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Recyclable NHC Catalyst for the Development of a Generalized Approach to Continuous Buchwald-Hartwig Reaction and Work-Up

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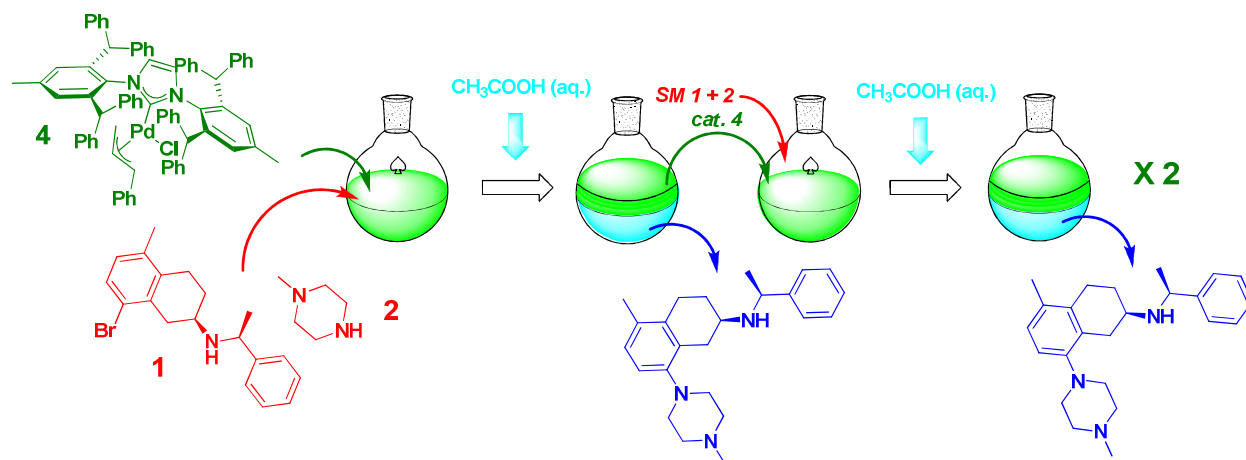
ABSTRACT

A generalized approach to the optimization and implementation of Buchwald-Hartwig reactions in flow is reported, through the combination of three key factors: a highly active palladium catalyst; a universal approach for continuous work-up and purification, and a methodology for catalyst recycling and reuse.   The palladium *N*-heterocyclic carbene (NHC) pre-catalyst [Pd(IPr*)(cin)Cl] **4** (IPr* = 1,3-*bis*(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene; cin = η^3-cinnamyl) is an excellent choice for continuous Buchwald-Hartwig reactions, due to its inherent high activity and stability. In preparation for running this reaction in flow (published concurrently), a detailed study has been carried out into its water stability, ultimately allowing the recycling of the catalyst in the organic phase up to 3 times in batch mode. A "right-first-time" work-up methodology has also been developed, resulting in a universal protocol that allows the selective extraction of the Buchwald-Hartwig product into the aqueous stream as a salt, while retaining the aryl bromide starting material in the organic stream with the catalyst, thus negating the requirement for further purification. It is therefore envisaged that this approach will particularly amenable to exploitation in the Pharmaceutical industry. An optimized, scalable synthesis of [Pd(IPr*)(cin)Cl] is also reported on multi-hundred gram scale.

KEYWORDS. Buchwald-Hartwig amination, NHC catalyst, palladium catalysis, catalyst recycle, continuous processing, flow chemistry, designed work-up.

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Introduction

C-N bond forming reactions are ubiquitous throughout industry and academia in the synthesis of naturally-occurring and pharmaceutically relevant targets, and the Buchwald-Hartwig reaction remains a fundamental methodology for their synthesis.[1] However, there remain a number of key challenges for putting these reactions into flow, not least the solid salt formation that is unavoidable due to the nature of the inorganic or alkali metal alkoxide bases that are most effective for this transformation. Not only is the resultant heterogeneous reaction mixture regarded as highly undesirable when dealing with flow reactors due to the potential risk of blocking, it also precludes the use of a solid-supported catalyst for the continuous reaction, a strategy typically adopted for running catalytic reactions in flow.[2] The use of soluble organic bases to avoid these issues has been assessed on a number of occasions,[3,4] however, a recent study stemming from this work has revealed them to be an unviable option in all but the minority of cases.[5] Other strategies to avoid this issue have included use of biphasic systems to solubilise the inorganic base, particularly in combination with packed-bed reactors to combat the mixing issues inherent in running such systems in continuous flow mode.[6]

AR-A2 (**3**) is a candidate drug (CD) that was previously under development at AstraZeneca for the treatment of CNS (central nervous system) disorders, reaching Phase II clinical trials.[7,8] One of the key bond-forming reactions in its synthesis is the Buchwald-Hartwig reaction between compound **1** and *N*-methylpiperazine to give key intermediate **2**. The existing process chemistry conditions have been published previously, however, we were interested in developing a continuous process for the manufacture and isolation of intermediate **2** as a viable manufacturing alternative to the current route.
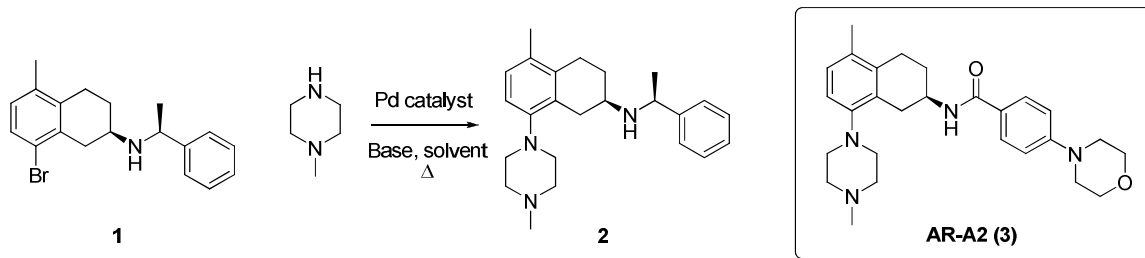
Scheme 1. Palladium-catalysed amination of **1** to give **2**, a key intermediate in the synthesis of AR-A2 (**3**).

