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A Microfluidic Approach to the Rapid Screening of Palladium-Catalysed Aminocarbonylation Reactions

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Abstract: The evaluation and selection of the most appropriate catalyst for a chemical transformation is an important process in many areas of synthetic chemistry. Conventional catalyst screening involving batch reactor systems can be both time-consuming and expensive, resulting in a large number of individual chemical reactions. Continuous flow microfluidic reactors are increasingly viewed as a powerful alternative format for reacting and processing larger numbers of small-scale reactions in a rapid, more controlled and safer fashion. In this study we demonstrate the use of a planar glass microfluidic reactor for performing the three-component palladium-catalysed aminocarbonylation reaction of iodobenzene, benzylamine and carbon monoxide to form *N*-benzylbenzamide, and screen a series of palladium catalysts over a range of temperatures. *N*-Benzylbenzamide product yields for this reaction were found to be highly dependent on the nature of the catalyst and reaction temperature. The majority of catalysts gave good to high yields under typical flow conditions at high temperatures (150 °C), however the palladium(II) chloride-Xantphos complex [$PdCl_2$(Xantphos)] proved to be far superior as a catalyst at lower temperatures (75–120 °C). The utilised method was found to be an efficent and reliable way for screening a large number of palladium-catalysed carbonylation reactions and may prove useful in screening other gas/liquid phase reactions.

Keywords: carbonylation; catalysis; catalyst screening; microfluidics; micro-reactor; palladium

Introduction

Since its initial discovery,[1–3] the palladium-catalysed carbonylation reaction of aryl, heteroaryl, vinyl and benzyl halides has developed into a highly versatile and effective synthetic route to an array of organic molecules possessing a carbonyl functional group.[4–6] Carboxylic acid derivatives, ketones, aldehydes, carbonates, carbamates and ureas may be readily prepared in one pot *via* the three-component reaction of an organic electrophile, nucleophile and carbon monoxide in the presence of a suitable palladium catalyst. Carbonylation reactions are of high interest in the fine chemical and pharmaceutical sectors where they are viewed as an atom-efficient method for preparing valuable carbonyl compounds from readily available aryl and vinyl halide precursors.[7–9] Although carbonylation reactions have attracted significant interest in recent years from academic groups, especially with regards to catalyst discovery and development, there are however several factors which have prevented the wider exploitation of this method within the academic field. Firstly, there are the obvious safety concerns of handling a poisonous gas such as carbon monoxide which may additionally need to be used at high pressures. This may also necessitate the use of specialised and expensive equipment. Secondly, carbonylation reactions are not as well characterised as other palladium-catalysed reactions such as cross-coupling reactions for C–C, C–N and C–O bond formation. Yields are highly dependent on the aryl substrates and nucleophiles and, moreover, can vary widely depending on the CO pressure, solvent and reaction temperature. In addition, the nature of the catalyst is known to have a particularly noticeable effect on the yield and reaction rates of particular carbonylation reactions.[10] Consequently much emphasis has been placed on catalyst development in recent years to permit reactions under milder temperatures and pressures in addition to allowing more challenging aryl chloride or tosylate substrates to be coupled.[7,11–18] The characteristics of the ligand bound to the metal centre are of significant importance for catalyst development. The most widely investigated ligand systems with regards to car-

bonylation reactions have been tertiary phosphines although carbene ligands are receiving much current interest.[19,20] Generally, however, chelating diphosphines are viewed as having ideal characteristics for controlling geometry at the palladium centre and for stabilising the active catalyst at higher temperatures by preventing the formation of Pd-black and Pd-carbonyl clusters which are thought to inhibit the reaction.[21,22]

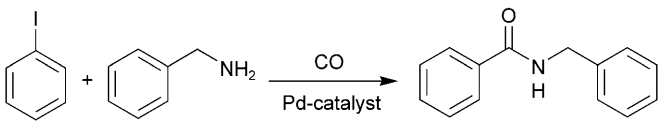
Determining the reaction conditions that achieve the highest chemical yields in the shortest possible times (space-time yields) usually involves striking the right balance between the main variables in the reaction.[23] This is often an arduous and iterative process, and can inevitably lead to delays and bottlenecks in process development. For carbonylation reactions CO pressure, temperature and catalyst are the key variables. Optimal pressures are normally in the range 5–20 atm while temperatures range from 50 to 150 °C depending on the solvent. However, there is an obvious desire to reduce both the pressures and temperatures of these reactions. Selecting the best catalyst can be more demanding because related ligands with structures that are seemingly very similar may produce contrasting results. Take the wide range of palladium diphosphine complexes, for example, where ligand structures and bite angles can vary by a few atoms or degrees with the result of profound changes in catalytic activities.[24]

