Alkoxy- and amidocarbonylation of functionalised aryl and heteroaryl halides catalysed by a Bedford palladacycle and dppf: a comparison with the primary Pd(II) precursors $(PhCN)_2PdCl_2$ and $Pd(OAc)_2$

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The versatility of a Bedford-type palladacycle **1**, namely [{Pd(μ-Cl){κ²-*P*,*C*-P(OC$_6$H$_2$-2,4-^{t}Bu$_2$)-(OC$_6$H$_3$-2,4-*t*Bu$_2$)$_2$}$_2$], as a primary Pd source, in combination with the ligand bis-1,1′-(diphenylphosphino)ferrocene (dppf) has been established in carbonylation reactions of aryl and heteroaryl bromides with methanol, piperidine and related nucleophiles. Palladacycle **1** has been compared with other primary Pd sources, *e.g.* $(PhCN)_2PdCl_2$ and $Pd(OAc)_2$. The efficacy of the carbonylation processes appear to be linked to the [Pd] concentration, substrate : catalyst ratio, CO pressure and reaction temperature. In amidocarbonylation, double carbonylation is observed for certain organohalides. In the case of 2,5-dibromopyridine, regioselective amination (Hartwig–Buchwald type) also occurs as a side-reaction.

Introduction

Transition metal-catalysed carbonylation of aryl halides in the presence of an appropriate nucleophile represents a valuable tool for the selective introduction of carboxylic functionality into aromatic derivatives. Pd,[1] Co,[2] and Ni[3] have been widely applied in aryl halide carbonylation. Depending on the nature of the nucleophilic component the products can be aryl esters, amides and aldehydes.[4] Valuable intermediate and final products increasingly find application in lead structures for use in therapeutic applications and biological studies.[5] Ever-increasing use of Pd catalysis in synthesis, particularly in cross-coupling, is evident in academic and industrial settings. Indeed, Pd-catalysed carbonylation processes are routinely used synthetic transformations. Pioneering studies on Pd-catalysed carbonylation of aryl, benzyl and alkyl halides were reported independently by Heck,[3a] and Stille and Wong.[6] A paper detailing the coupling of aryl chlorides in the presence of *n*-BuOH (butoxycarbonylation) was reported by Milstein and co-workers in 1989,[7] using an electron-rich phosphine ligand "dippp" [dippp = bis(diisopropylphosphino)propane]; dramatic ligand effects were seen in this study. More recently, Beller and co-workers have focused on the butoxycarbonylation of aryl chlorides employing modified ferrocenyl ligands.[8] The major hurdle to be overcome in aryl chloride carbonylation lies in the coordination of CO to the metal centre; when bound to the metal, the π-acceptor properties of CO significantly reduces the reactivity of the metal towards oxidative insertion into the C–Cl bond—a potential antagonistic effect for the use of electron-rich σ-donor ligands.[4] In addition, the presence of CO accelerates the formation of insoluble non-active palladium clusters—a well-known phenomena *vide infra.*

In certain circumstances double carbonylation is detected; a key observation first reported by Kobayashi and Tanaka,[9a] followed by Yamamoto and co-workers.[9b] It appears that double carbonylation arises independently of the formation of mono-carbonylation product, occuring mainly at elevated temperatures.[10] For bidentate ligands, product selectivity is influenced by the length of the carbon linker connecting the two diphenylphosphino groups; increasing linker size leads to higher ratios of double carbonylation product. In addition to these studies, double carbonylation of aryl iodides has been reported using highly active mono- and binuclear palladium complexes.[11] Kondo and co-workers have also demonstrated that the monophosphine, *t*-Bu$_3$P, promotes selective double carbonylation of electron-deficient aryl iodides.[12]

Typically, carbonylation reactions involve use of relatively high loadings of ligand and Pd (1–5 mol% Pd), high pressures of CO and elevated temperatures.[13] We initiated our studies on the carbonylation of aryl halides with the principal aim of improving on current known methods. Inspired by recent studies on palladacycle **1**, namely [{Pd(μ-Cl){κ²-*P*,*C*–P(OC$_6$H$_2$-2,4-^{t}Bu$_2$)(OC$_6$H$_3$-2,4-*t*Bu$_2$)$_2$}$_2$] (Fig. 1), a precatalyst described by Bedford and co-workers,[14] we anticipated that this would be an ideal Pd source for carbonylation processes. Our rationale for studying this stems from the ability of **1**, and related complexes, to slowly release catalytically active Pd^0 into a suitable reaction medium.[15]

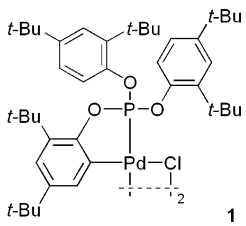

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Fig. 1 Bedford's palladacycle **1**.