Our vision for developing this reaction into a continuous system takes a different approach to the perceived issues highlighted above: ***develop*** a reactor capable of dealing with the solid salt formation inherent in the reaction; ***incorporate*** a recycle of a suitably stable catalyst *in situ*, and thereby ***create*** a generic reaction system, incorporating a continuous work-up that allows for the reuse of the catalyst and ultimately has the potential to be applicable beyond this immediate project. The intended reaction system is described in Figure 1. Employing our bespoke flow reactor (described in detail elsewhere)[9] for conducting the reaction, followed by a post-reaction acidic aqueous quench in a mixer-settler gives us two output streams: the aqueous containing the product salt, along with any dissolved inorganics, and the organic stream containing the residual palladium catalyst, with the intention that this could then be recycled and reused following a defined treatment protocol.
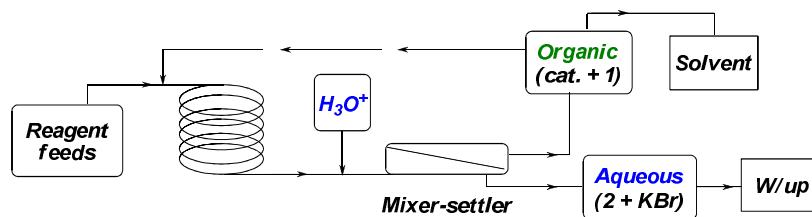
Figure 1. Schematic for the Buchwald-Hartwig reaction and work-up in flow, including catalyst recycle.

To achieve this vision, it was necessary to have a highly active catalyst that was stable enough to withstand the aqueous acidic work-up that would be developed for the process. Since the advent of their widespread use at the end of the 20th century, *N*-heterocyclic carbene (NHC) ligands have become an important and useful classes of ancillary ligands for organometallic catalysis. In particular, palladium NHC precatalysts (Figure 2) have proven to be highly active for various reactions,[10] not least Buchwald-Hartwig coupling,[11] where immobilized forms of these ligands have also been employed.[12] While several strategies exist for the formation of stable and efficient precatalysts, the [Pd(NHC)(cin)Cl] (cin = η^3-cinnamyl) family[13] has proven to be particularly reliable in terms of activity and stability. Among these, [Pd(IPr*)(cin)Cl] (IPr* = 1,3-*bis*(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) **4**,[14] incorporating one of the bulkiest NHC ligands reported to date, has been demonstrated to be amongst the most active precatalysts for the Buchwald-Hartwig amination reaction, allowing the formation of aromatic amines from challenging substrates under mild conditions and with low catalyst loadings.[15] For this reason, along with the inherent stability offered by the bulky aryl groups, this became the catalyst of choice for our study.
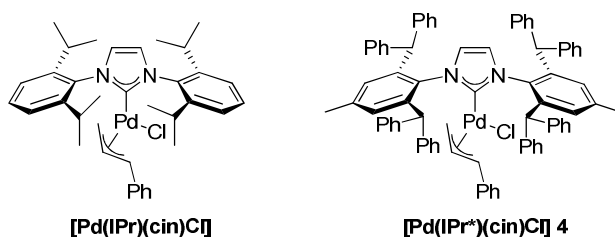

[Pd(IPr)(cin)Cl]　　　　**[Pd(IPr*)(cin)Cl] 4**

Figure 2. NHC's for cross coupling: [Pd(IPr)(cin)Cl] and [Pd(IPr*)(cin)Cl] **4**.

Discussion

The development of our flow methodology for this transformation required the investigation of a number of key aspects of the process as a whole. In particular, detailed investigations were carried out into the work-up and isolation stages of the process and as a consequence of this, a study into the stability of the NHC catalyst and its ability to undergo successful recycling was also deemed necessary. This manuscript is primarily concerned with the development of the separate aspects of the process and studies into the stability and recyclability of the NHC catalyst prior to running the scaled-up manufacture of the flow process.

Large Scale Manufacture of Pre-Catalyst:

As the above catalyst was not commercially available, it became necessary to develop a larger scale synthesis of the [Pd(IPr*)(cin)Cl] precatalyst **4** in order to meet the demands of a multi-kilo scale synthesis of **2**. The synthesis of the IPr* ligand was first reported by Marko *et al*. in 2010[16] and although this protocol was adequate to prepare the ligand on a laboratory scale (<10 g), it proved less efficient when scaling up the reaction process. It was therefore decided to optimize the synthesis to enable a more practical and scalable route.