Parallel reactor systems, where a number of reactions are run in tandem, are most commonly used for rapidly conducting catalyst and reaction condition screening. This equipment, extensively used in industry, is rather specialised and can be prohibitively expensive for smaller academic groups or more isolated investigations. An alternative to these batch reactors are continuous flow microfluidic systems which are particularly adept at handling, reacting and processing extremely small amounts of substrates and/or catalysts on the μg to low mg scale.[25,26] In recent times, microfluidic devices have gained recognition for efficiently performing a wide range of chemical reactions on extremely small scales.[27–30] Additionally, microfluidic reactors have a number of advantages over commonly used conventional laboratory batch reactors. These include the obvious reduction in reagent consumption which can be important when dealing with high value or precious substrates and catalysts. The unique environment within microfluidic channels can provide other less obvious advantages which include greater reaction control and enhancement of mass transport between reagent streams. Heat transfer into or out of the microchannels is also much improved because of the small convective distances and large surface-to-volume areas involved. Such advantages have been proven to have a positive impact on the rates, yields and/or selectivities of chemical reactions.[31–33]

Multiphase gas-liquid reactions such as hydrogenations,[34–36] oxidations,[37,38] fluorinations[39–41] and more recently carbonylations[42–45] are well suited for adaptation to a microfluidic format. This is because, in addition to the advantages stated above, significant gains in interfacial gas-liquid contact areas can lead to enhanced reactivity. This is particularly appealing for carbonylations because the low solubility and resultant poor reactivity of carbon monoxide may be enhanced without the need for excessively high pressures. Palladium-catalysed carbonylation reactions are proposed to proceed *via* three distinct steps in the catalytic cycle: oxidative addition of the aryl/vinyl halide to the active Pd catalyst; migratory insertion of carbon monoxide to form an acyl-Pd intermediate; nucleophilic attack followed quickly by reductive elimination to give the carbonyl compound and regenerate the active Pd species. At lower carbon monoxide pressures the migratory insertion of CO is thought to be rate-limiting. Thus there is the real possibility of enhancing the rate-limiting migratory insertion step of carbon monoxide at lower pressures which is both technically appealing and safer. We recently reported the first example of a palladium-catalysed carbonylation reaction on a microfluidic device[42] which showed significant advantages in terms of product yield and reaction rates over comparable batch reactions for the synthesis of secondary amides. In this study we specifically investigated the effects of aryl halide substrates and liquid flow rates on the product yields and distributions. Interestingly we found that two amide products were formed in the reaction; the expected single carbonyl amide and the double carbonyl alpha-ketoamide in varying amounts. The distribution of these products is known to be dependent on the catalyst and reaction conditions, with temperature playing a dominant role.[45] Herein we wish to extend these studies and report a method for the screening of a range of catalysts for a model aminocarbonylation reaction using microfluidic technology with the aim of rapidly identifying the best catalyst and reaction conditions.

Results and Discussion

The well characterised model aminocarbonylation reaction of iodobenzene, carbon monoxide and benzylamine to form *N*-benzylbenzamide (Scheme 1) was



Scheme 1. The aminocarbonylation reaction of iodobenzene with carbon monoxide gas and benzylamine forming *N*-benzylbenzamide.

selected to assess a number of palladium-based catalysts over a range of temperatures. The catalysts selected for testing include a range of palladium monodentate phosphine, bidentate phosphine, carbene and palladium dimer complexes (Table 1) which may allow us to infer the effect that catalyst stability, electronic effects, sterics and bite angles could have on these types of carbonylation reactions. Our microfluidic testing rig (Figure 1) is based around a soda-lime glass device (Figure 2) consisting of two inlets (for introducing liquid reagents and carbon monoxide), a T-junction to allow mixing, a long continuous serpentine channel with dimensions of $l = 5$ m, $w = 200$ μm, $d = 75$ μm and an outlet port for product collection. From our previous studies it was found that this long serpentine channel was necessary to retain the liquid reagents long enough on the device to react under an annular-type flow regime. Annular flow results when a gas stream flows through the centre of a channel or pipe and forces the liquid to adhere and flow along its internal walls.[46] This type of flow provides the largest gas-liquid contact surface area and therefore would be expected to give the highest chemical yields in the shortest time.

