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Immobilized tetrakis(triphenylphosphine) palladium(0) for Suzuki–Miyaura coupling reactions under flow conditions†

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An immobilized triphenylphosphine scaffold was prepared by precipitation polymerization and functionalized to afford a cost-effective source of solid-supported tetrakis(triphenylphosphine)palladium(0). The catalyst was characterised and used to perform biphasic Suzuki–Miyaura cross-coupling reactions using a packed-bed reactor under flow conditions. The approach afforded comparable yields to those obtained under batch conditions with a single pass through the packed-bed reactor (1 h vs. 18 h). The use of a recycling system was investigated on a model reaction and found to afford close to quantitative conversion within 3 hours.

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1. Introduction

Flow chemistry has seen rapid growth since the early 2000's and today its use as a manufacturing technology is strongly encouraged by bodies such as the US Food and Drug Administration and the Green Chemistry Institute. Flow chemistry is in many cases more efficient, safer and greener than batch-based chemistries.^{1–3} Key advantages afforded by the

technology include intensified heat and mass transfer, higher mass throughput, improved safety profiles, in-line reaction monitoring and direct scalability.^{1–3}

The use of immobilized catalysts affords a convenient and practical method for the clean and efficient preparation of novel chemical entities, often greatly simplifying downstream processing and purification.⁴ Several immobilization strategies have been developed based upon covalent bonding, ionic bonding, adsorption and encapsulation wherein the catalyst can be introduced through several different techniques such as impregnation, precipitation polymerization, co-precipitation, adsorption and ion exchange.⁵ The use of immobilized catalysts has started finding widespread application in the field of flow chemistry where reagent streams can be conveniently pumped across such catalysts housed in packed-bed reactors.^{1,2,4–6} The use of solid-supported catalysts, in conjunction with flow chemistry affords several benefits not available under batch conditions, namely; i) one is able to have fine control over exposure time to the catalyst by altering the flow rate, ii) as the reagent stream flows across the catalyst there is the benefit of a high local concentration of the catalyst often linked with increased reaction rates and higher turnover numbers, and iii) the catalyst can be easily and conveniently separated from the reaction mixture without having to resort to complicated downstream work-ups and purifications.⁵

The use of catalytic transition metal species in carbon–carbon bond forming coupling reactions have grown to the point where they are essential toolkits for the modern synthetic chemist.^{7,8} The Suzuki–Miyaura cross-coupling reaction affords the coupling of boronic acids to aryl halides and is typically catalyzed by palladium or nickel catalysts.⁸ The

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reaction is synthetically desirable as a wide range of substrates are tolerated, boronic acids are less toxic than organometallic reagents used in similar coupling reactions, removal of the inorganic by-products is reasonably easy, and the process is amenable to the use of water as a solvent.^{9–11} As such, the utilization of the Suzuki–Miyaura type reactions under flow conditions is desirable and has been a topic of numerous investigations.^{12–25} Unfortunately, the coupling processes often suffer from the need to use insoluble inorganic bases and from the precipitation of insoluble salt by-products making flow translation somewhat challenging,¹³ that being said, efficient Suzuki–Miyaura reactions have been reported in flow using biphasic solvent systems employing solid-supported palladium sources, including palladium on carbon and palladium nanoparticles.^{5,9,25,26}

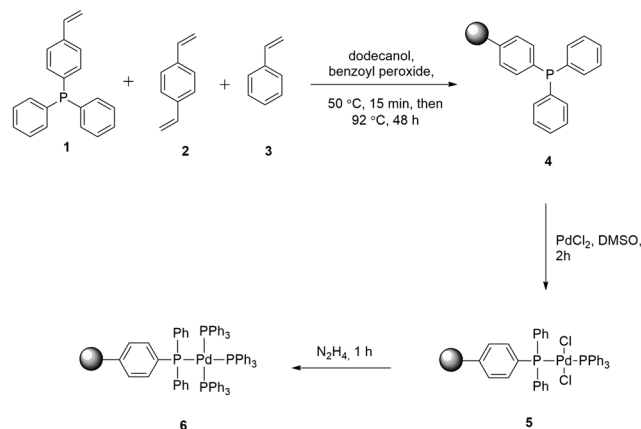
In this publication, we report the synthesis and characterisation of a cost-effective tetrakis(triphenylphosphine) palladium(0) catalyst heterogenized onto a polystyrene scaffold prepared by precipitation polymerization. The optimisation of the catalyst for performing Suzuki–Miyaura cross-couplings reactions is described and the scope of the catalyst is further shown with bench-marking against commercially available polystyrene supported tetrakis (Sigma Aldrich 511 579) under both flow and batch conditions using a biphasic solvent system.

2. Results and discussion

2.1. Synthesis of polymer-supported tetrakis(triphenylphosphine) palladium(0)

The preparation of the proposed polymer-supported tetrakis catalyst was envisaged through precipitation polymerisation to afford monolithic supports for use in continuous flow systems, adapting the method described by Ley and co-workers.²⁷ Initially, however, the approach was adopted to prepare the catalyst as a finely ground polymer-supported version for use under batch conditions. Precipitation polymerisation of diphenyl (4-vinylphenyl) phosphine **1**, divinylbenzene **2**, and styrene **3** was conducted in the presence of a porogen (1-dodecanol) and benzoyl peroxide with heating in a standard convection oven at 92 °C over the course of 48 hours (Scheme 1).

Upon cooling, the polymerised material **4** was finely ground with a mortar and pestle and washed by filtration with hot dry dichloromethane (DCM) to remove any occluded porogen prior to drying under vacuum. The polymeric scaffold **4** was then suspended in degassed dimethyl sulfoxide (DMSO) and treated with palladium chloride (PdCl₂) to produce supported Pd(PPh₂)Cl₂ **5**. Subsequent treatment with hydrazine hydrate facilitated the reduction of palladium(II) to palladium(0) affording polymer supported tetrakis(triphenylphosphine) palladium(0) **6a**. The spacial availability of the required four co-ordinating triphenyl phosphine groups in the polymerised scaffold was initially seen as an area of concern, and as such catalyst **6b** was prepared by treating **5** with additional triphenylphosphine prior to reduction with hydrazine hydrate.



Scheme 1 Preparation of polymer-supported tetrakis **6**.

