation and debenzoylation reactions,³ however, it is well documented that it can also catalyse cross-coupling reactions of activated systems.^{4,5} Currently, most of the palladium-catalysed cross-coupling processes performed in the fine chemical industry involve homogeneous catalysts, with PdCl₂(PPh₃)₂ and Pd(OAc)₂ being the most frequently adopted.⁶ Despite this fact, palladium on carbon is a cheaper catalyst than these and other soluble palladium species and therefore represents an attractive source worth consideration.

A second method for reducing cost in cross-coupling procedures which has received significant attention is the use of less activated and significantly cheaper coupling partners. Aryl chlorides,^{7,8} aryl mesylates⁹ and aryl tosylates¹⁰ have all been shown to be viable electrophilic building blocks. Unfortunately, these substrates frequently require more forcing conditions together with active catalysts to bring about cross-coupling reactions when compared to traditional aryl bromide and iodide substrates. Aryl halides are commonly prepared from aryldiazonium salts *via* the Sandmeyer reaction.^{11–13} Therefore, the direct cross-coupling of aryldiazonium salt species could shorten the synthesis and reduce the cost associ-

ated with this coupling partner. In addition, the high reactivity associated with aryldiazonium salts also allows less active catalysts to be used (Figure 1).

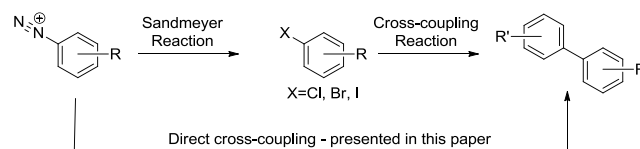
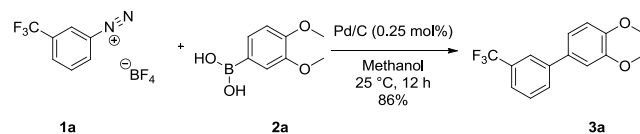


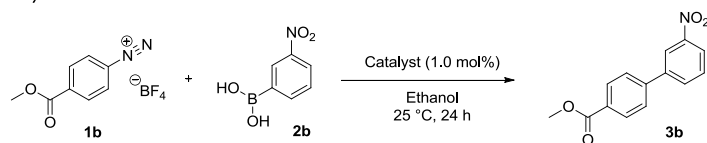
Figure 1. Direct cross-coupling of aryldiazonium salts.

Aryldiazonium salts have been previously demonstrated to be competent coupling partners in a number of palladium catalysed cross-coupling reactions on a laboratory scale.¹⁴ Felpin and co-workers reported their use in both Heck and Suzuki-Miyaura reactions^{15–19} and showed that the combination of palladium on carbon with an aryldiazonium salt was effective for such couplings. For example, treatment of 3-trifluoromethylbenzenediazonium tetrafluoroborate **1a** with 3,4-dimethoxy-phenylboronic acid **2a** in the presence of palladium on carbon (0.25 mol%) in methanol led to the bi-aryl product **3a** in 86% yield (Scheme 1).



Scheme 1. Aryldiazonium salts in the Suzuki-Miyaura reaction.

It is noteworthy that these reactions occur under very mild conditions (no base, ambient temperature) in the presence of an aryldiazonium salt whereas coupling of their halogenated

Table 1. Screening of different catalysts.

Entry	Catalyst	O.S. ^a	Structure	Moisture ^b	HPLC yield ^c	Isolated yield ^d
1	Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	>99%	95%
2	Johnson Matthey 10% Pd/C type 394	2	Egg shell	47.00%	85%	91%
3	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	88%	79%
4	Johnson Matthey 10% Pd/C type 58	0	Intermediate	58.10%	51%	52%
5	BASF 3% Pd CP M/R Code 00029	0	N.R.	56.68%	42%	44%
6	BASF 5% Pd CP M/R Code 00031	0	N.R.	57.22%	61%	64%
7	BASF 10% Pd CP M/R Code 00033	0	N.R.	54.91%	55%	68%
8	Johnson Matthey 5% Pd/C type 58	0	Intermediate	2.20%	83%	79%
9	Johnson Matthey 5% Pd/C type 39	2	Egg shell	58.10%	64%	73%
10	Johnson Matthey 10% Pd/C type 39	2	Egg shell	56.90%	75%	76%
11	Degussa 5% Pd/C E196 R/W 5%	0	Egg shell	56.30%	31%	37%
12	Degussa 10% Pd/C E196 XNN/W 10%	0	Egg shell	53.20%	68%	66%
13	Degussa 5% Pd/C E101 O/W 5%	2	Uniform	53.20%	45%	49%
14	BASF 3% Pd CP M/UR Code 00030	2	N.R.	57.86%	84%	82%
15	BASF 5% Pd CP M/UR Code 00032	2	N.R.	58.65%	90%	85%
16	BASF 10% Pd CP M/UR Code 00034	2	N.R.	59.70%	90%	86%
17	Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.R.	>99%	97%
18	Johnson Matthey 3% Rh/C + 2% Ru/C	0	Intermediate	2.10%	N.D.	-
19	Johnson Matthey 5% Ru/C type 97	0	Intermediate	59.00%	N.D.	-
20	Sigma-Aldrich 3% Cu/C	N.R.	N.R.	N.R.	N.D.	-

Reaction conditions: **1b** (1.5 eq) and **2b** (1.0 eq) are mixed in ethanol with catalyst (1.0 mol%) at 25 °C under a nitrogen atmosphere for 24 hours. ^aOxidation state of the metal species. ^bReported by manufacturer. ^cSee supporting information for details. ^dReactions were repeated at least in duplicate and average isolated yield after chromatography is shown. N.R.: Not Reported by the manufacturer. N.A.: Not Applicable. N.D.: Not Detected.

analogues would generally require thermal activation and addition of a stoichiometric base to bring about reaction with this catalyst.