An injector port with a 50 μL sample loop was incorporated between the solvent pump and the microfluidic reactor to allow a measured volume of catalyst/iodobenzene/benzylamine solution to be injected into a continuous flow of solvent and onto the device. Carbon monoxide was introduced and regulated into

Table 1. Catalyst screen.

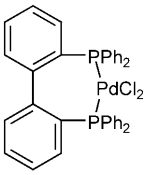
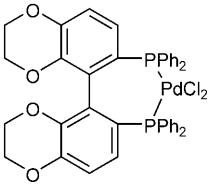
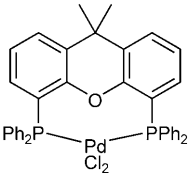
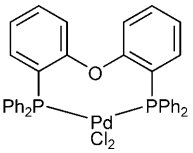
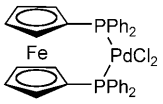
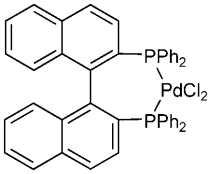
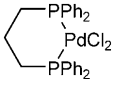
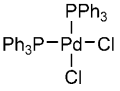
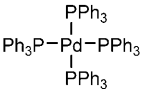
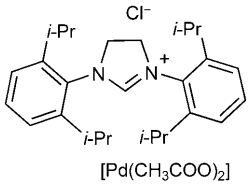
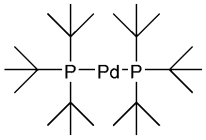
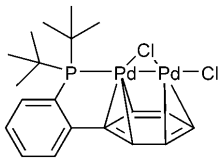
Catalyst structure	Catalyst	Bite angle
	[$PdCl_2$(Biphenphos)]	92°
	[$PdCl_2$(Synphos)]	93°
	[$PdCl_2$(Xantphos)]	108°
	[$PdCl_2$(DPEphos)]	104°
	[$PdCl_2$(dppf)]	99°
	*Rac*-[$PdCl_2$(BINAP)]	93°
	[$PdCl_2$(dppp)]	91°
	[$PdCl_2(PPh_3)_2$]	–
	[$Pd(PPh_3)_4$]	–

Table 1. (Continued)

Catalyst structure	Catalyst	Bite angle
	1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride + Pd acetate	–
	{Pd[P(*t*-Bu_3)]$_2$}	–
	{Pd_2(μ-Cl)Cl[μ-P(*t*-Bu)$_2$(Bph-H)]}	–

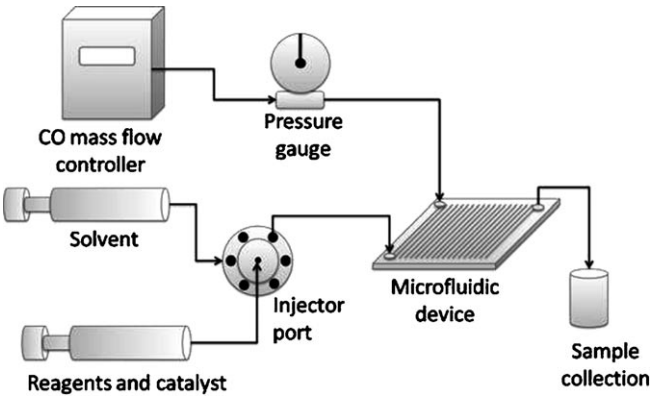


Figure 1. Schematic drawing of the reactor set-up.

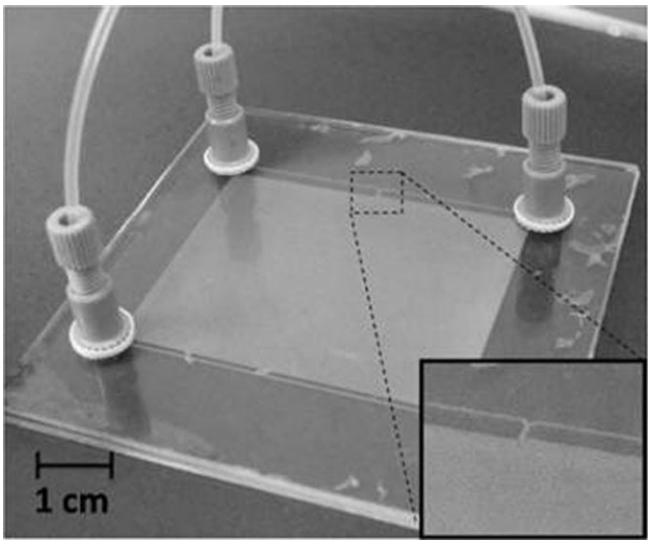


Figure 2. Glass fabricated microfluidic device used to perform gas-liquid aminocarbonylation reactions.

the chip device using a gas flow controller and metered at a constant flow rate. A pressure gauge was used to monitor the back pressure in the system. The chip device was heated using a heating plate with an associated thermocouple to ensure constant temperatures.