2.2. Characterisation of polymer-supported tetrakis(triphenylphosphine)palladium(0) **6a**

The catalysts were characterised using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). SEM scans revealed a largely uniform sub- μm particle size for both the immobilized triphenyl phosphine scaffold **4** and the catalyst **6a** (Fig. 1A and B), interestingly, catalyst **6b** prepared with excess triphenylphosphine showed distinctly larger particle sizes ranging from 1–4 μm (Fig. 1C), suggesting that the increased palladium loading observed in

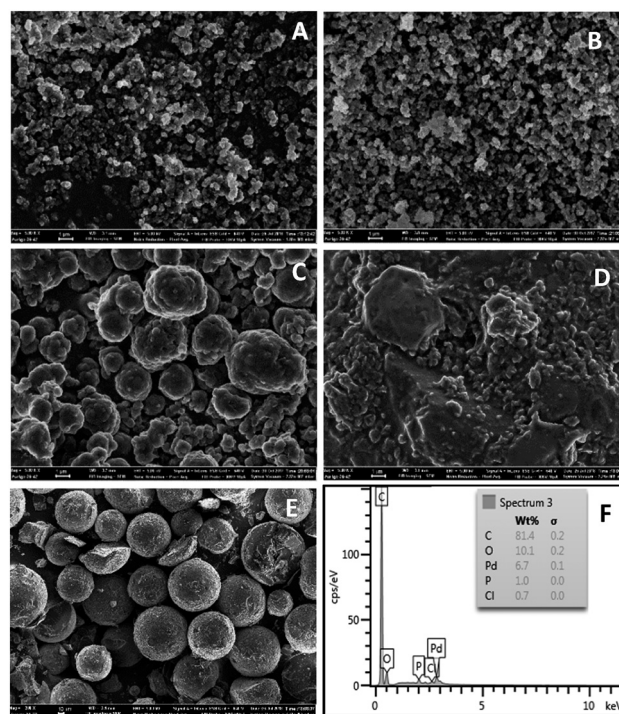


Fig. 1 SEM scans at 5000 \times magnification of immobilized triphenyl phosphine **4** (A), catalyst **6a** (B), catalyst **6b** (C) and commercial polystyrene supported tetrakis (Sigma Aldrich 511 579) (D). SEM scan at 200 \times magnification of commercial polystyrene supported tetrakis (Sigma Aldrich 511 579) (E). Representative EDX spectrum of **6a** (F).

6b comes at the cost of reduced surface area. In comparison commercial polymer-supported tetrakis (Sigma Aldrich, 511 579) has beads $>40\ \mu\text{M}$ in diameter (Fig. 1D and E). Energy dispersive X-Ray spectroscopy (EDX) performed concurrently revealed a palladium loading of 0.460 and 0.909 mmol g^{-1} for **6a** and **6b**, respectively (Fig. 1F).²⁸ The TEM scans of catalyst **6a** and commercial polymer-supported tetrakis (Sigma Aldrich, 511 579) are shown as a series of representative scans at 50 and 5 nm resolution (Fig. 2). The corresponding *d*-spacing plots confirmed the presence of palladium, and in both instances **6a** and the commercial alternative appeared comparable.

The presence of the supported tetrakis catalyst was further evidenced by comparison of **6a** and the commercial catalyst using ³¹P solid-state NMR, Fourier-transform infra-red (FTIR) spectroscopy, and powder x-ray diffraction (PXRD) (Fig. 3). In both instances **6a** showed close correlation with the commercial sample. Powder x-ray diffraction (PXRD) suggests that both catalysts possess an amorphous morphology with **6a** having some crystalline material present.

Brunauer–Emmett–Teller (BET) analysis revealed a type II nitrogen adsorption–desorption isotherm for **6a** indicating multi-layer adsorption (Fig. 4A), with a sharp uptake of the gas at the relative pressure of 0.90 due to capillary condensation. Pore size distribution was indicative of a wide range of pore-sizes (Fig. 4B). Interestingly a negative isotherm was obtained for the commercial catalyst suggesting low surface area and/or low pore volume.

Finally, particle size distribution was analysed with the particles dispersed in water. The polydispersity index (PDI) of **6a** (0.348) indicates that the particles follow a mid-range value to almost monodispersed pattern with an average particle size diameter of 321 nm (Fig. 5A). The presence of $\sim 10\%$ larger particles was observed and is likely arising as the pre-

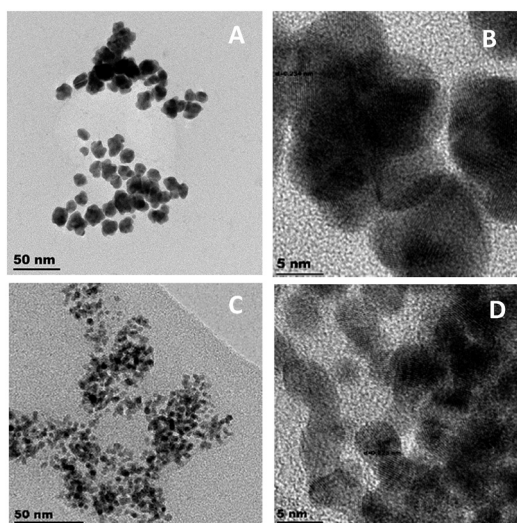


Fig. 2 TEM scans of catalyst **6a** (A and B) at a resolution of 50 nm and 5 nm respectively and commercial polystyrene supported tetrakis (Sigma Aldrich 511 579) (C and D) at a resolution of 50 nm and 5 nm respectively.