Synthesis of aniline **5** involves the condensation of neat *para*-toluidine with two equivalents of diphenylmethanol at 160 °C in the presence of zinc chloride and concentrated hydrochloric acid (Scheme 2).[16] Marko reported that this protocol yielded aniline **5** in 75 % yield on a 13.4 g scale.[16] In our case, using similar reaction conditions on a larger scale globally resulted in a slightly improved yield. Indeed, nine successive batches of aniline **5** (~250 g per batch) were prepared to give almost 2 kg of the aniline in excellent average yield (81 %). It is important to state that Marko performed this reaction in a sealed tube, however, for safety and practical

reasons due to the scale we were operating at, the reaction was run in an open system using a

Dean Stark apparatus to trap and eliminate the water formed during the reaction.
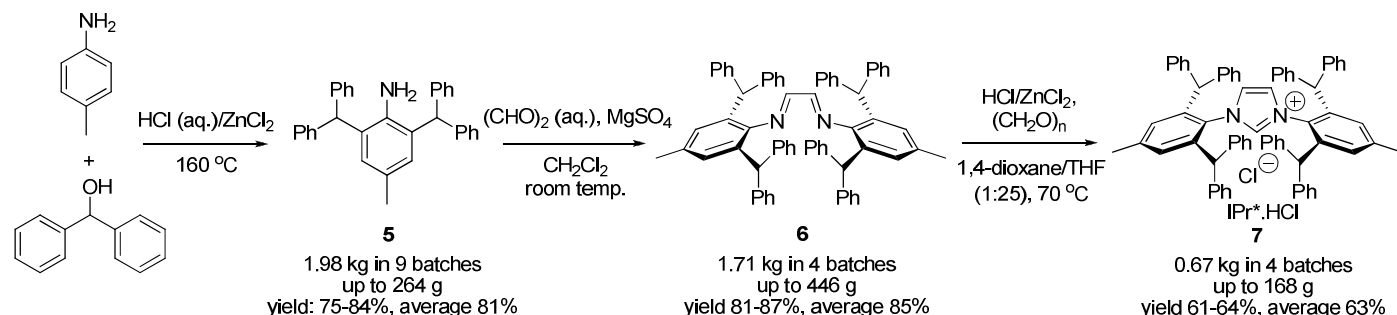

Scheme 2. Preparation of IPr*·HCl on a large scale.

Next, formation of diimine **6** was carried out by reaction of two equivalents of **5** with glyoxal in

the presence of $MgSO_4$ at ambient temperature in dichloromethane for 4 days. The reaction was

initially reported on an 8.1 g scale using a 2:1 ratio of aniline **5** to glyoxal, to give **6** in a yield of

90 %.[16] However, when similar reaction conditions were employed by us on a larger scale, this

ratio only resulted in partial conversion (~50 %) of the starting aniline after 4 days reaction time.

It was found that adding an additional 0.5 equivalents of glyoxal, along with $MgSO_4$ after 3 days

of reaction time was beneficial to the course of the reaction, giving a considerable increase in

yield for the preparation of diimine **6** on scale. In this way, 1.7 kg of the diimine was prepared

over 4 batches in an average yield of 85 %.

Next, formation of the IPr*·HCl salt **7** by ring closure of the diimine using paraformaldehyde in

the presence of $ZnCl_2$ and HCl (4 M in 1,4-dioxane) was carried out (Scheme 2). Marko

reported this step to yield IPr*·HCl in 60 % yield on a 3.4 g scale, using chloroform as the

reaction solvent.[16] Unfortunately these reaction conditions gave a yield of 45-50 % when carried

out on the larger scale required. Having such a low yielding step late on in the synthesis of the

precatalyst was clearly undesirable, therefore after investigating a range of alternative solvents, tetrahydrofuran (THF) was subsequently found to be an excellent alternative to chloroform in this case, as well as being a more process-friendly solvent on a larger scale. These conditions allowed the preparation of 0.67 kg of the ligand salt across 4 batches in an average yield of 63 % (Scheme 2). Tout modified route now represents an efficient and scalable synthesis of ligand salt **7** without the need for chromatography or any additional purification steps.
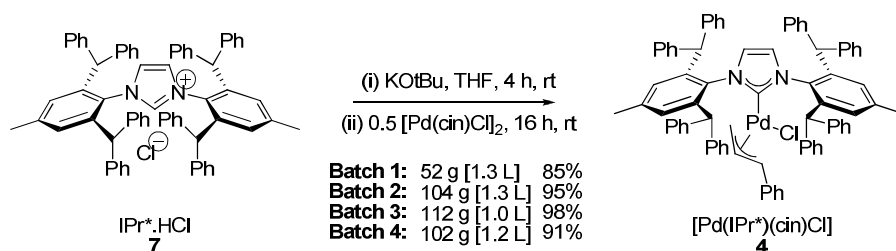
Scheme 3. Formation of [Pd(IPr*)(cin)Cl] (**4**).

Finally, the formation of the [Pd(IPr*)(cin)Cl] complex **4** by reaction of IPr*·HCl and [Pd(cin)Cl]$_2$ in the presence of potassium *tert*-butoxide in THF was investigated.[14] The preparation of the complex was reported in an excellent yield (95 %) on a 2 g scale, however, the use of high dilution in this step (0.025 M) made it unsuitable for scale-up. Ultimately, it was found that the synthesis of complex **4** could be carried out successfully at a concentration 0.1 M without significantly affecting the yield, giving 370 g of [Pd(IPr*)(cin)Cl] complex **4** over 4 batches in an excellent overall yield (92 %) and excellent purity, as indicated by elemental analysis.