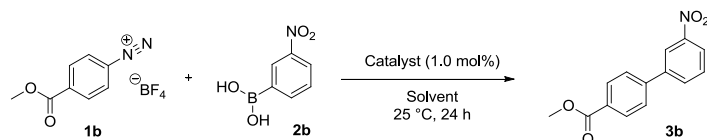
Despite the potential advantages offered by aryl diazonium salts they have not been widely adopted as coupling partners in large-scale synthesis presumably due to concerns over their instability which is well documented.^{20,21} Intrigued by the opportunity to routinely adopt aryl diazonium species into our repertoire of cross-coupling partners we sought to establish more knowledge about their synthesis, stability and applicability within the Suzuki-Miyaura reaction. Within this paper we present our studies on the preparation and reaction of aryldiazonium salts, including safety studies and the scale-up of a selected example. This work provides data to encourage the wider use of these mild, green and efficient coupling partners within the fine chemical and pharmaceutical industries.

RESULTS AND DISCUSSION

Although aryldiazonium salts have been reported as effective coupling partners, we have not found a systematic study on their use in the Suzuki-Miyaura coupling reaction. Initial investigations

focused on the choice of palladium catalyst and the properties which impact reaction efficiency, including metal loading, distribution, oxidation state and moisture content. For a test system we selected the coupling of methyl 4-diazoniobenzoate tetrafluoroborate **1b** and 3-nitrophenylboronic acid **2b** in ethanol (Table 1). As expected, all of the palladium on charcoal catalysts examined provided the desired product, albeit in variable yield. Alternative metal species, including copper(0) (Table 1, entry 20), ruthenium(0) (Table 1, entry 19) and a combination of rhodium(0) and ruthenium(0) (Table 1, entry 18) gave no conversion to the bi-aryl product **3b**. Interestingly, palladium(II) species (Table 1, entries 1, 2, 9, 10, 13, 14, 15, 16 and 17) gave generally better results than palladium(0) species (Table 1, entries 3, 4, 5, 6, 7, 8 and 11) while the impact of metal loading and distribution showed no clear trend. It is also noteworthy that low levels of moisture had little impact on the reaction as both wet (Table 1, entry 3) and dry (Table 1, entry 8) variants of the same catalyst delivered the product **3b** in identical isolated yield. Alternatively, soluble palladium(II) acetate (Table 1, entry 17) exhibited a very good catalytic activity with this system and provides a useful alternative to palladium on charcoal depending on the intended isolation protocol.

Solvent choice is extremely important during reaction scale-up both for efficiency of the reaction, and during **Table 2**. Screening of solvents.



Entry	Solvent	Catalyst reference	O.S. ^a	Structure	Moisture	HPLC yield ^b	Isolated yield ^c
1		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	6%	-
2	EtOAc	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	4%	-
3		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	81%	83%
4		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	29%	30%
5	Water	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	11%	-
6		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	54%	54%
7		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	4%	-
8	Toluene	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	2%	-
9		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	22%	21%
10		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	N.D.	-
11	DMSO	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	N.D.	-
12		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	N.D.	-
13		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	89%	95%
14	Methanol	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	73%	82%
15		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	84%	91%
16		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	>99%	95%
17	Ethanol	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	81%	79%
18		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	>99%	97%
19		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	N.D.	-
20	NMP	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	N.D.	-
21		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	3%	-
22		Johnson Matthey 5% Pd/C type 394	2	Egg shell	56.70%	N.D.	-
23	MeCN	Johnson Matthey 5% Pd/C type 58	0	Intermediate	48.00%	N.D.	-
24		Sigma-Aldrich Pd(OAc) ₂	2	N.A.	N.A.	N.D.	-

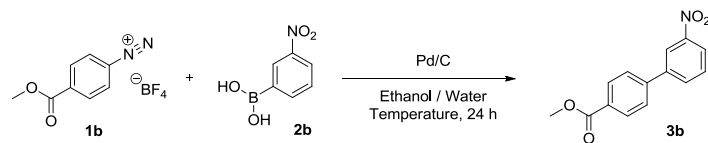
Reaction conditions: **1b** (1.5 eq) and **2b** (1.0 eq) are mixed in solvent with catalyst (1.0 mol%) at 25 °C under a nitrogen atmosphere for 24 hours. ^aOxidation State of the metal species. ^bSee supporting information for details. ^cReactions were repeated at least in duplicate and average isolated yield after chromatography is shown. N.A.: Not Applicable. N.D.: Not Detected.

downstream workup and isolation stages. Johnson Matthey 5% Pd/C type 394, Johnson Matthey 5% Pd/C type 58 and Pd(OAc)₂ all gave good results in the catalyst screening (Table 1) while being different in terms of metal oxidation state and structure. These catalysts were therefore used in a screen of common organic solvents selected from an in-house PCA model²² to examine a wide range of reaction medium properties (Table 2). As expected from previous reports,^{14,17,23,24} reactions performed in methanol (Table 2, entries 13-15) and ethanol (Table 2, entries 16-18) provided high yields (≥80%) of the product **3b**. Despite widespread use for this transformation, in our hands, methanol was less attractive as significant amounts of the methyl 4-methoxybenzoate (from displacement of the diazonium group by methanol) were observed in the crude reaction mixture, a problem not encountered in ethanol. The use of toluene (Table 2, entries 7-9) and ethyl acetate (Table 2,

entries 1-3) gave poor results with palladium on carbon, possibly due to the poor solubility of methyl 4-diazoniobenzoate tetrafluoroborate **1b** in these solvents, as switching to the soluble Pd(OAc)₂ catalyst only partially restored activity. The activity of the palladium catalyst appears to be inhibited by coordinating solvents such as DMSO, NMP and MeCN (Table 2, entries 10-12 and 19-24). We postulate that complexation of these solvents to the metal at this temperature may prevent the oxidative addition of the palladium into the carbon-diazonium bond. Finally, while low levels of water from the catalyst do not inhibit the catalytic activity of the palladium (Table 1), moderate yields were obtained using water as the sole solvent (Table 2, entries 4-6) and traces of methyl 4-hydroxybenzoate were detected by LC/MS. Overall, the reaction profiles for each of the screening reactions described in Tables 1

and **2** were very clean with the main impurity, methyl benzoate, arising from proto-dediazotisation.

Table 3. Design of Experiments reactions.