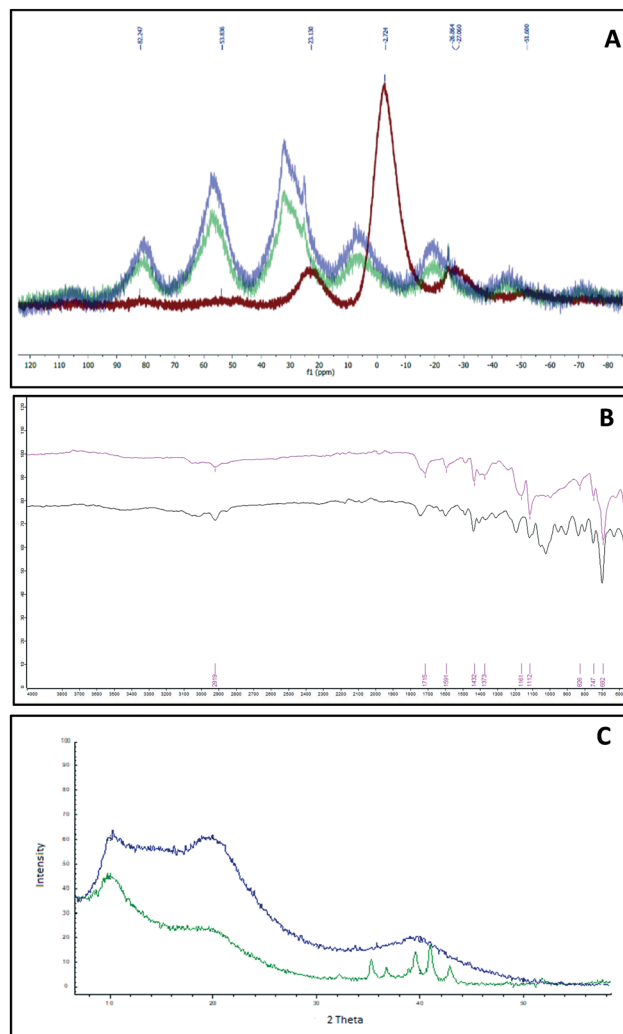


Fig. 3 Solid-state ³¹P NMR of **6a** (A, blue), commercial polystyrene supported tetrakis (Sigma Aldrich 511 579) (A, green) and triphenylphosphine scaffold **4** (A, red). FTIR of commercial polystyrene supported tetrakis (Sigma Aldrich 511 579) (B, pink) and **6a** (B, black). PXRD of commercial polystyrene supported tetrakis (C, blue) (Sigma Aldrich 511 579) and **6a** (C, green).

catalyst **4a** is manually ground by hand prior to functionalisation to afford **6a**. In contrast, the commercial catalyst has a very broad distribution (PDI = 1) with an average particle size diameter of 895 nm.

The characterisation is indicative of the formation of solid supported tetrakis, and in the case of the in-house prepared catalyst **6a** a significantly larger surface area is observed relative to the commercial alternative. The textural properties of catalyst **6a** are listed in Table 1.

2.3. Assessment and optimisation of catalyst **6** for Suzuki–Miyaura coupling reactions

The prepared catalyst **6a** was assessed and optimized for the Suzuki–Miyaura coupling of phenyl boronic acid **7** and iodoanisole **8** to afford biaryl anisole **9** (Scheme 2). An initial

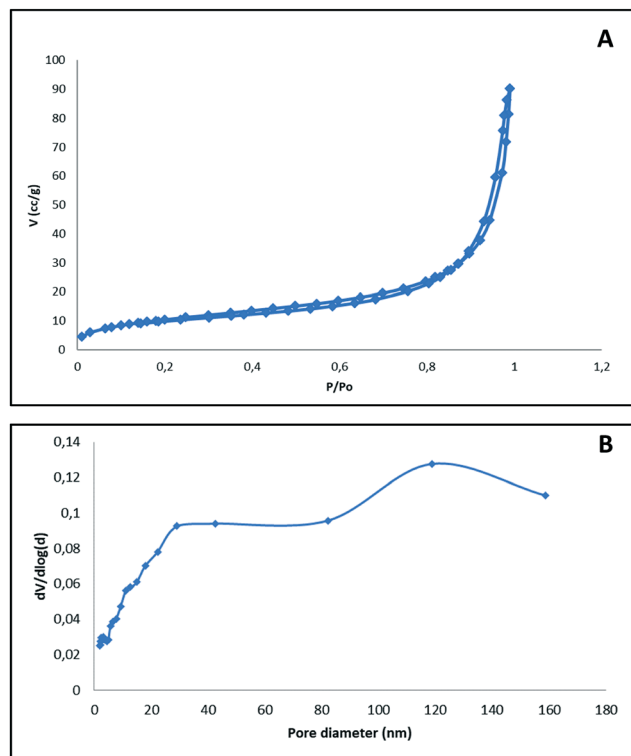


Fig. 4 Nitrogen adsorption/desorption isotherms of catalyst **6a** at 77 K (A). Pore size distribution of catalyst **6a** (B).

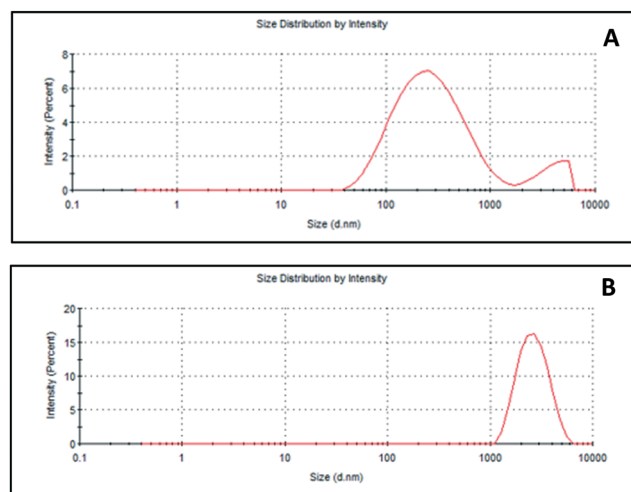


Fig. 5 Particle size distribution **6a** PDI = 0.348 (A), commercial polystyrene supported tetrakis (Sigma Aldrich 511579) PDI = 1.000 (B).

Table 1 Textural properties of **6a** and Sigma Aldrich 511579

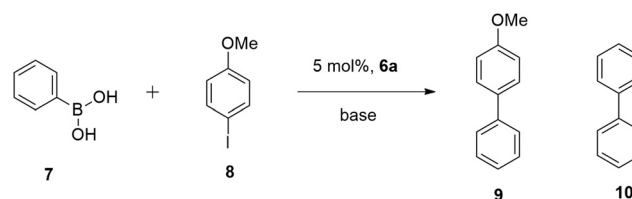
	6a	Sigma Aldrich 511579
BET surface area ($\text{m}^2 \text{g}^{-1}$)	35.2	0.0128
Mesopore volume ($\text{cm}^3 \text{g}^{-1}$)	0.143	N/A
Pore diameter (nm)	16.2	N/A
Average particle size diameter (nm)	321	895
Palladium loading (mmol g^{-1})	0.460	0.5–0.9

solvent screen was performed using excess phenyl boronic acid (3 eq.) and potassium phosphate tribasic (3 eq.) in the presence of 5 mol% of catalyst **6a**. The use of typical Suzuki–Miyaura solvent systems (Table 2, entries 1–3) proved successful with isolated yields of 75–85% and only trace amounts (2–3%) of the unwanted homo-coupled biaryl product **10**. Unfortunately, the potassium phosphate tribasic is not fully soluble in dioxane, toluene or THF and as a homogeneous solvent system was desired for flow translation an organic–aqueous binary solvent system was adopted (Table 2, entries 4–8). A 1:1 mixture of THF:H₂O proved most successful (Table 2, entry 8) with a 92% yield of **9** and only 3% of the unwanted **10**. Several other bases, including potassium carbonate, potassium hydroxide and triethylamine were screened using the biphasic solvent system (Table 2, entries 5–7) and although good conversions 74–89% were observed the isolated yields were significantly lower than when using potassium phosphate tribasic.