Choice of Reaction Solvent and Base:

Previous reports on the use of [Pd(IPr*)(cin)Cl] **4** in Buchwald-Hartwig reactions have highlighted the combination of potassium *tert*-amylate and dimethoxyethane (DME) as the

superior base and solvent for this reaction at ambient temperature, however, when moving to lower catalyst loadings and higher temperatures, toluene was found to be more effective.[15] When selecting a base and solvent for our flow process, factors other than high conversions needed to be taken into consideration; although the organic soluble base potassium *tert*-amylate was amenable to our flow set-up, the water-soluble solvent DME would not be a viable option for the continuous work-up, as well as being undesirable from a SHE (Safety, Health and Environmental) perspective. Both toluene and 2-methyltetrahydrofuran (2-MeTHF) were investigated as possible alternatives but ultimately, despite slightly higher catalyst activities being obtained using 2-methyltetrahydrofuran, it was the superior water immiscibility of the toluene that made it the preferred choice for our process.

Work-up and Isolation Stages:

A key part of the reaction system shown in Figure 1 was the construction of a mild and efficient work-up that could be easily translated to a flow reactor, allowing the selective extraction of the product as its salt, whilst being mild enough for the catalyst to survive and be effectively recycled. Quantitative analysis of the extraction of the two species **1** and **2** at varying pH was therefore carried out in a system closely resembling the genuine reaction work-up: equal volumes of toluene and water in the presence of KBr and *tert*-amyl alcohol at 30 °C, titrated with 5 M acetic acid. This revealed that although the two species are predicted to have very similar pK_as,[17] their extraction profiles are remarkably different (Figure 3).
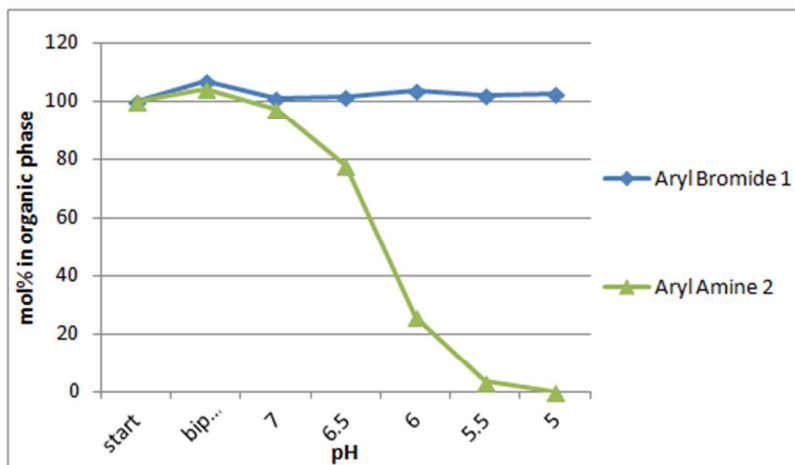
Figure 3. Extraction profiles of **1** and **2** at varying pH (Conditions: 1 mmol **1**, 1 mmol **2**, 1 mmol KBr, 1 mmol *t*-AmOH, 10 mL PhMe, 10 mL water, titrant: 5 M acetic acid, 30 °C. Analysed by ^{1}H NMR against internal standard (1,3,5-trimethoxybenzene)).

Figure 3 reveals that a pH window exists around pH 5-5.5 where the product **2** can be selectively extracted, leaving behind any unreacted aryl bromide **1** in the organic phase. The aryl bromide **1** does not begin to be extracted into the aqueous phase until pH<5. This had two consequences for our flow process: firstly, it meant that our work-up and isolation stage would also be amenable to running in flow by means of a pH-controlled mixer-settler, giving efficient and clean extraction of the product into the aqueous phase; and secondly, in order to successfully recycle our chosen NHC catalyst it would need to withstand a mild (pH ~5.5) aqueous acidic wash prior to being reused. It is envisaged that the opportunity of an "extraction window" is likely to be applicable to the vast majority of Buchwald-Hartwig reactions and as such this "right-first-time" approach to work-ups can be employed universally for the optimization of extractions and purifications in this class of reaction under flow conditions.[18]

Catalyst Stability:

In order to effect a successful recycle of the catalyst, it was necessary to have a quantitative understanding of its sensitivity to water. With this aim five batches of toluene containing

different amounts of water were prepared and the reactivity of the catalytic system in each batch

was studied, ranging from "still-dried" (Batch A) to water saturated (Batch E). The system was

shown to be particularly sensitive to the presence of water, as observed in Figure 4; a dramatic

decrease in conversion occurs from 98 % in 1 hour when "dry" toluene was employed, to 42 %

when the water-saturated toluene was used without any drying treatment.   It is, however,