Reaction solutions consisted of a 1 M solution of iodobenzene in benzylamine, which has the role of reagent, base and solvent, and 2 mol% of palladium catalyst. In each reaction a 50 μL injection of the catalyst/reagent solution was introduced into a continuous flow of THF solvent driving the mixture on to the chip where it mixed and reacted with carbon monoxide. Each 50 μL slug of reagent solution contained 10.2 mg of iodobenzene and approximately 1 mg of the catalyst. Although it could be expected that much smaller quantities of reagents and catalysts could be used we found these quantities convenient for testing. The residence time of the liquid reagents on the chip, which can be taken as the reaction time, was previously measured[42] to be approximately 2 min while the total processing time for each independent reaction was 12 min from initial injection to collection of the reacted product. In total 12 different catalysts were tested and approximately 100 reactions performed at temperatures ranging from 75 °C to 150 °C. The reaction temperature was found to have a pronounced effect on the yields of *N*-benzylbenzamide. As may be expected, chemical yields were found to increase with temperature, however, it should be noted this is not always the case with carbonylation reactions since higher temperatures can degrade the catalyst.[47] Yields were significantly increased when the temperatures were increased from 120 °C to 150 °C compared to changes from 100 °C to 120 °C. The higher temperature regimes also resulted in the exclusive formation of *N*-benzylbenzamide with no evidence of the double carbonylation α-ketoamide product previously observed at lower temperatures.[42] The reaction catalysed by [$PdCl_2$(dppf)] (Figure 3), for example, gave average yields of 14% at 100 °C and 36% at 120 °C, however when the temperature

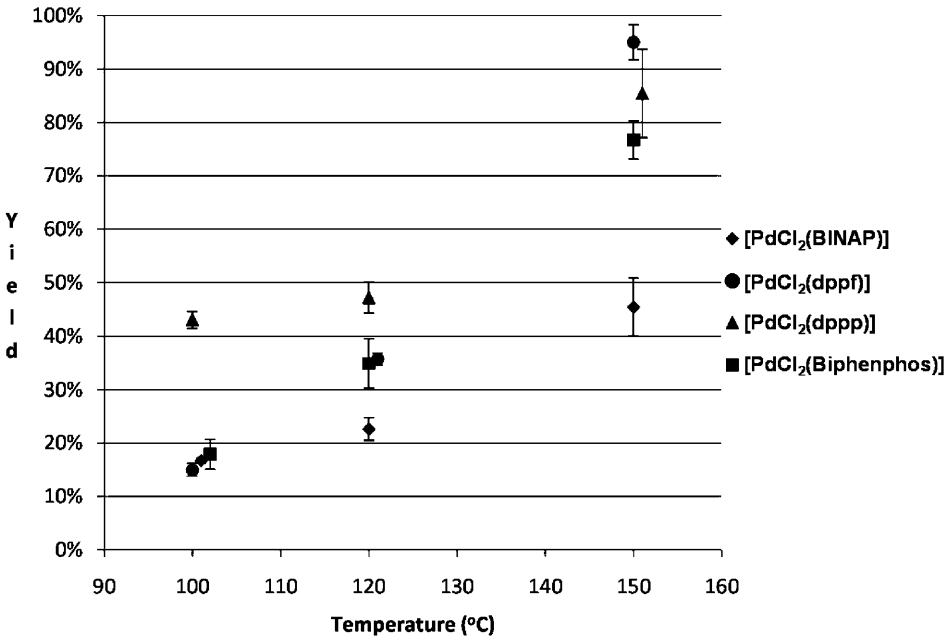


Figure 3. Results of a catalyst screen of 4 palladium diphosphine complexes. Each data point represents the average yield (GC). Error bars show the standard deviation about the mean value ($n=3$).