We then investigated how temperature and reactant stoichiometric ratios affected the performance of the reaction. Initially, the reaction was screened at different temperatures using one equivalent of both the boronic acid **7** and the base (Table 3 entries 1–3) with 5 mol% catalyst **6a**. The results suggested that the temperature within the studied range of 70–90 °C did not influence the conversion significantly, with reaction at 90 °C arguably affording a slight improvement over those performed at lower temperatures.

Increasing the stoichiometric amount of boronic acid **7** while maintaining the base at one equivalent (Table 3, entries 3–5) resulted in an increase in yield from 65 to 90%, while increasing the stoichiometric amount of base and maintaining the boronic acid at one equivalent (Table 3, entries 3 and 7) afforded an increase in yield from 65 to 76%. Interestingly, increasing the stoichiometric equivalents of the boronic acid **7** and the base together did not seem to have a significantly compounded effect (Table 3, entry 6) affording a yield of 92%.

The use of 1.2 equivalents of the boronic acid **7** and 1.5 equivalents of the base (potassium phosphate tribasic), gave a good conversion 85% but with only a moderate yield of 72% (Table 3, entry 9), increasing the amount of base to 3 equivalents then afforded an 87% isolated yield with no observed homocoupled product **10** (Table 3, entry 10, TON of 17.4 in 18 h, TOF of $2.69 \times 10^{-4} \text{ s}^{-1}$). Although not as efficient as when using large excesses of the boronic acid, we selected to continue the Suzuki–Miyara studies with 1.2 equivalents of boronic acid and 3.0 equivalents of base.



Scheme 2 Model Suzuki–Miyaura reaction screened.

Table 2 Optimization of model Suzuki batch reactions in terms of solvent and base

Entry	Solvent	Base	% conversion	% yield biaryl	% yield product
1	Toluene	K ₃ PO ₄	84	3	79
2	Dioxane	K ₃ PO ₄	87	3	75
3	THF	K ₃ PO ₄	99	2	85
4	Dioxane: H ₂ O	K ₃ PO ₄	88	2	85
5	THF/H ₂ O	K ₂ CO ₃	89	3	69
6	THF/H ₂ O	NEt ₃	74	7	54
7	THF/H ₂ O	KOH	87	3	63
8	THF/H ₂ O	K ₃ PO ₄	95	3	92

Reaction conditions, **7** (3 eq.), **8** (1 eq.), base (3 eq.), **6a** (5 mol%), 90 °C, 18 h. Conversions and yields determined by GC-FID as the average of two experiments with anisole as internal standard.

Table 3 Optimization of model Suzuki–Miyaura batch reactions in terms of temperature and stoichiometric equivalents of reagents

Entry	Equivalents of boronic acid	Equivalents of base	Temp °C	% conversion	% yield biaryl	% yield product
1	1	1	70	64	2	62
2	1	1	80	61	2	57
3	1	1	90	67	2	65
4	2	1	90	69	2	67
5	3	1	90	92	3	90
6	3	3	90	95	3	92
7	1	3	90	81	2	76
8 ^a	1	3	90	62	2	60
9	1.2	1.5	90	85	1	72
10 ^b	1.2	3	90	—	0	87

Reaction time of 18 h, (5 mol% with regards to palladium). Conversions and yields determined by GC-FID as the average of two experiments with anisole as internal standard. ^a Reaction time of 4 hours. ^b Isolated yield determined.

The decision was driven by a desire to minimize the amount of the boronic acid utilized as it is typically the largest cost contributor to the process. In addition, the approach was more waste conscious, and reduced purification complications.

The polymerized catalysts **6a** and **6b** were then benchmarked against commercially available polystyrene-supported (Sigma Aldrich, 511 579) and unsupported tetrakis (Sigma Aldrich, 216 666) using the conditions from Table 3, entry 10 (Table 4). In comparison, catalyst **6a** performed comparably to the unsupported catalyst (87 vs. 84%) and better than the commercially available solid-supported tetrakis (87 vs. 79%). Interestingly, although catalyst **6b** had a higher palladium loading (0.909 vs. 0.460 mmol g⁻¹) it performed worse than **6a** (75% vs. 87%). This is hypothesised to be due to the reduced surface area observed in **6b** as evidenced by the SEM scans (Fig. 1).

2.4. Development of a flow-based protocol for the preparation and use of catalyst **6a**

To afford a monolithic form of the catalyst, the polymerisation was carried out in a 10 mL glass Omnifit™ column which was sealed at both ends and allowed to polymerize upright in a standard convection oven at 92 °C over 48 hours. Upon cooling, the column was mounted in a heating block on a Uniqsis FlowSyn SS reactor and attempts were undertaken to remove the porogen by pumping a stream of heated dichloromethane (60 °C) through the monolith. Unfortunately, even in the absence of a back-pressure regulator (BPR) and at low flow rates (~0.01 mL min⁻¹) we were unable to consistently prepare viable monoliths. Considering these inconsistencies, we elected to grind the monolith and employ a packed-bed reactor (PBR) approach. We further felt that the

Table 4 Catalyst comparison for Suzuki–Miyaura coupling reactions

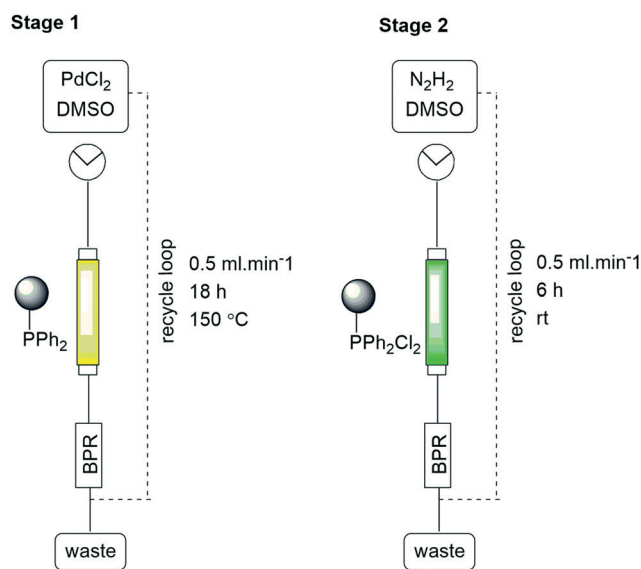
Entry	Tetrakis catalyst	Pd loading mmol g ⁻¹	% yield
1	Unsupported	—	84
2	Commercial PS supported	0.500	79
3	Catalyst 6a	0.460	87
4	Catalyst 6b	0.909	75

Reactions conducted using conditions from Table 3 entry 10.

latter approach, although not achieving the high surface contact typical of a monolithic support, is more easily implemented and if required is more amenable to scale-up. The PBR containing the finely ground polymer-supported triphenylphosphine **4** was again mounted into a Uniqsis FlowSyn SS column heating block and washed with dichloromethane at 60 °C. Thereafter, the system was re-plumbed, with the output stream passed through a back-pressure regulator and fed back into the reagent stock vessel to afford a simple recycling system (Scheme 3, Fig. 6).