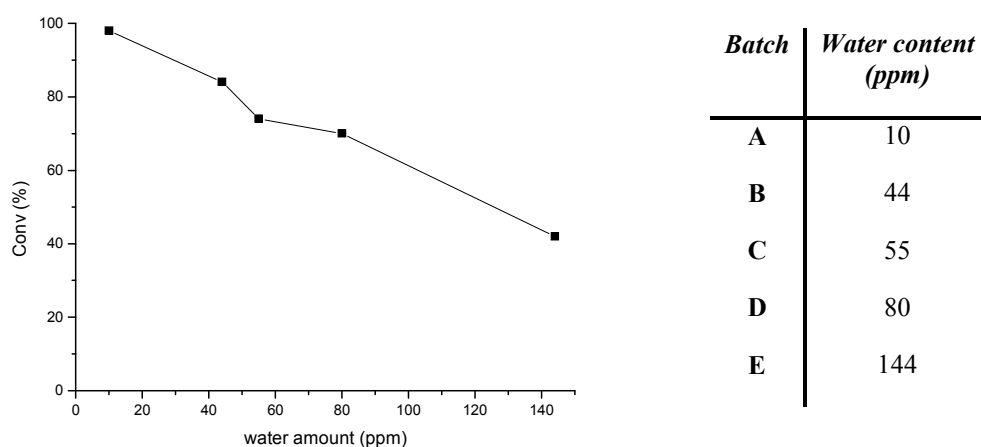remarkable that in no case was the precipitation of palladium black observed.

Batch	Water content (ppm)
A	10
B	44
C	55
D	80
E	144

Figure 4. Impact of varying levels of water on conversion at 1 hour reaction time (analysed by GC relative to an internal standard, undecane).

Exploring the possibility that the drop in conversion could potentially be due to quenching of the

base by the additional water present, additional equivalents of the potassium *tert*-butoxide base

were added to the reactions using water-spiked toluene to determine if the same levels of activity

could be obtained with less dry toluene. The results in Figure 5 demonstrate that at the higher

water levels (80 ppm), it was not possible to increase the conversion of the amination reaction,

even by adding an extra 2 equivalents of base, however, at lower water levels (45 and 55 ppm)

the conversion was successfully increased by employing 1.5-2 equivalents of base (94-99 %

conversion).   Increasing the base levels further to 3 equivalents was observed to have a deleterious effect on the reaction, suggesting a shift in equilibrium between the active catalytic species and other less active off-cycle palladium species.   Further investigations into the catalytic cycle are required to fully define this.
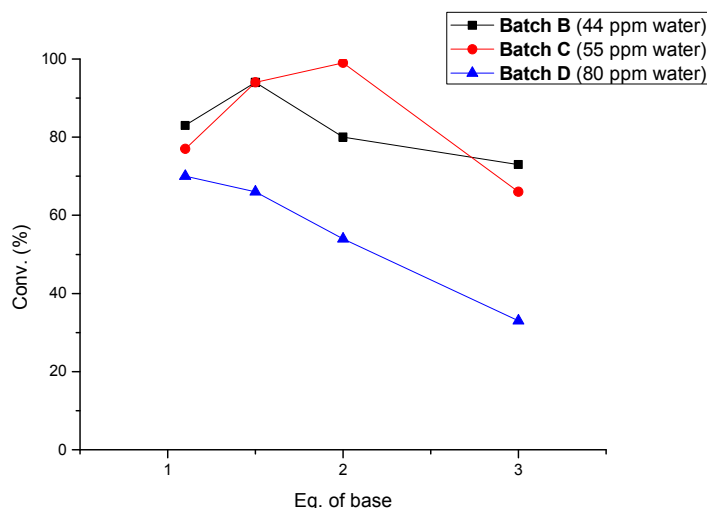

Figure 5. Impact of additional base on conversion at varying water levels at 1 hour reaction time (analysed by GC relative to an internal standard, undecane).

This informed us that at lower water levels, the "drying" effect of excess potassium *tert*-amylate can counteract the inhibitory effect of the water in the reaction, suggesting that the catalyst itself is robust to water levels ≤55 ppm.

Recycling Studies:

Due to the observed water sensitivity of the reaction system, as highlighted in Figure 4, various methods of controlling the water levels in the recycled catalyst stream were assessed. The usual solid drying agents ($MgSO_4$, SiO_2 etc.) were rejected due to the necessity for an additional filtration step, which would be impractical for a flow process. A brief study was therefore

conducted into alternative liquid organic reagents that could potentially react with the water present in the organic phase, but not have a detrimental effect on the catalyst. However, all reagents assessed (including trimethylchlorosilane, acetyl chloride and acetic anhydride) were found to be inefficient in effecting the recycling of the palladium species, giving < 60 % conversion on recycling of the catalyst-containing organic phase.

The difficulty encountered in efficiently removing the water from the organic phase while retaining activity led to an alternative approach being attempted. In the standard reaction conditions where the aryl halide is the limiting reagent, the palladium catalyst should be present as an [IPr*-Pd(0)] species once all of the starting material is consumed. By switching to conditions where either the amine or the base are the limiting reagents, in a theory more stable Pd(II) species (**8** or **9**) could be obtained, which would potentially be better able to withstand the acidic quench (Scheme 4).
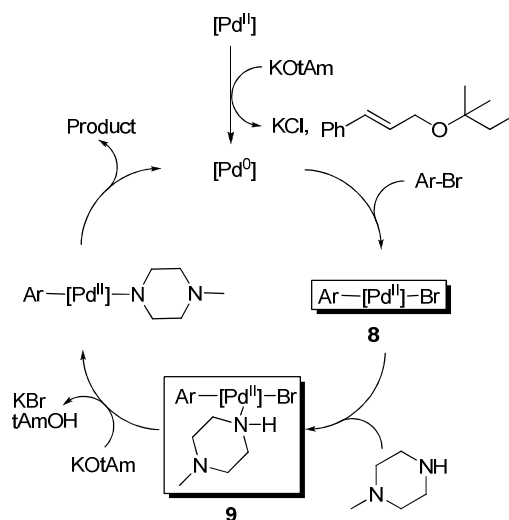
Scheme 4. Theoretical Pd(II) complexes resulting from running Buchwald-Hartwig reaction under base- or amine-starved conditions.