Entry	Settings	Aryldiazonium Equivalent ^a (A)	Temperature (°C) (B)	Palladium Loading (mol%) (C)	Solvent Volumes ^a (D)	Ethanol ^b (%) (E)
1	Minimum	1.0	0	0.1	10	50
2	Centre	1.25	20	1.05	55	75
3	Maximum	1.5	40	2	100	100
4	Selected	1.1	30	1.0	10	100

Reaction conditions: **1b** and **2b** (1.0 eq) were mixed in solvent with Johnson Matthey 5% Pd/C type 394 under a nitrogen atmosphere for 24 hours. ^aWith respect to **2b**. ^bWater content.

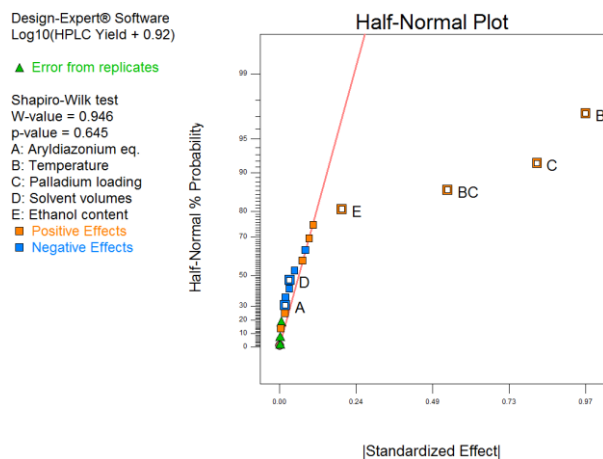


Figure 2a. Half-Normal Plot (HPLC Yield response).

With suitable catalysts and solvents established, we sought to further optimise the reaction through a Design of Experiment (DoE) study. Given the relative simplicity of the reaction, we were able to screen all of the important reaction parameters including aryldiazonium salt equivalent (**A**), temperature (**B**), palladium loading (**C**), volumes of solvent (**D**) and solvent ethanol content (%v/v with respect to water) (**E**) (Table 3) in 20 runs (16 factorials and 4 centre points) using a fractional factorial two level resolution V where HPLC yield (calibration curve) was used as the response. Following a \log_{10} transformation with 0.92 as constant in the software *Design-Expert* (version 7.1.1, Stat-Ease, Inc), a good model was obtained ($R^2=0.9806$, $\text{Adj } R^2=0.9751$, $\text{Pred } R^2=0.9591$) and a Half-Normal Plot (Figure 2a) indicated that the number of equivalents of aryldiazonium salt **1b** (**A**) and the solvent volumes (**D**) did not have an impact on the reaction outcome within the ranges investigated. It is therefore possible to use only a small excess of the aryldiazonium salt coupling partner at high concentration, significantly reducing the cost of the process. This finding is in contrast to a previous study by Felpin which indicated that 100 volumes of solvent were optimal and an excess of diazonium coupling partner (1.5 eq) was required.¹⁷ Decreasing the temperature

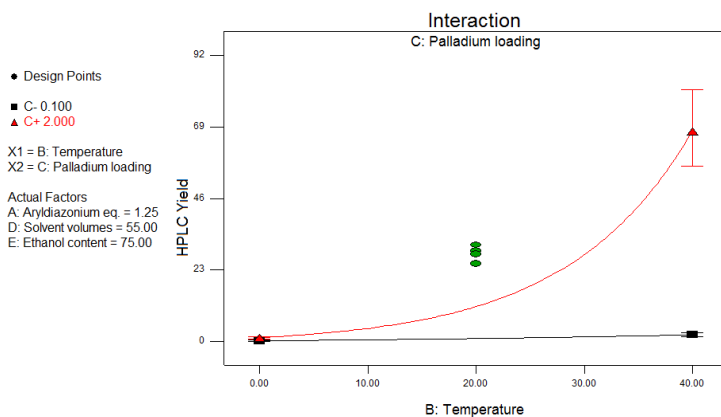
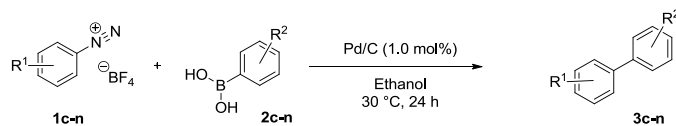


Figure 2b. Palladium loading/Temperature Interaction Plot.

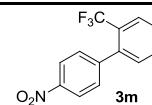
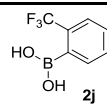
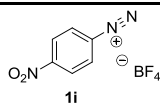
(**B**) and palladium loading (**C**) gave marked reductions in yield while the presence of water (**E**) had a small negative impact (Figure 2a). The interaction temperature – palladium loading (**BC**) was found to be important as this interaction was not linear (Figure 2b). At low palladium loading, the effect of the temperature was negligible whereas at high palladium loading, the effect of temperature became much more marked. As a consequence of this screen the recommended conditions to maximise yield and efficiency of the coupling were selected as shown in Table 3, entry 4 which involved reaction of 1.1 equivalents of aryldiazonium salt in 10 volumes of ethanol at 30 °C in the presence of 1.0 mol% of palladium catalyst. Although higher temperatures were found to be beneficial for the reaction, it must be noted that aryldiazonium salts are potentially thermally unstable^{20,21} and appropriate investigations should be undertaken before running these reactions at elevated temperatures.

Having optimized reaction conditions, we turned our attention to the scope of the process by investigating a challenging range of coupling partners (Table 4). The requisite aryldiazonium species were prepared using standard methods (see supporting infor-

mation for full details) and their thermal stability assessed using Differential Scanning Calorimetry (DSC). The recommended maximum operating temperature (T_{MR}) was calculated using the formula $T_{MR} = 0.7 \cdot T_{SO} - 46$ where T_{SO} is the starting temperature of the exothermic onset.²⁵ It should be noted that the lowest temperature onset for an exothermic event was observed at 63 °C (compound **1i**) which gives a T_{MR} below ambient temperature. Given the relatively small scale of the reactions used to investigate the substrate scope, we felt that the risk associated with running the **Table 4**. Scope of the reaction.