A stock solution of palladium chloride in DMSO (0.1 M) was recycled across the PBR for 18 hours (0.5 mL min^{-1} , 150 °C) affording the pre-catalyst **5** (Scheme 3, stage 1). The PBR was then washed with pure DMSO to remove any unreacted PdCl_2 (failure to include the final DMSO wash, resulted in rapid blockage of the downstream flow paths). Thereafter, hydrazine hydrate was recycled through the column for 6 hours (0.5 mL min^{-1} , 0 °C, Scheme 3, stage 2) to give the desired catalyst **6a**, showing a characteristic dark green colouration (Fig. 2). The catalyst was again characterised and in this instance EDX analysis showed an improved loading of $0.689 \text{ mmol g}^{-1}$ with a Pd:P mol% ratio of 0.88 (unsupported tetrakis requires 0.86). The catalyst **6a** was then validated under flow conditions by the reaction of 3-bromo-2-methoxynaphthalene **11** and phenyl boronic acid **7** using the batch optimized conditions (Table 3, entry 10).

In a typical flow set-up (Scheme 4), a stock solution of phenyl boronic acid **7** (1.2 eq.) and 3-bromo-2-methoxynaphthalene **11** (1 eq.) in THF (1 M) was combined with a stock solution of potassium phosphate tribasic (3.0 eq.) in water (3 M) at a T-piece mixer. Thereafter, the reaction stream was passed through a PBR housing **6a** (5 mol%) followed by a BPR. A single pass at $0.183 \text{ mL min}^{-1}$ and 90 °C (1 h residence time) afforded the desired biaryl product **12a** in 65% yield.



Scheme 3 Two stage flow-based preparation of supported tetrakis catalyst **6a**.

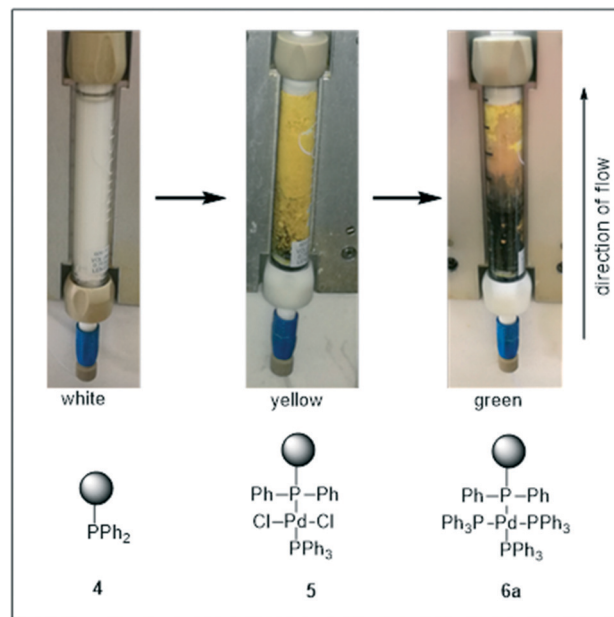
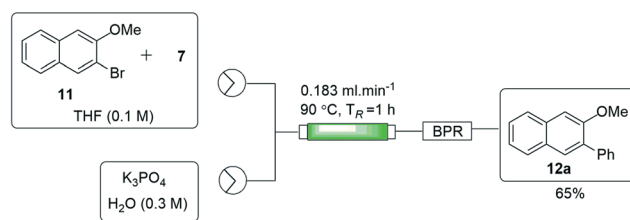


Fig. 6 Observed colour changes during catalyst **6a** preparation.

The scope of the reaction was then screened under both batch and flow conditions (Table 5) through the coupling of a range of boronic acids with 3-bromo-2-methoxynaphthalene **11** and 3-bromopyridin-2-amine **13** affording a small range of coupled naphthalene **12** and pyridine **14** derivatives. Batch reactions were conducted by reacting the boronic acid (1.2 eq.), potassium phosphate tribasic (3 eq.) and the catalyst (5 mol%) at 90 °C for 18 h (as described in Table 3 entry 10) and flow reactions were conducted as described in Scheme 4 with a residence time of only 1 h (single pass of the PBR).

As expected, the Suzuki–Miyaura coupling of aryl boronic acids (Table 5, entries 1–3 and 7–9) performed better than that of alkyl and benzylic boronic acids (Table 5, entries 5, 6, 11 and 12). Under batch conditions, the use of unsupported tetrakis in general afforded superior results compared to the commercial polymer supported tetrakis and catalyst **6a**. Under flow conditions both the commercial catalyst and **6a** performed comparably. Notably, the performance of immobilized tetrakis under flow conditions with a 1 h residence time (single pass of the PBR) afforded yields that were comparable to those achieved in 18 h under batch conditions. It should be noted that the reaction time under batch conditions was not stringently optimized, however, in all cases reactions had failed to reach completion after 18 h.



Scheme 4 General approach for Suzuki–Miyaura under flow conditions.

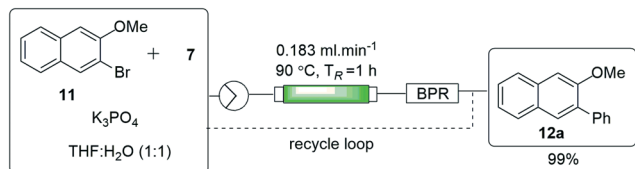
Table 5 Scope of Suzuki–Miyaura reaction under batch and flow conditions

Entry	Aryl halide	Boronic acid	Product	Batch			Flow	
				Pd(PPh ₃) ₄	PS-Pd(PPh ₃) ₄	6a	PS-Pd(PPh ₃) ₄	6a
1			12a	84	79	76	63	65
2			12b	91	44	35	65	63
3			12c	70	31	29	56	54
4			12d	NR	NR	NR	NR	NR
5			12e	20	10	8.3	21	18
6			12f	NR	NR	NR	NR	NR
7			14a	88	37	56	—	58
8			14b	90	58	68	—	71
9			14c	88	58	67	—	65
10			14d	24	18	7	—	21
11			14e	NR	NR	NR	—	NR
12			14f	75	15	10	—	20
13			15a	NR	NR	NR	—	NR
14			16a	NR	NR	NR	—	NR

Reactions conducted using conditions from Table 3 entry 10 and the flow set-up from Scheme 4. Isolated yields given. NR indicates no product formation, — indicates reaction not performed.