Thus, the reaction was conducted under both amine-starved and base-starved conditions on an initial run and then the organic phase subjected to the standard reaction conditions on a recycled run (Table 1). This protocol showed better conversion on recycle, especially when base-starved conditions were employed (entry 2), indicating that the Pd(II) species present at the end of the reaction was indeed more stable to the aqueous acidic work-up, although it must be noted that this was at the expense of sacrificing conversion (relative to the more expensive coupling partner, the aryl bromide **1**) on the first reaction run. It is interesting to note, that combining the reagent-starved protocols with azeodrying of the organic phase proved counter-productive (entries 3 and 4).

Table 1. Catalyst recycling after amine and base starved reactions.

Entry	Base (equiv.)	Amine (equiv.)	Conversion (%)[a]	
			1st run	2nd run
1	1.1	0.9	86	75
2	0.95	1.1	96	89
3[b]	1.1	0.9	87	71
4[b]	0.95	1.1	94	63

[a] Conversion measured by GC against an internal standard (undecane). Conversion refers to conversion of aryl bromide **1** in all cases.
[b] Azeotropic drying of the organic phase after phase separation

Finally, conditions combining the protocols described above with the use of an excess of base in the second run were employed, as this protocol had already been observed to enhance conversion in the presence of low levels of water (Figure 5). Running the initial reaction under the standard conditions (1 equivalent of **1**, 1.1 equivalents of potassium *tert*-amylate, 1.1 equivalents of *N*-methylpiperazine), and the subsequent recycled runs with 1.5 equivalents of base allowed efficient recycling of the catalyst, with full conversion being observed on the second run, and a

satisfactory 77 % conversion on the third run (Table 2, entry 1), a conversion level that is easily tolerated by the designed extractive work-up (Figure 3). Combining this approach with the other methods described was not as efficient (entries 2-4), and therefore an additional recycle was not attempted.

Table 2. Efficient recycling of catalyst **4** employing additional KO*t*Am on recycled runs.

Entry	Conditions	Conversion (%)[a]		
		1st run	2nd run	3rd run
1	Standard	>99	98	77
2	Base-starved	94	86	n/a
3	Amine-starved	85	80	n/a
4	Standard, with Azeo-drying	>99	68	n/a

[a] Conversion measured by GC against an internal standard (undecane). Conversion refers to conversion of aryl bromide **1** in all cases.

The methodology demonstrated here in batch mode, can now be applied to the continuous Buchwald-Hartwig reaction of **1** with effective catalyst recycle.

Conclusions

We have now reported for the first time a scalable and efficient synthesis of the palladium NHC pre-catalyst [Pd(IPr*)(cin)Cl] **4**, carried out on multi-hundred gram scale. Through in-depth studies of its sensitivity to acid, water and other reagents we have also established a protocol to reuse and recycle the catalyst up to 3 times in the Buchwald-Hartwig reaction of a key pharmaceutical intermediate in batch. Through a quantitative study of the work-up conditions, we have also established a precise and universal work-up protocol for Buchwald-Hartwig reactions. This "right-first-time" approach to extractions allows selective separation of the

Buchwald-Hartwig product from the catalyst and other species present, despite their apparent similar pK_as, negating the requirement for further purification, and is therefore particularly amenable to exploitation in pharmaceutical processes. This work forms the foundation of a multi-kilo process for the Buchwald-Hartwig reaction run in a continuous flow reactor with continuous work-up, which is reported in tandem.[9] It is envisaged that this combination of a highly active catalyst, a generalized approach to continuous work-up and purification and an efficient methodology for catalyst recycling could form the basis for a universal approach for the implementation of Buchwald-Hartwig reactions in flow beyond the immediate case study.

Experimental

[Pd(cinnamyl)(Cl)]$_2$ was generously supplied by Johnson Matthey and (*R*)-8-bromo-5-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)-(*S*)-1-(phenylethyl)amine hydrochloride was donated by AstraZeneca plc.[7,8] All other reagents were used as received from suppliers unless otherwise stated. NMR data were acquired on Bruker 300, 400 or 500 MHz spectrometers at 303 K (unless stated otherwise) in the specified deuterated solvent. All chemical shifts are given in ppm and coupling constants in Hz. Signals on the $^{13}C\{^1H\}$ spectra are singlets unless otherwise stated. Spectra were referenced to residual protonated solvent signals (for ^1H) or solvent signals (for $^{13}C\{^1H\}$): (CD$_2$Cl$_2$ ^1H δ 5.32 ppm, ^{13}C δ 53.84 ppm; CDCl$_3$ ^1H δ 7.26 ppm, ^{13}C δ 77.16 ppm). GC-MS analyses were carried out on an Agilent 7890A with a MS 5975C detector using a HP-5 column (30 m, 0.25 mm, 0.25 μm). Elemental analyses were performed by Stephen Boyer at London Metropolitan University, 166-220 Holloway Road, London, N7 8DB.