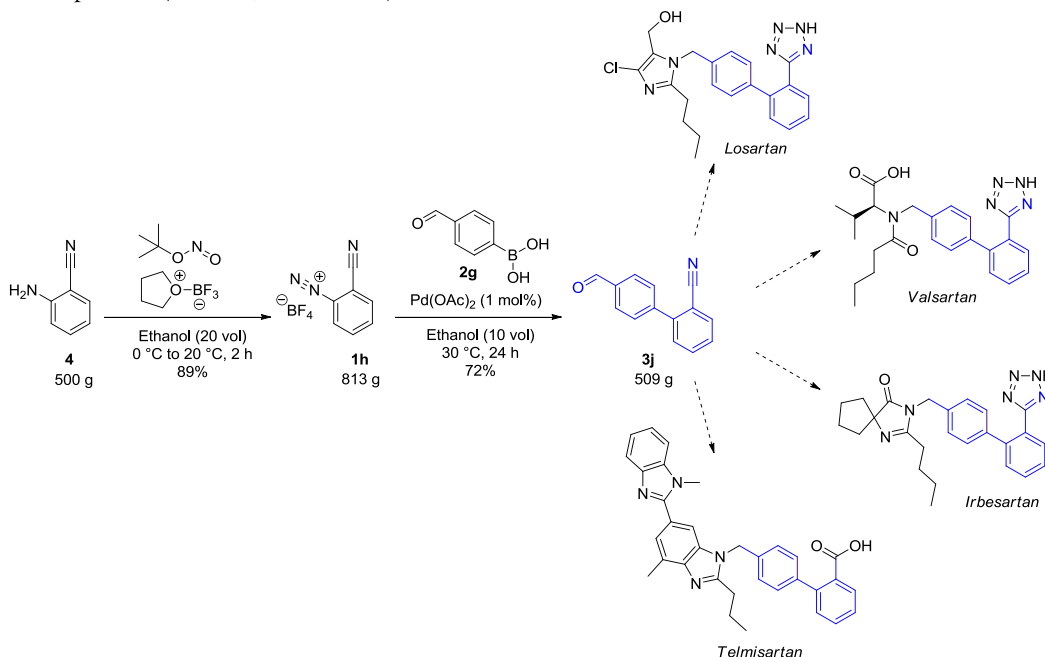
Entry	RMPT ^a	Aryldiazonium salt	Arylboronic acid	Product	Isolated yield ^b
1	19 °C				6%
2	41 °C				90%
3	19 °C				0%
4	41 °C				94%
5	41 °C				90%
6	16 °C				35%
7	-2 °C				7% (35%) ^c
8	27 °C				92%
9	54 °C				18% (72%) ^c
10	38 °C				72%
11	34 °C				42%



Reaction conditions: **1c-j** (1.1 eq) and **2c-j** (1.0 eq) were mixed together with Johnson-Matthey 5% Pd/C type 394 (1.0 mol%) in 10 volumes of ethanol for 24 hours at 30 °C under a nitrogen atmosphere. ^aRecommended Maximum Processing Temperature. ^bIsolated yield after chromatography. ^cYield in parentheses refers to the reaction using Pd(OAc)₂ as catalyst.

reaction at 30 °C was minimal, however a full risk assessment is strongly recommended when handling any aryldiazonium species.

Initial investigations sought to understand the impact of the electronics of each partner (Table 4, entries 1-4) where it



Scheme 2. Scale up synthesis of biaryl **3k**, a precursor of angiotensin II inhibitors.

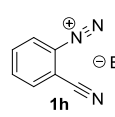
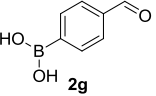
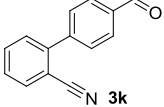
was found that electron-rich aryldiazonium salts gave poor results (unreacted starting material) whereas electron-poor aryldiazonium salts performed well (Table 4, entries 2, 4-6 and 10). The electronics of the arylboronic acid coupling partner showed much less impact on the reaction outcome as both electron-rich (Table 4, entries 2, 5 and 8) and electron-poor (Table 4, entries 4, 9 and 10) substrates gave good conversion. Further substrate expansion showed that the reaction was compatible with a range of functional groups including nitro (Table 4, entries 2, 4, 5 and 10), ether (Table 4, entry 2), sulfonamide (Table 4, entries 5 and 8), aldehyde (Table 4, entries 9 and 11), nitrile (Table 4, entries 6 and 9), primary amide (Table 4, entry 10) and ester (Table 3). As previously reported,^{14,24} the reaction was found to be sensitive to steric encumbrance on both coupling partners. While the diazonium species tolerated the relatively small *ortho*-cyano group, albeit with diminished yield (Table 4, entry 9), the more sterically hindered *ortho*-CF₃ group on the arylboronic acid **2j** was not tolerated and returned starting material (Table 4, entry n). Unfortunately, aromatic heterocycles did not perform well under these conditions. Pyridinediazonium salt **1f** was converted to the desired pyridyl-aryl product **3h** in only 7% yield with the protodediazotised species 2-

trifluoromethyl-pyridine as the major product (as observed by LC/MS). The yield of this product was improved to 35% when Pd(OAc)₂ was used, indicating that alternative catalysts may facilitate the coupling of this class of reaction partner.

In order to help break down the perception that aryldiazoniums cannot be handled on larger scale we decided to demonstrate our methodology on a multi-mole batch size. Compound **3j** (Table 4, entry 9) is an intermediate in the synthesis of a number of important angiotensin II inhibitors²⁶ including Telmisartan, Irbesartan, Valsartan and Losartan (Scheme 2).

Prior to embarking on scale-up, the thermal stability of each compound was investigated through DSC analysis of the isolated solids. 2-Cyano-benzenediazonium tetrafluoroborate **1h** and 4-formyl-phenylboronic acid **2g** both showed exothermic events, with onset temperatures of 142 °C and 164 °C respectively (Table 5). Using the formula $T_{MR} = 0.7.T_{SO} - 46$,

Table 5. DSC scans for thermal stability assessment.