The PBR could also be successfully re-used with only a small drop-off in yield between runs. In the case of the coupling of phenyl boronic acid 7 and 3-bromo-2-methoxynaphthalene 11 a single PBR was used for three consecutive runs using the set-up shown in Scheme 4 affording yields of 65, 64 and 61% respectively for 12a. As each run was only a single pass, with a residence time of 1 h, the results suggested a three-hour residence time under flow conditions would afford close to quantitative conversion. Finally, a sim-

ple recycling study was conducted to see if the conversions could be increased further under flow conditions (Scheme 5). Employing a similar set-up to that shown in Scheme 4, the boronic acid 7, aryl halide 11 and potassium phosphate tribasic were prepared as a single stock solution in THF:H₂O (1:1). The stock solution was then pumped directly through the PBR housing 6a at 0.183 ml min⁻¹ and 90 °C prior to passage through a BPR. The outlet was then fed directly back into the stock reagent reservoir creating a simple recycle loop. The



Scheme 5 General approach for Suzuki-Miyaura under flow conditions with recycling.

Table 6 Flow recycling study

Entry	Time (hours)	% conversion
1	1	82
2	2	94
3	3	99

Reaction conditions, **7** (1.2 eq.), **11** (1 eq.), K_3PO_4 (3 eq.), **6a** (5 mol%), 90 °C. Conversions and yields determined by GC-FID as the average of two experiments.

reagent reservoir was then sampled hourly (Table 6) affording 99% conversion after three hours (TON of 19.8 in 3 h, TOF of $1.83 \times 10^{-3} \text{ s}^{-1}$).

3. Conclusions

In conclusion, we have demonstrated the preparation of immobilized triphenylphosphine using precipitation polymerization and its conversion to a solid-supported tetrakis(triphenylphosphine) palladium(0) catalyst **6a**. The prepared catalyst **6a** offers an economical alternative to expensive commercial solid-supported versions of the catalyst with comparable performance. The utility of the catalyst **6a** was demonstrated for Suzuki-Miyaura cross-coupling reactions under batch and flow conditions, with the flow translation requiring the use of a biphasic solvent system to ensure the solubilization of the inorganic base (potassium phosphate tribasic) and reaction salt by-products. Under flow conditions, preparation of the catalyst **6a** was conveniently achieved by the sequential passage of the palladium source and the reducing agent across the PBR. Under these conditions the catalyst **6a** has a higher palladium loading (0.689 *vs.* 0.460 g mmol⁻¹) and no detectable traces of Cl (as determined by EDX) the latter of which remain present in trace amounts when prepared under batch conditions. Passage across a heated packed-bed reactor housing the catalyst **6a** afforded comparable yields to those obtained under batch conditions but in a largely reduced reaction time (1 h *vs.* 18 h) with only a single pass across the catalyst bed. Finally, multiple passes across the catalyst bed using a recycle loop could be used to improve the overall conversion.

4. Experimental

4.1. General information

All reactions were carried out in oven or flame-dried glassware. Dry solvents were distilled under nitrogen before being used. Tetrahydrofuran was distilled from sodium with benzo-

phenone added as indicator, dichloromethane was distilled from calcium hydride. All reagents and solvents from commercial sources were used without further purification. Thin Layer Chromatography analysis was carried out on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254), which was visualized by ultraviolet light. Column chromatography was carried out using silica gel (Fluorochem Silica Gel 60, 40–63 micron) as the stationary phase.

Nuclear Magnetic Resonance spectra were recorded in $CDCl_3$ solutions using a Bruker Ultrashield 300 MHz spectrometer for ¹H NMR and a Bruker Ultrashield Plus 400 MHz for ¹³C NMR. Chemical shifts are reported relative to tetramethylsilane as the internal standard at 0.00 ppm for ¹H NMR and $CDCl_3$ at 77.36 ppm for ¹³C NMR as the internal standard. Spectral features for ¹H NMR were recorded in the following order: chemical shift (δ_H , ppm); coupling constant(s) (*J*, Hz); multiplicity; number of protons; assignment. ¹³C NMR spectral data is recorded in the form: chemical shift (δ_C , ppm); assignment. Solid-state NMRs were run on a Bruker 500 MHz Avance III spectrometer equipped with a solids probe. FTIR spectra were obtained on a Bruker Platinum ATR Tensor 27 spectrometer instrument with neat samples. Spectral features are tabulated as wavenumbers (cm⁻¹).

SEM samples were prepared by placing a small piece of double sided conductive tape on a sample stub and sprinkling a small amount of sample on to it. The samples were all prepared on different stubs and then coated with carbon to render them conductive. The stubs were then placed onto a viewing stage. SEM and EDX data were processed using ZEISS Auriga SEM and an Oxford x-max detector with the software for SEM being SMART SEM version V05.04.05.00. and for EDX being Aztec 2.2 SP1. TEM samples were dispersed on enough ethanol to create a very lightly disperse solution. This was then sonicated for 30 minutes in an ultra-sonicator at room temperature. A carbon coated Cu grid was then dipped into the solution and left to dry at room temperature. Samples were then run using JEOL JEM 2100 instrument.

Powder XRDs were run on the Bruker D2 Phaser XRD machine and data was analysed using DiffractDW 1.3.0.1, 200 mg of each sample was placed on a low background sample holder and run at 2 seconds per 0.05 2 theta increments ranging from 5 to 60 2 theta. BET physisorption was performed by degassing the samples at 90 °C for 4 h before nitrogen adsorption using Tristar II Micromeritics Instrument. Particle size distribution was measured on a Zetasizer nano series Malvern instrument, 10 mg of the samples were put into a vial with 1 mL distilled water and vial was vortexed. Samples were then filtered into sample holder and run 3 times to get an average.

4.2. Batch synthesis

Synthesis of immobilized tetrakis **6a.** To a suspension of polymer-supported triphenylphosphine⁸ (1.005 g) in degassed DMSO (20 mL) was added palladium chloride (0.246 g, 1.0 eq.) and the mixture was refluxed for 2 h under argon.