2,6-Bis(diphenylmethyl)-4-methylaniline (5). In a 3 L round-bottomed flask equipped with a stirrer bar and fitted with Dean-Stark apparatus, *p*-toluidine (72.8 g, 679 mmol, 1 equiv.) and

diphenylmethanol (250 g, 1.36 mol, 2 equiv.) were melted together at 100 °C. Once fully melted, an addition funnel containing a solution of $ZnCl_2$ (46.2 g, 339 mmol, 0.5 equiv.) in concentrated HCl (37%, 57.4 mL, 1.89 mol, 2.8 equiv.) was fitted on the flask, and the $ZnCl_2$ solution added to the hot melt, keeping the flask open. The reaction media was then heated to 160 °C, and stirred until the mixture became solid (*ca*. 3 hours). The reaction media was then allowed to cool to room temperature, dissolved in dichloromethane (2 L), and washed with saturated aqueous NH_4Cl (1 L) and brine (1 L). After drying over anhydrous K_2CO_3, silica (170 g) was added to the solution and the mixture was filtered. After evaporation, the resulting solid was washed with EtOAc (1 L) and dried. Yield : 260 g, 87%. **^{1}H NMR (CDCl$_3$, 400 MHz):** δ (ppm) 7.34-7.20 (m, 12H), 7.14-7.09 (m, 8H), 6.40 (s, 2H), 5.47 (s, 2H), 3.30 (s, 2H), 2.04 (s, 3H). **^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz):** δ (ppm) 142.9 (C_q), 139.8 (C_q), 129.7 (CH), 129.4 (C_q), 129.2 (CH), 128.6 (CH), 52.5 (CH), 21.3 (CH_3). Spectroscopic data matched those reported in the literature.[16]

***N,N'*-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)diazabutadiene (6).** The aniline **5** (500 g, 1.14 mol, 2 equiv.) was dissolved in dichloromethane (2 L) in a 5 L glass reactor. Glyoxal (40 % in H_2O, 62.5 mL, 545 mmol, 0.97 equiv.), anhydrous $MgSO_4$ (275 g, 2.28 mol, 2 equiv.) and formic acid (5.00 mL, 132 mmol, 0.2 equiv.) were then added, and the reaction mixture was stirred for 3 days, before additional glyoxal (40 % in H_2O, 31.2 mL, 272 mmol, 0.48 equiv.) and $MgSO_4$ (138 g, 1.14 mol, 1 equiv.) were added. The mixture was stirred for 1 more day. The crude mixture was poured on a frit, and the bright yellow $MgSO_4$ cake was washed with dichloromethane (*ca*. 20 L) until all colour had been removed. Solvent use could be minimised by evaporating *ca*. 1.5 L of washings at a time on the rotary evaporator, and reusing this solvent for subsequent washings of the filter cake. After evaporation of the solvents, the bright yellow

solid was washed with hot EtOAc (250 mL), and dried under vacuum. Yield : 446 g, 87%. **¹H**

NMR (CDCl₃, 400 MHz): δ (ppm) 7.24-7.13 (m, 26H), 7.00-6.95 (m, 16H), 6.65 (s, 4H), 5.22

(s, 4H), 2.11 (s, 6H). **¹³C{¹H} (CDCl₃, 100 MHz):** δ (ppm) 164.0 (CH), 146.9 (C_q), 143.9 (C_q),

133.7 (C_q), 132.0 (C_q), 129.6 (CH), 129.2 (CH), 128.4 (CH), 126.4 (CH), 51.1 (CH), 21.5 (CH_3).

Spectroscopic data matched those reported in the literature.[16]

1,3-Bis(2,6-dibenzhydryl-4-methylphenyl)-1H-imidazol-3-ium chloride (IPr*·HCl) (7). The

diimine (**6**) (250 g, 277 mmol, 1 equiv.) was dissolved in THF (2.5 L) in a 5 L reactor. $ZnCl_2$

(37.8 g, 277 mmol, 1 equiv.) and paraformaldehyde (9.15 g, 305 mmol, 1.1 equiv.) were added

sequentially and the mixture was heated to 70 °C. Finally, HCl (4 M solution in dioxane, 104

mL, 416 mmol, 1.5 equiv.) was carefully added dropwise *via* a dropping funnel, and the medium

stirred for 3 hours at 70 °C. After this time, the solvent was evaporated, and the crude residue

was dissolved in EtOAc (1 L), washed with water (1 L) and brine (1 L), and the solvent removed

by evaporation. The resulting off-white powder was dried overnight at 130 °C under vacuum.

Yield : 168 g, 64%. **¹H NMR (CDCl₃, 400 MHz):** δ (ppm) 11.85 (br s, 1H), 7.30 (d, *J* = 7.5 Hz,

8H), 7.20-7.03 (m, 24H), 6.77 (d, *J* = 7.1 Hz, 8H), 6.71 (s, 4H), 5.52 (s, 4H), 5.39 (s, 2H), 2.06

(s, 6H). **¹³C{¹H} (CDCl₃, 100 MHz):** δ (ppm) 143.0 (C_q), 142.4 (C_q), 141.0 (C_q), 140.6 (C_q),

131.1 (CH), 130.5 (CH), 129.4 (CH), 128.6 (CH), 126.8 (CH), 126.7 (CH), 51.3 (CH), 21.9

(CH_3). Spectroscopic data matched those reported in the literature.[16]

[Pd(IPr*)(cin)Cl] (4). In a glovebox, the IPr*·HCl salt **7** (98.0 g, 103 mmol, 1 equiv.) was

dissolved in THF (1.3 L) in a 2 L round-bottomed flask equipped with a stirrer bar, and KO*t*Bu