	Onset Temperature	Intensity	RMPT ^a
Mixture end of diazotisation	56 °C – 97 °C	+72.66 J/g	N.A. ^b
	142 °C – 174 °C	+352.29 J/g	54 °C
	164 °C – 238 °C	-133.88 J/g +334.35 J/g	69 °C
	111 °C – 171 °C	+27.65 J/g - 119.28 J/g	None
Mixture 1h + 2g in ethanol	40 °C – 92 °C	+194.50 J/g	N.A. ^b

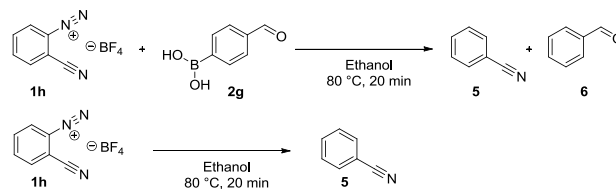
^aRecommended Maximum Processing Temperature

^bNot Applicable due to the low energies the high heat capacity of the solvent can contain the events.

we established a recommended maximum operating temperature of 54 °C for aryldiazonium **1h** and 69 °C for the boronic acid **2g** which were both compatible with the intended processes. DSC analysis of the coupling product **3j** only revealed a negligible exothermic event (+27.65 J/g) which was not considered hazardous. Finally, DSC analysis of the reaction mixture showed an exotherm onset starting above or at 40 °C with a relatively low severity (+72.66 J/g and +194.50 J/g) and the substantial heat capacity of ethanol allowed us to run the diazotisation reaction from 0 °C to 20 °C and the coupling reaction at 30 °C with minimal risks. The diazotisation of 2-cyano-aniline **4** was carried out on a 500 g scale to deliver 813 g (89%) of aryldiazonium tetrafluoroborate product **1h** which was coupled with 4-formylphenyl boronic acid **2g** (0.91 eq) in the presence of 1.0 mol% of Pd(OAc)₂ in 10 volumes of ethanol. After 24 hours, the reaction was treated with an aqueous solution of *N*-acetyl-cysteine (10 mol%) to scavenge the palladium and help to precipitate the product which was then filtered, washed and dried to give 509 g (72%) of the target product **3j** that was found to contain 1900 ppm of palladium by ICP analysis. Both reactions were exothermic with temperature rising from -1.2 °C to 6.8 °C during the addition of *tert*-butyl nitrite in the diazotisation and from 25 °C to 43 °C during the early stages of the coupling reaction. While the exotherms could be adequately managed on this scale, further reaction calorimetry investigations would be strongly recommended for further scale-up.

The presence of exothermic events during DSC assessment of reaction mixtures prompted us to investigate whether the coupling reaction could be carried out in the absence of a catalyst. Two control reactions were carried out on a small scale to minimise the consequences of an uncontrolled decomposition (Scheme 3). The thermal reaction (80 °C) of **1h** and **2g** in ethanol did not yield the desired product **3j** as determined by LC/MS, but instead gave the proto-dediazotised and deborylated products **5** and **6**, whose iden-

tity were confirmed by comparison with commercial samples. Heating 2-cyanobenzene diazonium tetrafluoroborate **1h** in ethanol at



Scheme 3. Thermal decomposition of **1h** and **2g**.

80 °C resulted in the formation of benzonitrile **5**, suggesting that the boronic acid is not required for this dediazotisation to occur.

From the observations made during this work and in line with the work of others,^{27,28} we propose the catalytic cycle shown in Figure 3. We believe that the palladium catalyst first inserts into the carbon-diazonium bond to give the intermediate **II**. The diazonium group is then displaced by a fluoride from the tetrafluoroborate counter-ion to form the intermediate **III**. It has been previously observed by Jutand and co-workers²⁸ that the palladium-fluoride complex **III** undergoes transmetalation with the arylboronic acid through the formation of a strong fluorine-boron bond which is the driving force of this step. Finally the bi-aryl product is formed by classic reductive elimination. According to our previous observations, the proto-dediazotised product is formed by thermal decomposition in ethanol although palladium may also catalyse this degradation, presumably to give acetaldehyde as a byproduct, although we are yet to study this mechanism in detail. Given that electron-rich aryldiazonium salts gave little

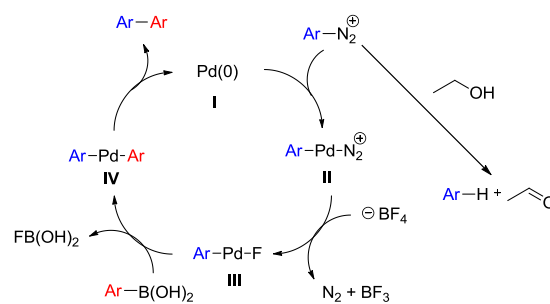


Figure 3. Postulated mechanism for the transformation.

or no reaction during investigation into the substrate scope (Table 4, entries 1 and 3) whilst electron-poor arylboronic acids performed well (Table 4, entries 4, 9 and 10), we suspect that oxidative insertion is still the rate determining step of the catalytic cycle despite the expected high reactivity of these species. However it is also possible that the electronics of the Pd-bound aromatic ring in intermediates **II** and **III** impact the rates of the ligand exchange or transmetalation steps and further work will be required to elucidate the details of this mechanism.

CONCLUSION

In conclusion, we have established optimal conditions for the Suzuki-Miyaura cross-coupling of aryldiazonium salts through Design of Experiment investigations. Optimal reaction conditions were then applied to a range of substrates to demonstrate this reaction was compatible with functionalities frequently found within pharmaceutically relevant molecules. In addition, non-compatible groups have also been identified. By investigating the thermal decomposition of the aryldiazonium salts, we were able to safely scale-up this method to prepare mole quantities of the challenging pharmaceutically relevant intermediate **3h** which is used in the preparation of a number of angiotensin II inhibitors. This method provides a robust, cheap and green alternative to classic cross-coupling reactions involving homogeneous palladium sources and aryl-halide coupling partners.

EXPERIMENTAL SECTION

Safety considerations: Aryldiazonium salts have been reported to decompose violently under certain conditions.^{20,21} Therefore, all of the aryldiazonium tetrafluoroborate salts described in this paper were initially prepared on a small scale (<50 mg) and assessed for shock, friction and thermal stability before scale-up (see supporting information for details). Any reaction involving aryldiazonims must be adequately risk-assessed prior to being carried out.