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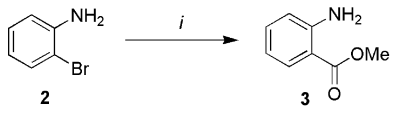
In this report the first methoxy- and amidocarbonylation reactions of aryl halides mediated by **1** at low Pd loadings (0.05 mol%) are described.[16] Catalytic activity has been correlated against $Pd(OAc)_2$ and/or $PdCl_2(PhCN)_2$ for several benchmark reactions. Alteration of the ligand has a dramatic effect on product conversion and selectivity (mono-carbonylation *versus* double-carbonylation) in amido-carbonylation.

Results and discussion

The functionalised benchmark substrate 2-bromoaniline **2** was selected for methoxycarbonylation to give **3** (conversions monitored by GC/MS) (Scheme 1).



2 3

i, Pd (1 mol%), dppf (3 mol%), Et_3N (1.3 equiv.), CO (10 Bar), toluene/MeOH (4/1, v/v), 12 h, 120 °C

Scheme 1 Methoxycarbonylation of 2-bromoaniline **2**.

The catalytic activity of palladacycle **1** was compared with $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$ by employing dppf as a ligand (dppf = bis-1,1′-(diphenylphosphino)ferrocene), since it was readily available (Pd : dppf = 1 : 3)—note that dppf is a *necessary* ligand for carbonylation using these Pd sources.

Using MeOH as the solvent, no consumption of **2** was observed, possibly due to the poor solubility of dppf in MeOH. Changing to a solvent mixture of toluene–MeOH (4 : 1, v/v) with **1** (1 mol%) as the precatalyst, showed 64% conversion. The precise ratio of Pd : dppf (1 : 3) appears to be important, and the optimum reaction temperature is 120 °C; notably slower conversion is seen at lower Pd : L ratios (Pd black precipitate is also evident when lower Pd : L ratios are used) and lower temperatures. Changing the solvent to dioxane–MeOH (4 : 1, v/v), under the same conditions, increased the conversion to 82%.

The effect of the base was evaluated next as it has been reported that organic amine bases react with **1** affording $[\mathbf{1}_{-X}]\cdot Et_3NH$ adducts.[15] The mineral bases Cs_2CO_3 and K_2CO_3 were compared in parallel reactions with Et_3N. Using **1** it was found that **2** was completely consumed using these inorganic bases (using 3 equiv.). On a general note, K_2CO_3 is cheaper than Cs_2CO_3, and therefore more attractive (compare K_2CO_3, £0.02 g^{-1} and Cs_2CO_3, £0.25 g^{-1}; source: Sigma-Aldrich).

The precatalysts $(PhCN)_2PdCl_2$ and $Pd(OAc)_2$ were next investigated (Table 1). Although these Pd sources exhibited higher conversions for this reaction, extensive formation of palladium black was seen at the end of the reaction, standing in constrast to **1**, where little palladium black was observed (Table 1). This indicated a faster release of palladium, faster agglomeration and the production of insoluble palladium nanoparticles in the case of $(PhCN)_2PdCl_2$ and $Pd(OAc)_2$.

A recent study into the effects of CO pressure by Beller and co-workers showed that high conversions are seen at low CO pressures (<10 bar), "moderate" CO pressures (15–70 bar) resulted in a decrease in the catalytic activity, while high pressures (>75 bar) show an increase compared to moderate pressures.[17] In our study, in parallel reactions conducted with **1** (1 mol% Pd) at 10 bar and 23 bar over a period of 3 h showed conversions of 38% and 19%, respectively. A further pressure increase to 60 bar resulted in no detectable conversion.

Table 1 A comparison of the Pd source in methoxycarbonylation of **2**[a]

Pd Source	Conversion (%)
Palladacycle **1**	47
$Pd(OAc)_2$	61[b]
$(PhCN)_2PdCl_2$	79[b]

[a] Reaction conditions as for Scheme 1, using 3 equiv. K_2CO_3 as the base. [b] Formation of insoluble Pd black is observed.

Table 2 Effect of catalyst loading of **1** in methoxycarbonylation of **2**[a]

[**2**]/M L^{-1}	[**1**]/M L^{-1}	S : C ratio	Conversion (%)
0.1	1×10^{-3}	100 : 1 (1 mol% Pd)	47
0.5	1×10^{-3}	500 : 1 (0.2 mol% Pd)	100
1	1×10^{-3}	1000 : 1 (0.1 mol% Pd)	63

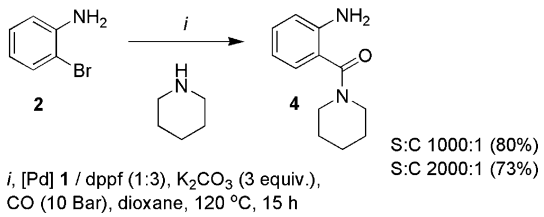
[a] Reaction conditions as for Scheme 1, using 3 equiv. K_2CO_3 as the base.