Thereafter the solution was cooled to 0 °C and hydrazine hydrate (0.25 mL, 2.0 eq.) was added, the mixture was stirred for 1 h. The immobilized catalyst **6a** was then filtered under argon and washed with degassed ethanol (50 mL) followed by degassed diethyl ether (50 mL) to yield **6a** as a green solid, 0.460 mmol g⁻¹ Pd as determined by EDX.

Synthesis of immobilized tetrakis 6b. To a suspension of polymer-supported triphenylphosphine⁸ (1.005 g) in degassed DMSO (20 mL) was added palladium chloride (0.246 g, 1.0 eq.) and the mixture was refluxed for 2 h under argon. Thereafter triphenylphosphine (0.227 g, 1.5 eq.) in degassed ethanol (5 mL) was added and the mixture was stirred for another 3 hours. The solution was then cooled to 0 °C and hydrazine hydrate (0.25 mL, 2.0 eq.) was added, the mixture was stirred for 1 hour. The immobilized catalyst **6a** was then filtered under argon and washed with degassed ethanol (50 mL) followed by degassed diethyl ether (50 mL) to yield **6a** as a green solid, 0.909 mmol g⁻¹ Pd as determined by EDX.

General procedure 1 for Suzuki coupling reactions using 6a. To a flame dried flask under argon was added aryl halide (1.0 eq.), boronic acid (1.2 eq.), base (1.5 eq.), **6a** (0.07 eq.), dry degassed THF (2.0 mL) and degassed water (2.0 mL) and the suspension was refluxed for 18 h at 90 °C under argon. Thereafter, the crude reaction mixture was quenched with aqueous NH₄Cl (10 mL) and diluted with EtOAc (20 mL). The immobilized catalyst **6a** was then removed by filtration. The reaction mixture was separated, and the aqueous phases extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (MgSO₄), filtered, evaporated *in vacuo*, and purified using column chromatography using 5% EtOAc/hexane as eluent.

General procedure 2 for synthesis of Suzuki coupling reactions using commercial unsupported tetrakis. To a flame dried flask under argon was dissolved aryl halide (60 mg, 1.0 eq.), boronic acid (1.2 eq.), base (3.0 eq.) and commercial tetrakis (Sigma Aldrich, 216 666) (0.05 eq.) in dry degassed THF (2.0 mL) and degassed water (2.0 mL) and the suspension was refluxed overnight at 90 °C under argon. The crude mixture was then quenched with NH₄Cl (10 mL) and diluted with EtOAc (20 mL). The reaction mixture was separated, and the aqueous phases extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (MgSO₄), filtered, evaporated *in vacuo*, and purified using column chromatography using 5% EtOAc/hexane as eluent.

General procedure 3 for synthesis of Suzuki coupling reactions using commercial polystyrene-supported tetrakis. To a flame dried flask under argon was added aryl halide (1.0 eq.), boronic acid (1.2 eq.), base (3.0 eq.), polystyrene-supported tetrakis (Sigma Aldrich, 511 579) (0.05 eq.), dry degassed THF (2.0 mL) and degassed water (2.0 mL) and the suspension was refluxed for 18 h at 90 °C under argon. Thereafter, the crude reaction mixture was quenched with aqueous NH₄Cl (10 mL), diluted with EtOAc (20 mL) the immobilized catalyst **6a** was then removed by filtration. The reaction mixture was separated, and the aqueous phases extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (MgSO₄),

filtered and evaporated *in vacuo*, and purified using column chromatography using 5% EtOAc/hexane as eluent.

4.3. Flow synthesis

Synthesis of immobilized tetrakis 6a. A 10 mL glass OmnitFit™ column was loaded with ground, washed, immobilized **6a** (1.005 g). The column was mounted in a Uniqsis FlowSyn SS reactor heating block using the set-up shown in Scheme 3. The column was washed with DMSO at 1.0 mL min⁻¹ for 30 minutes, thereafter, PdCl₂ (246 mg, 0.1 M) in DMSO (20 mL) was recycled across the column for 18 hours at 0.5 mL min⁻¹ and 150 °C during which time the material changed from white to yellow. The column was then washed with DMSO for 1 h at 1.0 mL min⁻¹ while cooling to room temperature to remove any unreacted PdCl₂. The column was then cooled to 0 °C and hydrazine hydrate (0.25 mL, 0.3 M) in DMSO (10 mL) was recycled through the column at 0.5 mL min⁻¹ for 6 hours. The column was then washed sequentially with degassed ethanol (50 mL) and degassed diethyl ether (50 mL) affording **6a** as a green solid, 0.689 mmol g⁻¹ Pd as determined by EDX.

General procedure 4 for synthesis of Suzuki coupling reactions using 6a. A 10 mL glass OmnitFit™ column was purged with argon and packed with **6a** (0.07 eq.). The column was mounted in a Uniqsis FlowSyn SS reactor heating block using the set-up shown in Scheme 4 and washed with degassed THF:H₂O (1:1) for 5 minutes. A stock solution containing the aryl halide (0.1 M, 1.0 eq.) and the boronic acid (1.2 eq.) in degassed THF was mixed with a stock solution of base (0.3 M, 3.0 eq.) in degassed H₂O in a 1:1 ratio at a T-piece mixer. Thereafter the flow stream was passed through the glass OmnitFit™ column housing **6a** at 90 °C. A total flow rate of 0.183 mL min⁻¹ (T_R = 1 h) was used. A post-reaction wash with THF:H₂O (1:1) was performed at 0.5 mL min⁻¹ for 1 hour. The biphasic mixture was then separated, and the aqueous layers extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, evaporated *in vacuo* and purified by column chromatography using 5% EtOAc/hexane as eluent.

General procedure 5 for synthesis of Suzuki coupling reactions using commercial polystyrene-supported tetrakis. A 10 mL glass OmnitFit™ column was purged with argon and packed with, polystyrene-supported tetrakis (Sigma Aldrich, 216 666) (0.05 eq.). The column was mounted in a Uniqsis FlowSyn SS reactor heating block using the set-up shown in Scheme 4 and washed with degassed THF:H₂O (1:1) for 5 minutes. A stock solution containing the aryl halide (0.1 M, 1.0 eq.) and the boronic acid (1.2 eq.) in degassed THF was mixed with a stock solution of base (0.3 M, 3.0 eq.) in degassed H₂O in a 1:1 ratio at a T-piece mixer. Thereafter the flow stream was passed through the glass OmnitFit™ column housing **6a** at 90 °C. A total flow rate of 0.183 mL min⁻¹ (T_R = 1 h) was used. A post-reaction wash with THF:H₂O (1:1) was performed at 0.5 mL min⁻¹ for 1 hour. The biphasic mixture was then separated, and the aqueous layers extracted

with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, evaporated *in vacuo* and purified by column chromatography using 5% EtOAc/hexane as eluent.