General diazotisation procedure with tert-butyl nitrite: To a stirred solution of the aniline (1.0 eq) in reported solvent at 0 °C was added BF₃•THF complex (1.5 eq) followed by dropwise addition of tert-butyl nitrite (1.2 eq) over 15 minutes. The resulting reaction mixture was stirred for 30 minutes at 0 °C and was allowed to warm to room temperature for 30 minutes. The product precipitates from solution. After careful filtration, the product was washed with a small amount of the same solvent and dried at room temperature. When indicated, the product was purified by dissolving the crude in a minimum amount of acetone followed by precipitation by dropwise addition of TBME.

General diazotisation procedure with sodium nitrite: To a slurry of the aniline (1.0 eq) in 3 vol of water at 0 °C, was added 2.5 vol of a 48% solution of HBF₄ in water (2.6 eq) and a solution of sodium nitrite (1.1 eq) in 1.5 volumes of water was added dropwise to the mixture under stirring. The resulting reaction mixture was stirred for 30 minutes at 0 °C and was allowed to warm to room temperature for 30 minutes. The product precipitates from solution. After careful filtration, the product was washed with a small amount of water and dried at room temperature. The crude product was purified by dissolution in a minimum amount of acetone and precipitated by dropwise addition of TBME in every case.

Methyl 4-benzoatediazonium tetrafluoroborate (1b). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 66 volumes of THF. The product was purified via acetone/TBME reprecipitation. White solid, 68%-77% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 8.80 (d, 2H, J = 8.9 Hz), 8.44 (d, 2H, J = 8.9 Hz), 3.96 (s, 3H) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): 163.8 (C_{IV}), 139.2 (C_{IV}), 133.1, 131.2, 120.2 (C_{IV}), 53.4 ppm.

3,4-Methylenedioxy-benzenediazonium salt (1c). Prepared according to the general diazotisation procedure with sodium nitrite in water. Brown solid, 1.20 g, 51% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 8.42 (d, 1H, J = 8.8 Hz), 8.04 (s, 1H), 7.48 (d, 1H, J = 8.8 Hz), 6.45 (s, 2H) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): δ = 158.8 (C_{IV}), 148.5 (C_{IV}), 134.2, 110.6, 109.4, 105.5, 104.3 (C_{IV}) ppm.

3-Nitro-benzenediazonium tetrafluoroborate (1d). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of THF. The product was purified via acetone/TBME reprecipitation. White solid, 725 mg, 73% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 9.61 (s, 1H), 9.03-8.98 (m, 2H), 8.24 (at, 1H, J = 8.4 Hz) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): δ = 147.6 (C_{IV}), 137.9, 135.0, 132.7, 128.1, 118.2 (C_{IV}).

4-Cyano-benzenediazonium tetrafluoroborate (1e). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of isopropanol. The product was not purified further. White solid, 1.68 g, 91% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 8.84 (d, 2H, J = 8.1 Hz), 8.46 (d, 2H, J = 8.1 Hz) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): δ = 134.8, 133.0, 121.8 (C_{IV}), 121.0 (C_{IV}), 116.3 (C_{IV}) ppm.

2-Trifluoromethyl-pyridine-5-diazonium tetrafluoroborate (1f). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of ethanol. The product was not purified further. White solid, 2.25 g, 70% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 9.93 (s, 1H), 9.40 (dd, 1H, J₁ = 8.7 Hz, J₂ = 1.5 Hz), 8.60 (d, 1H, J = 8.7 Hz) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): δ = 153.0, 152.8 (q, J = 36.3 Hz), 144.1, 122.6 (C_{IV}), 119.9 (q, J = 275.4 Hz), 119.6 (C_{IV}) ppm.

2-Methyl-chromone-7-diazonium tetrafluoroborate (1g). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 30 volumes of ethanol. The product was not purified further. Beige solid, 69%-88% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 9.11 (s, 1H), 8.62 (d, 1H, J = 8.7 Hz), 8.49 (d, 1H, J = 8.7 Hz), 6.54 (s, 1H), 2.50 (s, 3H) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): δ = 174.8 (C_{IV}), 169.2 (C_{IV}), 154.2 (C_{IV}), 130.2 (C_{IV}), 128.3, 127.1, 124.2, 120.0 (C_{IV}), 111.6, 20.0 ppm.

2-Cyano-benzenediazonium tetrafluoroborate (1h). Prepared according to the general diazotisation procedure with tert-butyl nitrite in 20 volumes of ethanol. The product was not purified further. Pale yellow solid, 86%-89% yield. ¹H NMR (DMSO-d₆, 400 MHz): δ = 9.00 (dd, 1H, J₁ = 8.3 Hz, J₂ = 1.0 Hz), 8.59 (dd, 1H, J₁ = 7.9 Hz, J₂ = 1.0 Hz), 8.46 (atd, 1H, J₁ = 7.9 Hz, J₂ = 1.0 Hz), 8.32 (atd, 1H, J₁ = 8.3 Hz, J₂ = 1.0 Hz) ppm. ¹³C NMR (DMSO-d₆, 100 MHz): δ = 141.0, 136.4, 135.6, 134.6, 118.6 (C_{IV}), 113.8 (C_{IV}), 112.4 (C_{IV}) ppm.

Catalyst and solvent screening reactions: To a glass tube equipped with a stirrer bar were introduced 3-nitro-phenyl boronic acid **2b** (56 mg, 0.335 mmol), methyl 4-benzoatediazonium tetrafluoroborate **1b** (126 mg, 0.503 mmol) and palladium catalyst (1.0 mol%). The air inside was replaced by nitrogen via vacuum/nitrogen cy-

cles. Solvent (5 mL) was then injected into the glass tube and the reaction mixture was stirred under a nitrogen atmosphere at 25 °C for 24 h. Ethyl acetate was then added to the mixture and the catalyst removed by filtration over Celite®. The filtrate was analysed by HPLC to determine a solution yield (see supporting information) before being evaporated to dryness. The crude product was purified by silica gel chromatography eluting with a heptane/ethyl acetate mixture to give **3b** as a white solid.