(12.7 g, 113 mmol, 1.1 equiv.) was added.   The mixture was stirred for 4 hours, then

[Pd(cinnamyl)(Cl)]₂ (24.3 g, 46.9 mmol, 0.91 equiv. Pd) was added, and the reaction mixture

stirred overnight at ambient temperature. The reaction flask was then taken out of the glovebox

and the mixture was concentrated and filtered through Celite to remove the Pd black and KCl. The crude product was then filtered through silica gel (elution with dichloromethane), and dried over $MgSO_4$. After evaporation of the solvents, the yellow powder was dried for several days under high vacuum at 80 °C. Yield : 104 g, 95%. **^{1}H NMR (CDCl$_3$, 400 MHz):** 7.49 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.4Hz, 2H), 7.36-7.17 (m, 21H), 7.10-7.06 (m, 12H), 6.86-6.83 (m, 8H), 6.80-6.77 (m, 4H), 6.10 (s, 2H), 5.71 (s, 2H), 5.32 (s, 2H), 5.04-4.96 (m, 1H), 4.63 (d, J = 13.1 Hz, 1H), 2.60 (d, J = 6.5 Hz, 1H), 2.23 (s,6H), 1.25 (d, J = 11.4 Hz, 1H). **^{13}C{^{1}H} (CDCl$_3$, 100 MHz):** δ (ppm) 182.6 (C_q), 144.6 (C_q), 143.8 (C_q), 141.4 (C_q), 140.6 (C_q), 138.5 (C_q), 137.8 (C_q), 135.9 (C_q), 130.6 (CH), 130.3 (CH), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 126.4 (CH), 126.4 (CH), 123.5 (CH), 109.0 (CH), 91.3 (CH), 51.6 (CH), 47.4 (CH_2), 22.0 (CH_3). Elemental analysis: Calculated for $C_{78}H_{65}ClN_2Pd$: C, 79.92; H, 5.59; N, 2.39. Found: C, 79.80; H, 5.73; N, 2.46. Spectroscopic data matched those reported in the literature.[14]

General procedure for the Buchwald-Hartwig reaction of 1 with [Pd(IPr*)(cin)Cl] 4, and reuse of the organic phase: The aryl bromide **1** (86.1 mg, 0.25 mmol, 1 equiv.), [Pd(IPr*)(cin)Cl] (2.9 mg, 1 mol%) and toluene (0.84 mL) were added to a dried 4 mL vial equipped with a stirrer bar and sealed with a screw cap fitted with a septum. To this mixture was then added *N*-methylpiperazine (30 µL, 0.270 mmol, 1.1 equiv.), followed by KO*t*Am 160 µL, 0.275 mmol, 1.1 equiv., 1.7 M solution in toluene) *via* syringe. The reaction mixture was then stirred (800 rpm) at 50 ºC for 1 h. After this time, a solution of AcOH (250 µL of a 5 M solution + 750 µL of distilled H_2O) was added to the reaction mixture. After phase splitting, the organic phase was transferred *via* syringe under inert atmosphere to a dried 4 mL vial containing a second portion of aryl bromide **1** (86.1 mg, 0.25 mmol, 1 equiv.), *N*-methylpiperazine (30.0 µL,

0.270 mmol, 1.1 equiv.) and KOtAm (160 µL, 0.275 mmol, 1.1 equiv., 1.7 M solution in toluene). The reaction was then repeated as above.

The conversion was quantified by GC-MS employing undecane as internal standard. The chromatographic method was the following: 5 min at 45°C; 45-250 ºC, 10 °C/min; final hold time of 10 min. Retention time of aryl bromide **1**: 27.64 minutes, retention time of **2**: 33.58 minutes.

Supporting Information. Additional experimental detail on the procedures for the pH titrations, water-doping experiments and recycling studies can be found in the supporting information.

Acknowledgements

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ABBREVIATIONS

NHC, CD, CNS, cin, IPr*, THF, SHE

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[1] For recent publications using Buchwald-Hartwig chemistry to synthesise natural products and medicinal chemistry targets see: Trabanco, A. A.; Duvey, G.; María Cid, J.; Macdonald, G. J.; Cluzeau, P.; Nhem, V.; Furnari, R.; Behaj, N.; Poulain, G.; Finn, T.; Poli, S.; Lavreysen, H.; Raux, A.; Thollon, Y.; Poirier, N.; D'Addona, D.; Ignacio Andrés, J.; Lutjens, R.; Le Poul, E.; Imogai, H.; Rocher, J.-P. *Med. Chem. Commun.*, **2011**, *2*, 132; Pandya, V.; Jain, M.; Chakrabarti, G.; Soni, H.; Parmar, B.; Chaugule, B.; Patel, J.; Joshi, J.; Joshi, N.; Rath, A.; Raviya, M.; Shaikh, M.; Sairam, K. V. V. M.; Patel, H.; Patel, P. *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 5701; Kumar, V. P.; Gruner, K. K.; Kataeva, O.; Knölker, H.-J. *Angew. Chem. Int. Ed.*, **2013**, *52*, 11073; Nguyen, T.; Yang, T.; Go, M.-L. *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 1830; Krasavin, M. *Letters in Org. Chem.*, **2013**, *10***,** 235

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[18] Further details on this methodlogy will be reported in due time: Ashworth, I. A.; Hose, D.; Meadows, R. E. *manuscript in preparation*