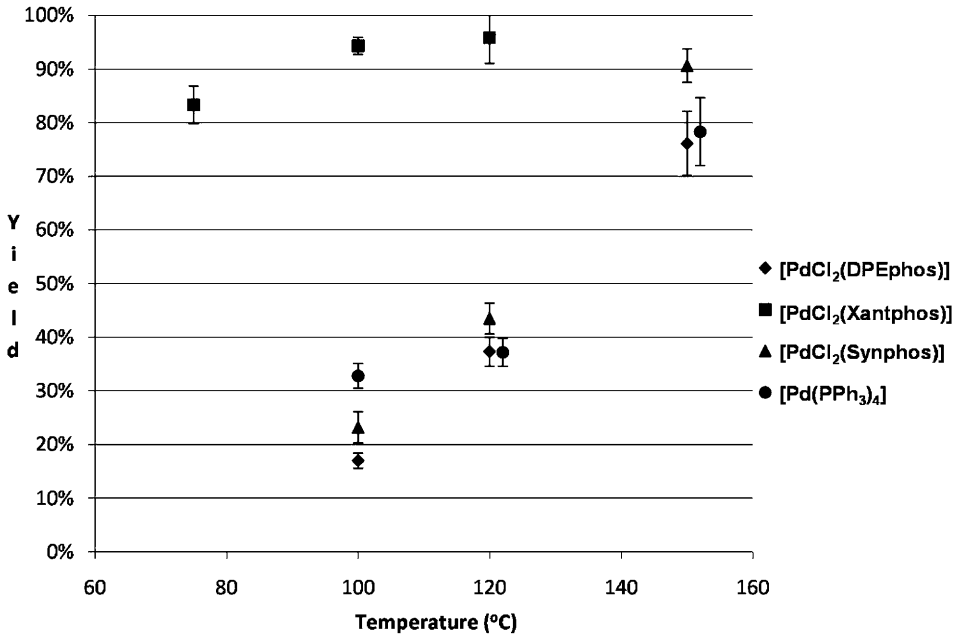


Figure 4. Results of a catalyst screen of 4 palladium complexes. Each data point represents the average yield (GC). Error bars show the standard deviation about the mean value ($n=3$).

was increased to 150 °C yields were almost quantitative. This indicates that some of the catalysts, such as [$PdCl_2$(dppf)] and [$Pd(PPh_3)_4$], are much more active at higher temperatures than might otherwise be expected on simple extrapolation of the lower temperature data. Reaction yields were generally good to excellent at higher temperatures despite the short residence times (~2 min) of the liquid reagents on the device. Normally, such carbonylation reactions are considered sluggish taking several hours to reach completion at higher pressures. However, under the right reaction conditions and with the appropriate catalysts, they can be surprisingly fast and high yielding as seen with our system, albeit with a relatively reactive aryl iodide substrate.

Diphosphine-based catalysts have been widely used for a range of catalytic reactions. The effect of P–M–P bite angle of the diphosphine complexes has been extensively investigated and known to be important in determining the selectivities and rates of catalytic reactions.[48,49] In this study we tested seven palladium diphosphine catalysts which have bite angles ranging from 92° to 108°. Ligands with wider bite angles, such as Xantphos, have been generally recognised as having a positive effect on hydroformylation, hydrocyanation, CO/alkene copolymerisation, cross-coupling and carbonylation reactions.[24,50,51] At higher temperatures (150 °C) all the palladium diphosphine catalysts gave good yields (>75%, Figure 3 and Figure 4) of *N*-benzylbenzamide, the only exception being the [$PdCl_2$(binap)] complex which gave a moderate yield of 45%. This was surprising considering its structural similarity to the biphenphos and synphos ligands, and previous reports of highly successful methoxycarbonylation reactions of heteroaryl chlorides.[13] However, a recent report showed the binap ligand to be completely ineffective for the preparation of *N*-methoxy-*N*-methylamides (Weinreb amides) *via* the aminocarbonylation of aryl bromides.[47] At lower temperatures (100 °C and 120 °C) moderate to low yields of amide were obtained for all the diphosphine ligand complexes except for the Xantphos complex which showed remarkable conversions at both 100 °C and 120 °C. Average yields of amide in excess of 94% (Figure 4) were obtained for the Pd-Xantphos catalyst which greatly surpassed any of the other catalysts we tested at these lower temperatures. The Pd-Xantphos complex still showed remarkable activity giving an average yield of 83% even when the reaction temperature was lowered to 75 °C.