4'-Methylbenzoate-3-nitro-biphenyl (3b). White solid, mp 146-148 °C. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 8.51 (at, 1H, J = 2.0 Hz), 8.28 (bd, 1H, J = 8.2 Hz), 8.22 (bd, 1H, J = 7.8 Hz), 8.08 (d, 2H, J = 8.4 Hz), 7.95 (d, 2H, J = 8.4 Hz), 7.80 (at, 1H, J = 8.0 Hz), 3.89 (s, 3H) ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 165.9 (C_{IV}), 148.5 (C_{IV}), 142.2 (C_{IV}), 140.4 (C_{IV}), 133.5, 130.7, 129.9, 129.5 (C_{IV}), 127.4, 123.0, 121.5, 52.3 ppm. HRMS (ESI⁺): calculated for C₁₄H₁₁NO₄ [M+H]⁺ 258.0761, found 258.0761.

Design of Experiments reactions: To a glass tube equipped with a stir bar were introduced 3-nitro-phenyl boronic acid **2b** (1.0 eq), methyl 4-benzoatediazonium tetrafluoroborate **1b** (Factor A) and Johnson Matthey 5% Pd/C type 394 (moisture: 56.70%) (Factor C). The air inside was replaced by nitrogen via vacuum/nitrogen cycles. Ethanol/water (Factor D and E) is then injected into the glass tube and the reaction mixture is stirred under a nitrogen atmosphere at the indicated temperature (Factor B) for 24 h. Ethyl acetate was then added to the mixture and the catalyst removed by filtration over Celite®. The filtrate was analysed by HPLC to determine a solution yield (see supporting information).

General cross-coupling procedure for substrate scope: To a glass tube equipped with a stir bar were introduced aryl boronic acid (500 mg, 1.0 eq), aryldiazonium tetrafluoroborate (1.1 eq) and catalyst (Johnson Matthey 5% Pd/C type 394, moisture: 56.70%, 1.0 mol %). The air inside was replaced by nitrogen via vacuum/nitrogen cycles. Ethanol (5 mL, 10 vol) was then injected into the glass tube and the reaction mixture was stirred under a nitrogen atmosphere at 30 °C for 24 h. Ethyl acetate or acetone was then added to the mixture and the catalyst removed by filtration over Celite®. The filtrate was evaporated to dryness and the crude product was purified by silica gel chromatography eluting with heptane/ethyl acetate or heptane/acetone mixtures to give the bi-aryl product.

3'-Nitro-3,4-methylenedioxy-biphenyl (3c). Beige solid, mp 119-120 °C. 6%-90% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 8.33 (s, 1H), 8.14 (d, 1H, J = 8.1 Hz), 8.05 (d, 1H, J = 7.5 Hz), 7.69 (t, 1H, J = 7.8 Hz), 7.35 (s, 1H), 7.24 (d, 1H, J = 8.1 Hz), 7.02 (d, 1H, J = 8.1 Hz), 6.09 (s, 2H), ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 148.3 (C_{IV}), 148.2 (C_{IV}), 147.7 (C_{IV}), 141.5 (C_{IV}), 132.9, 131.9 (C_{IV}), 130.3, 121.6, 120.9, 120.7, 108.8, 107.3, 101.4 ppm. HRMS (ESI⁺): calculated for C₁₃H₉NO₄ [M+H]⁺ 244.0604, found 244.0602.

3',3-Dinitro-biphenyl (3e). White solid, mp 207-208 °C. 688 mg, 94% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 8.57 (s, 2H), 8.29 (t, 4H, J = 9.1 Hz), 7.83 (t, 1H, J = 8.0 Hz) ppm. ¹³C

NMR (DMSO-*d*₆, 100 MHz): δ = 148.5 (C_{IV}), 139.4 (C_{IV}), 133.7, 130.7, 123.2, 121.8 ppm. HRMS (ESI⁺): calculated for C₁₂H₈N₂O₄ [M+H]⁺ 245.0557, found 245.0556.

3'-Nitro-4-N-methylsulfonamide-biphenyl (3f). Beige solid, mp 145-150 °C. 612 mg, 90% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 9.98 (s, 1H), 8.41 (t, 1H, J = 2 Hz), 8.19 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.5 Hz), 8.12 (d, 1H, J = 8.3 Hz), 7.79-7.73 (m, 3H), 7.35 (d, 2H, J = 8.7 Hz), 3.06 (s, 3H) ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 148.5 (C_{IV}), 141.1 (C_{IV}), 138.9 (C_{IV}), 132.9 (C_{IV}), 132.8, 130.5, 128.0, 121.8, 120.6, 119.7, 39.5 ppm. HRMS (ESI⁺): calculated for C₁₃H₁₂N₂O₄S [M+NH₄]⁺ 310.0856, found 310.0854.

4-(Benzofuran-2-yl)-benzointrile (3g). White solid, mp 141-144 °C. 237 mg, 35% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 8.10 (d, 2H, J = 8.4 Hz), 7.96 (d, 2H, J = 8.6 Hz), 7.74-7.66 (m, 3H), 7.40 (ddd, 1H, J₁ = 8.0 Hz, J₂ = 8.0 Hz, J₃ = 1.3 Hz), 7.33 (ddd, 1H, J₁ = 8.0 Hz, J₂ = 8.0 Hz, J₃ = 1.3 Hz) ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 154.6 (C_{IV}), 153.2 (C_{IV}), 133.8 (C_{IV}), 133.0, 128.4 (C_{IV}), 125.7, 125.2, 123.6, 121.8, 118.7 (C_{IV}), 111.4, 110.7 (C_{IV}), 105.3 ppm. HRMS (ESI⁺): calculated for C₁₅H₉NO [M+H]⁺ 220.0757, found 220.0756.

5-(3',4'-Methylenedioxyphenyl)-2-trifluoromethyl-pyridine (3h). Off-white solid, mp 117-125 °C. 7%-35% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 9.05 (s, 1H), 8.30 (d, 1H, J = 8.0 Hz), 7.93 (d, 1H, J = 8.3 Hz), 7.47 (s, 1H), 7.34 (d, 1H, J = 8.1 Hz), 7.09 (d, 1H, J = 8.3 Hz), 6.12 (s, 2H) ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 148.3 (C_{IV}), 148.2 (C_{IV}), 147.9, 144.6 (q, J = 33.8 Hz), 138.5 (C_{IV}), 135.5, 129.5 (C_{IV}), 121.8 (q, J = 273.4 Hz), 121.5, 120.7, 109.0, 107.5, 101.5 ppm. HRMS (ESI⁺): calculated for C₁₃H₈F₃NO₂ [M+H]⁺ 268.0580, found 268.0578.