Synthesis of 2-methoxy-3-bromonaphthalene 11. Naphthol (0.500 g, 3.46 mmol, 1.0 eq.) was dissolved in dry dichloromethane (10 mL) under argon and diisopropylamine (0.0351 g, 0.347 mmol, 0.1 eq.) was added, followed by slow addition of *N*-bromo succinimide (0.679 g, 3.815 mmol, 1.1 eq.). The reaction mixture was stirred at 40 °C overnight, after which time the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 10–20% EtOAc/hexane as eluent affording bromonaphthalenol as a brown solid in 86% yield. A solution of bromonaphthalenol (1.50 g, 6.75 mmol, 1.0 eq.), potassium hydroxide (0.758 g, 13.51 mmol, 2.0 eq.) and methyl iodide (2.52 mL, 40.54 mmol, 6.0 eq.) in dry acetonitrile (40 mL) were stirred at room temperature overnight under argon. Thereafter, the mixture was washed with water (20 mL) and extracted with dichloromethane (3 × 30 mL). The organic fraction were collected and dried (MgSO₄), filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography using 10% EtOAc/hexane as eluent affording 2-methoxy-3-bromonaphthalene 11 as a brown solid in 94% yield.

2-Methoxy-3-phenylnaphthalene (12a). White solid, ¹H NMR (300 MHz, CDCl₃) δ 7.84–7.69 (m, 2H), 7.47–7.18 (m, 9H), 3.74 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 154.06, 136.76, 133.94, 131.30, 129.42, 129.35, 128.50, 128.17, 127.41, 126.63, 125.72, 125.61, 123.85, 114.15, 57.12.

2-Methoxy-3-(3,4,5-trimethoxyphenyl)naphthalene (12b). Brown solid, ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.86–7.79 (m, 1H), 7.73–7.62 (m, 1H), 7.60–7.51 (m, 1H), 7.49–7.43 (m, 1H), 7.42–7.33 (m, 3H), 3.96 (s, 3H), 3.89 (s, 3H), 3.84 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 153.89, 153.30, 137.12, 133.93, 129.42, 128.86, 128.73, 128.11, 126.69, 125.57, 123.85, 114.01, 108.15, 61.18, 57.09, 56.32.

4-(3-Methoxynaphthalen-2-yl)benzaldehyde (12c). Yellow oil, ¹H NMR (300 MHz, CDCl₃) δ 10.11 (s, 1H), 8.05–7.99 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 4.2 Hz, 1H), 7.88–7.82 (m, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.46–7.32 (m, 4H), 3.85 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 192.48, 153.86, 143.80, 135.45, 133.23, 132.18, 130.23, 129.88, 129.22, 128.36, 127.06, 124.90, 124.03, 123.98, 113.66, 56.82.

2-Butyl-3-methoxynaphthalene (12e). Yellow solid, ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, *J* = 8.7 Hz, 1H), 7.82–7.67 (m, 2H), 7.51–7.42 (m, 1H), 7.39–7.27 (m, 1H), 3.94 (s, 3H), 1.67–1.53 (m, 4H), 1.52–1.41 (m, 2H), 0.97 (t, *J* = 14.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 154.58, 133.33, 129.61, 128.82, 127.60, 126.37, 124.78, 123.71, 123.42, 113.88, 56.95, 32.72, 30.06, 23.43, 14.44.

3-Phenylpyridin-2-amine (14a). Brown solid, ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 6.0 Hz, 1H), 7.51–7.42 (m, 2H), 7.41–7.33 (m, 2H), 7.43–7.38 (m, 2H), 6.81–6.72 (m, 1H), 4.56 (s, 2H, br); ¹³C NMR (101 MHz, CDCl₃) δ 155.78, 147.04, 138.88, 133.90, 129.86, 129.49, 128.99, 123.12, 114.37.

3-(3,4,5-Trimethoxyphenyl)pyridin-2-amine (14b). Orange solid, ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, *J* = 6.6 Hz, 1H),

7.71–7.61 (m, 1H), 7.58–7.51 (m, 1H), 7.40–7.33 (m, 1H), 6.79–6.69 (m, 1H), 4.63 (s, 2H, br), 3.89 (s, 3H), 3.88 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 156.17, 153.97, 147.55, 137.91, 133.8, 132.34, 122.22, 114.62, 105.99, 61.23, 56.51.

4-(2-Aminopyridin-3-yl)benzaldehyde (14c). Yellow oil, ¹H NMR (400 MHz, CDCl₃) δ 10.06 (s, 1H), 8.18–8.06 (m, 1H), 7.61–7.50 (m, 1H), 7.48–7.43 (m, 3H), 7.40–7.32 (m, 1H), 6.84–6.74 (m, 1H), 4.73 (s, 2H, br); ¹³C NMR (101 MHz, CDCl₃) δ 191.89, 155.78, 148.42, 144.77, 138.27, 135.80, 133.10, 130.74, 129.61, 128.87, 128.75, 116.50, 114.89.

3-(1*H*-Inden-2-yl)pyridin-2-amine (14d). Red oil, ¹H NMR (400 MHz, CDCl₃) δ 8.08–8.07 (m, 1H), 7.72–7.62 (m, 2H), 7.59–7.51 (m, 2H), 7.50–7.42 (m, 3H), 6.78–6.71 (m, 1H), 6.68–6.60 (m, 1H), 4.65 (s, 2H, br); ¹³C NMR (101 MHz, CDCl₃) δ 156.60, 147.60, 144.53, 143.74, 140.69, 132.46, 132.36, 126.70, 125.69, 124.51, 120.85, 115.33, 114.18, 38.94.

3-Benzylpyridin-2-amine (14f). Brown oil, ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, *J* = 6.0 Hz, 1H), 7.75–7.62 (m, 1H), 7.47–7.43 (m, 1H), 7.36–7.28 (m, 2H), 7.18–7.12 (m, 2H), 6.72–6.63 (m, 1H), 4.36 (s, 2H, br), 3.82 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 157.35, 146.69, 138.44, 132.43, 129.14, 128.86, 127.07, 119.66, 114.80, 37.93.

Conflicts of interest

There are no conflicts to declare.

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