Tetrakis(triphenylphosphine)palladium is often used as a benchmark catalyst for cross-coupling reactions. Carbonylation reactions using catalysts based on monodentate phosphines have often been observed to degrade at higher temperatures to catalytically inactive Pd-black or Pd-CO clusters. Under our reaction conditions [$Pd(PPh_3)_4$] performed on-par with the diphosphine catalysts at the higher temperature of 150 °C achieving average yields >75%. At this temperature, however, palladium black was observed to coat the channels of the microfluidic chip. The other triphenylphosphine-based catalyst, [$PdCl_2(PPh_3)_2$], gave lower yields and also produced significant quantities of Pd-black at 120 °C. The palla-

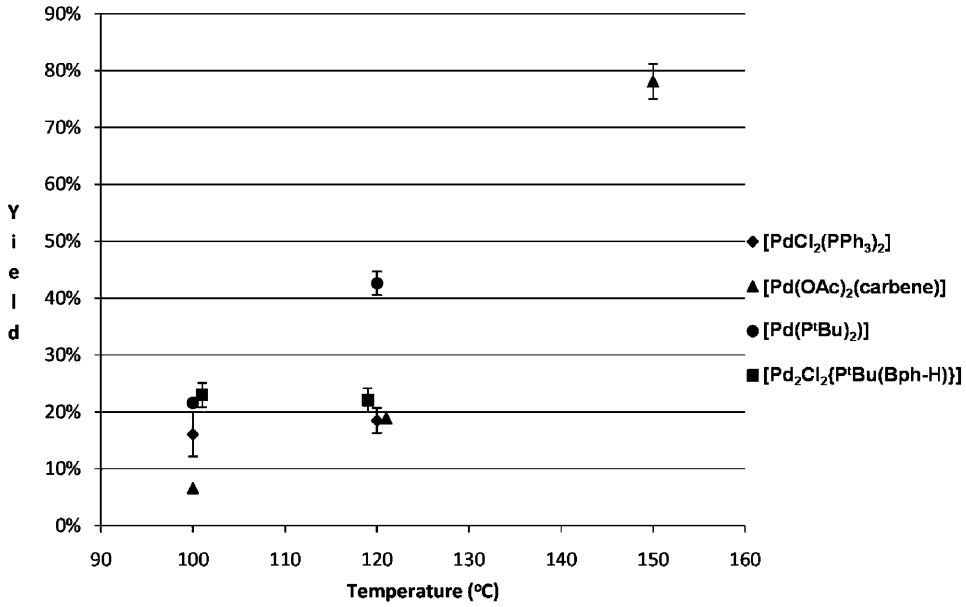


Figure 5. Results of a catalyst screen of 4 palladium complexes. Each data point represents the average yield (GC). Error bars show the standard deviation about the mean value; $n=3$ for $[PdCl_2(PPh_3)_2]$ and $[Pd(OAc)_2$carbene$]$; $n=2$ for {Pd[P(*t*-Bu)$_2$]} and $[Pd_2(\mu\text{-Cl})Cl\{\mu\text{-P}(t\text{-Bu})_2\text{-(Bph-H)}]$.

dium dimer complex [Pd(μ-Cl)Cl(*t*-Bu-biphen)] was of particular interest because of recent reports of its high catalytic activity for cross-coupling reactions at low temperatures.[52] Unfortunately [Pd(μ-Cl)Cl(*t*-Bu-biphen)]was only sparingly soluble in the iodobenzene/benzylamine solution and therefore the reaction was conducted in DMF. Disappointingly low yields of amide (<30%, Figure 5) were obtained at 100 °C and 120 °C with significant amounts of palladium black obscuring the microchannels of the reactor. The {Pd[P(*t*-Bu$_3$)$_2$]} complex bearing the highly bulky and electron rich tri-*tert*-butylphosphines has also been regarded as a highly active catalyst for cross-coupling and carbonylation reactions[10,53] and was therefore of high interest to test. A low average yield of 22% was obtained at 100 °C, while at 120 °C an encouraging yield of 43% was obtained which is the highest of the monodentate ligand catalysts at this temperature.

N-heterocyclic carbene (NHC) ligands have attracted much attention as alternative ligand systems to phosphines, and have consequently been tested for a range of catalytic reactions including, quite recently, carbonylation reactions.[19] NHC ligands have widely been considered to supersede phosphines under more harsh reaction conditions because of the degradation of P–C bonds in phosphine-based catalyst systems at higher temperatures. Pd-NHC complexes are also often less sensitive to oxygen and moisture, in addition to having a higher thermal stability, which potentially makes them more catalytically robust than Pd-phosphine catalysts. Unlike the previous preformed Pd-phosphine catalysts, the Pd-NHC catalyst we used was generated *in situ* from palladium acetate and 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride. Yields of *N*-benzylbenzamide obtained using this catalyst system at 100 °C were very low (<10%) but improved to >75% when the temperature was increased to 150 °C (Figure 5). At this higher temperature, however, a significant amount of palladium black was observed in the microchannels of the device suggesting that the catalyst was degrading.