7-(4'-N-Methylsulfonamid-phenyl)-2-methyl-chromone (3i). Beige solid, mp 226-228 °C. 705 mg, 92% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 10.00 (s, 1H), 8.01 (d, 1H, J = 8.3 Hz), 7.81-7.78 (m, 3H), 7.72 (d, 1H, J = 8.3 Hz), 7.34 (d, 2H, J = 8.5 Hz), 6.23 (s, 1H), 3.07 (s, 3H), 2.39 (s, 3H) ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 176.4 (C_{IV}), 166.8 (C_{IV}), 156.4 (C_{IV}), 144.8 (C_{IV}), 139.2 (C_{IV}), 133.0 (C_{IV}), 128.2, 125.4, 123.2, 121.5 (C_{IV}), 119.5, 114.9, 110.0, 39.5, 20.0 ppm. HRMS (ESI⁺): calculated for C₁₇H₁₅NO₄S [M+H]⁺ 330.0795, found 330.0794.

2'-Cyano-4-formyl-biphenyl (3j). White to beige solid, mp 164-165 °C. 18%-72% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 10.13 (s, 1H), 8.08 (d, 2H, J = 8.0 Hz), 8.02 (d, 1H, J = 7.8 Hz), 7.88-7.83 (m, 3H), 7.72-7.65 (m, 2H) ppm. ¹³C NMR (DMSO-*d*₆, 100 MHz): δ = 192.8, 143.4 (C_{IV}), 143.3 (C_{IV}), 136.0 (C_{IV}), 134.0, 133.6, 130.2, 129.7, 129.6, 129.0, 118.2 (C_{IV}), 110.2 (C_{IV}) ppm. HRMS (ESI⁺): calculated for C₁₄H₉NO [M+H]⁺ 208.0757, found 208.0756.

3'-Carboxamido-4-nitro-biphenyl (3k). White solid, mp 182-186 °C. 529 mg, 72% yield. ¹H NMR (DMSO-*d*₆, 400 MHz): δ = 8.35 (d, 2H, J = 8.5 Hz), 8.29 (s, 1H), 8.17 (bs, 1H), 8.06 (d, 2H, J = 8.8 Hz), 7.97 (t, 2H, J = 7.6 Hz), 7.64 (t, 1H, J = 7.8 Hz), 7.50 (bs, 1H)

ppm. ^{13}C NMR (DMSO- d_6 , 100 MHz): δ = 167.4 (C_{IV}), 146.9 (C_{IV}), 146.0 (C_{IV}), 137.8 (C_{IV}), 135.2 (C_{IV}), 130.0, 129.3, 128.1, 128.0, 126.2, 124.1 ppm. HRMS (ESI $^+$): calculated for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 243.0764, found 243.0761.

4'-Formyl-4-bromo-biphenyl (3l). White solid, mp 144–149 °C. 366 mg, 42% yield. ^1H NMR (DMSO- d_6 , 400 MHz): δ = 10.07 (s, 1H), 8.00 (d, 2H, J = 8.3 Hz), 7.92 (d, 2H, J = 8.3 Hz), 7.75–7.70 (m, 4H) ppm. ^{13}C NMR (DMSO- d_6 , 100 MHz): δ = 192.7, 144.5 (C_{IV}), 137.9 (C_{IV}), 135.3 (C_{IV}), 132.0, 130.2, 129.2, 127.3, 122.2 (C_{IV}) ppm. HRMS (ESI $^+$): calculated for $\text{C}_{13}\text{H}_9\text{BrO}$ [$\text{M}+\text{H}$] $^+$ 260.9910, found 260.9909.

Multi-mole scale diazotisation step: A 20 L CLR reactor fitted with an overhead stirrer was flushed with nitrogen and charged with 500 g of 2-aminobenzonitrile **4** (4.23 mol, 1.0 eq) followed by 10 L of ethanol. The solution was cooled to 0 °C and 700 mL of $\text{BF}_3\cdot\text{THF}$ complex (6.35 mol, 1.5 eq) were charged portionwise to the reactor without significant exotherm. 673 mL of *tert*-butyl nitrite (technical grade 90%, 5.08 mol, 1.2 eq) were pumped into the reactor with a peristaltic pump over 20 min and the temperature rose from -1.2 °C to +6.7 °C. The reaction was stirred with a mechanical stirrer for 30 minutes at 0 °C and 30 minutes at 20 °C. The product precipitated from ethanol and the slurry was filtered. The resulting solid was collected and dried in a vacuum oven overnight at 20 °C to give 813 g of 2-cyano-benzenediazonium tetrafluoroborate **1h** (3.75 mol, 89% yield).

Multi-mole cross-coupling step: A 20 L CLR reactor fitted with an overhead stirrer was flushed with nitrogen and charged with 813 g of 2-cyano-benzenediazonium tetrafluoroborate **1h** (3.75 mol, 1.1 eq), 510 g of 4-formyl-phenylboronic acid **2g** (3.40 mol, 1.0 eq) and 7.64 g of palladium(II) acetate (34.0 mmol, 0.01 eq). 5.1 L of ethanol were then added to the reactor at 25 °C and the temperature rose to 43 °C meanwhile the jacket was reset to -5 °C to control the exotherm. Once the temperature stabilised at 30 °C, the slurry was stirred at 30 °C for 24 h under a nitrogen atmosphere. 5.1 L of an aqueous solution of *N*-acetyl cysteine (55.5 g, 0.34 mol, 10 mol%) were then added to the reaction mixture and the slurry was stirred for 2 h at 30 °C before being filtered. The resulting solid was collected and dried in a vacuum oven for 48 hours at 30 °C to give 509 g of 2'-cyano-4-formyl-biphenyl **3j** (2.46 mol, 72% yield). ICP analysis of the product showed it contained 1900 ppm of palladium.

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