The bidentate phosphine catalysts appear to have a greater thermal stability, producing less palladium black, than the monophosphine or NHC complexes and are therefore better suited to higher temperature aminocarbonylation reactions. The Xantphos catalyst was a clear outlier, performing significantly better than all the other catalysts we tested under these reaction conditions. The wide bite angle (108°) and flexible nature of the Xantphos ligand has been widely reported to have a beneficial effect on a number of catalytic reactions compared to other diphosphine ligands.[50] It is suggested to provide a dynamic and flexible coordination environment which is important for stabilising the metal centre in various oxidation states and geometries. Although DPEphos and dppf have similar bite angles to Xantphos they gave much less impressive yields at lower temperatures which suggests that the flexibility of the Xantphos ligand may play an important role in these reactions. Xantphos has, in fact, recently been reported to be an active ligand for aminocarbonylation reactions giving impressive conversions when other bidentate and monodentate phosphine ligand systems failed com-

pletely.[47] However, in another report involving a palladium-catalysed aminocarbonylation/amidation cascade reaction for the one-pot synthesis of quinolones, the Xantphos catalyst system did not perform as well as the other catalysts that were screened.[54] Although the positive effects of the Xantphos ligand are well recognised with regards to Rh-catalysed hydroformylation reactions, its effect on palladium-catalysed aminocarbonylation, as seen with our results and others,[47] are particularly encouraging.

A key feature of our system is that reactions are performed in microfluidic channels and in continuous flow whereby the annular gas/liquid arrangement provides a high surface area for enhancing reactivity. Although we have found that this leads to much improved space-time yields when compared to equivalent batch carbonylation reactions, the system is limited by the fact that reaction (or residence) times are very short (~2 min). While such short reaction times proved sufficient to achieve excellent yields of amides *via* the aminocarbonylation of aryl iodides, they may prove too short to provide good yields for more challenging carbonylations such as the reaction of deactivated aryl bromides or aryl chloride substrates. However, one straightforward solution to this would be to impose a different flow regime on the gas and liquid mixture such as alternate slugs of gas and liquid (i.e., a segmented flow). Although this method can give more controlled residence times of the gas and liquid mixtures (that would be suitable for longer reaction times), this may be at the expense of surface area effects seen for the annular flow regime. An added feature of our reaction system is the speed and reliability with which reactions could be performed, with each reaction taking only 12 min. In total 12 different catalysts were tested at various temperatures, with 2 or 3 reactions being run at each temperature to ensure reproducibility. Although no attempt was made to scale-up any of the reactions under study, the data obtained clearly suggest that the Xantphos ligand system at a minimum temperature of 100 °C is best for the aminocarbonylation of iodobenzene. This rapid methodology for screening reactions may therefore provide a useful 'snap-shot' of catalyst activity, and may prove important in identifying the best catalysts and reaction conditions at an early stage of development prior to in-depth catalyst screening or scale-up using standard batch reaction methods.

Conclusions

Microfluidic reactors are playing an increasingly important role in chemical synthesis especially in areas such as high throughput synthesis and analysis where there is a drive to perform large numbers of reactions on smaller volumes of material within shorter time frames. The method we have described for the aminocarbonylation of aryl halides possesses certain advantages over conventional batch reactor systems for these types of reactions. It is a safer approach using only minute quantities of reagents and small volumes of poisonous carbon monoxide. Although the quantities of reagent used for our amminocarbonylation reactions were small by normal laboratory standards (10.2 mg iodobenzene, ~1 mg catalyst) these reactions could be conducted on a much smaller scale (at least an order of magnitude smaller) without the need to modify our existing experimental set-up. The equipment is relatively unsophisticated, inexpensive and commercially available; standard and bespoke glass fabricated microfluidic devices are now readily available from a number of commercial suppliers. In addition to these technical advantages, performing reactions within a continuous flow microfluidic format also often gives enhanced reactivities compared to batch systems. Under our reaction conditions moderate to excellent yields of *N*-benzylbenzamide were obtained within extremely short reaction times, albeit at high temperatures. The notable exception to this was the Xantphos ligand system which showed excellent conversions at much lower temperatures. Interestingly this was in agreement with a previous carbonylation study using Xantphos as a ligand[47] and further highlights the beneficial effect of such wide bite angle diphosphine ligands. As mentioned above, the short reaction times imposed by the flow regimes in this system may be considered as a limitation to its wider applicability. Nevertheless this system has proven extremely useful for rapidly identifying the most suitable reaction conditions for a given aminocarbonylation reaction.

Experimental Section

General Considerations

All preparations were carried out using standard Schlenk line techniques under an inert atmosphere of N_2 unless otherwise stated. Solvents were dried over standard drying agents and freshly distilled under nitrogen before use. All starting materials and ligands were of reagent grade and purchased from either Sigma–Aldrich Chemical Company or Strem Chemicals. ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra were recorded on Bruker Av-400, DRX-400, Av-500 spectrometers. Chemical shifts are reported in ppm using the residual proton impurities in the solvents.

Catalyst Preparation

Preformed diphosphine catalysts were prepared by the reaction of 1:1 stoichiometry amounts of the appropriate diphosphine ligand and $[PdCl_2(COD)]$ in dichloromethane. Catalysts $[Pd(PPh_3)_4]$ and $[PdCl_2(PPh_3)_2]$ were purchased from commercial sources. The palladium N-heterocyclic carbene

complex was prepared *in situ* by the 1:1 stoichiometric reaction of 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride and palladium acetate. The palladium dimer complex [Pd_2(μ-Cl)Cl{μ-P(*t*-Bu)$_2$(Bph-H)] (Bph-H = biphenyl) was prepared according to the literatutre procedure.[55] The {Pd[P(*t*-Bu)$_3$]$_2$} complex was prepared by a modified procedure to that previously reported in the literature.[56] To a suspension of [Pd_2(dba)$_3$] (1.0 mmol, 0.916 g) in toluene (80 mL) was added tri-*tert*-butylphosphine (4.95 mmol, 1.0 g) and the reaction mixture stirred for 48 h at ambient temperature. The solution was then filtered into a new flask *via* cannula and toluene removed under reduced pressure. This crude solid was then dissolved in dry diethyl ether (30 mL) and placed in a freezer at −35 °C overnight to yield white crystals. The supernatant was removed using a cannula and the crystals washed with dry diethyl ether (2 × 4 mL) and dried under reduced pressure; yield. 0.56 g (55%) ^{1}H NMR (benzene-d_6, 400 MHz): δ = 1.65–1.62 (m, 54 H), ($^3J_{P,H}$ = 5.7 Hz); ^{31}P{^{1}H} NMR (benzene-d_6, 162 MHz): δ = 84.9 (s).

Microfluidic Reactor Set-Up

A detailed description of the microfluidic reactor structure and design has been previously reported.[42] Briefly, the device was fabricated from a soda-lime glass substrate with channels being etched into the glass using an HF/NH_4F solution. External holes were drilled at the reagent entry and exit points prior to thermal bonding of the glass cover plate. Nanoports (part no. N-333) were bonded to the entrance and exit holes of the device which allowed external tubing to be easily connected. The flow of carbon monoxide gas was regulated directly from the gas cylinder using a Sierra 100 series Smart-Trak mass flow controller and metered at 2 sccm into the chip device. A Harvard syringe pump (pump 11) was used to continuously infuse THF into the chip device at a flow rate of 10 μL/min *via* a six-way Rheodyne injector (part no. 7725i) complete with a 50 μL sample loop.

Microfluidic Reactions

Reaction mixtures were prepared by dissolving the required catalyst (2 mol%) in a 1 M iodobenzene/benzylamine solution. In a typical reaction 0.02 mmol of catalyst was dissolved in iodobenzene/benzylamine solution (1 mL, 1 M). The reaction solution was loaded into the 50 μL loop and the injector switched to redirect the flow of THF into the sample loop which drives the reaction mixture into the chip device where it mixes and reacts with CO gas. The device was heated to the required temperature using a heating block and the product solution collected at the device outlet into a sample vial. After a processing time of 10 min the flow rate of the THF from the pump was increased to flush off any residual product on the device and collected into the sample vial. The collected samples were allowed to evaporate and then diluted using a dichoromethane/phenyl ether standard solution. GC samples were run on an HP5890 series II fitted with a Supelco Omegawax column (dimensions; 30 m, 0.25 mm, and 250 μm film thickness) using helium as the carrier gas. Quantitative analysis was conducted by gas chromatography using the peak area of the product *N*-benzylbenzamide normalised in response to the internal diphenyl ether standard.

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