The substrate : catalyst (S : C) ratio was evaluated to assess its affect on conversion. On lowering the catalyst loading of **1** to 0.2 mol% Pd loading (S : C, 500 : 1) consumption of **2** was recorded. At 0.1 mol% Pd loading (S : C, 1000 : 1), the conversion was reduced to 63%, a conversion higher than that recorded at a Pd loading an order of magnitude higher (Table 2).

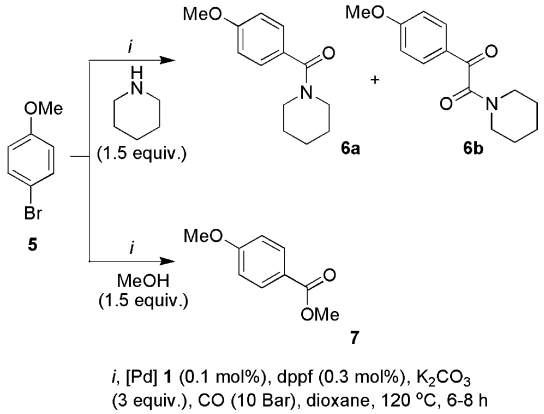
The inverse correlation[18] in catalytic activity no doubt relates to clustering/agglomeration of mononuclear palladium species in solution,[19] which are either catalytically inactive, after precipitation, or which release mononuclear species back into solution, albeit slowly in an unfavourable equilibrium. The optimal Pd loading for this particular reaction is 0.2 mol% **1** (S : C, 500 : 1). It ought to be borne in mind that it has been shown by Dupont and co-workers that the size of the clusters may be kept small by the continuous reaction of the aryl halide at the outer rim of any such clusters.[20] Thus at higher aryl halide concentrations, faster erosion occurs leading to smaller clusters (shown by TEM experiments). It was stated by de Fries[18a] that the Pd : substrate ratio is likely more important than the global palladium concentration *per se.* In other informative studies, Trzeciak and co-workers[21] have reported similar findings in methoxycarbonylation of aryl iodides, under phosphine-free conditions. More broadly, this unusual inverse correlation has been observed in Heck[22] and Sonogashira[23] cross-coupling processes, both of which employed palladacycles as the Pd source.

We have further established that nitrogen-based nucleophiles can be utilised in the amidocarbonylation of **2** mediated by palladacycle **1**. For example, piperidine reacts with **2** to afford the carbonylated product **4** in 73% yield at a S : C ratio of 2000 : 1; a slightly better yield (80%) was recorded at a S : C ratio of 1000 : 1 (Scheme 2).

4-Methoxyphenyl bromide **5** was next employed as a benchmark substrate in both methoxycarbonylation and amidocarbonylation (Scheme 3). At a S : C ratio of 1000 : 1, amidocarbonylation of **5** occurred to give **6a**, but interestingly, for the first time, formation of the bis-carbonylated product **6b** was observed (entry 1, Table 3). All Pd sources showed complete consumption of **5**, however the ratio of mono- to bis-carbonylated product (**6a** : **6b**)



Scheme 2 Amidocarbonylation of **2**.



Scheme 3 Amido- and methoxy-carbonylation of **5**.

varied according to the type of Pd source used (compare entries 1–3, Table 3). Curiously, palladacycle **1** exhibits a similar CO consumption profile to both $(PhCN)_2PdCl_2$ and $Pd(OAc)_2$, while different selectivities[24] are observed, *e.g.* the rates of carbonylation are similar for all the Pd sources tested. Methoxycarbonylation of **5** gave the mono-carbonylation product **7**, exclusively. On lowering the catalyst loading to 0.05 mol% Pd (S : C 2000 : 1), product conversion was maintained with similar product selectivity (entry 4). Switching the precatalyst to $(PhCN)_2PdCl_2$ resulted in lower conversion and selectivity (entry 5). It is important to note that increasing the temperature from 120 °C to 140 °C for both palladacycle **1** and $(PhCN)_2PdCl_2$ results in an increase in selectivitity towards **6a**; for $(PhCN)_2PdCl_2$ conversion is dramatically improved. Use of methanol as the nucleophile at a S : C ratio of 2000 : 1 affords the mono-carbonylated product **6a** exclusively (entry 6), although modest conversion is recorded $(PhCN)_2PdCl_2$ (entry 7). The CO consumption profiles for entries 4–5 simply

Table 3 A comparison of the Pd source in amidocarbonylation of **5**[a]

Entry	Pd Source	S : C	Conversion (%)	**6a** : **6b**
1	Palladacycle **1**	1000 : 1	>99	99 : 1
2	$(PhCN)_2PdCl_2$	1000 : 1	>99	91 : 9
3	$Pd(OAc)_2$	1000 : 1	>99	94 : 6
4	Palladacycle **1**	2000 : 1	>99	96 : 4
			>99[c]	98 : 2
5	$(PhCN)_2PdCl_2$	2000 : 1	40	93 : 7
			>99[c]	97 : 3
6	Palladacycle **1**[d]	2000 : 1	>99	100 : 0
7	$(PhCN)_2PdCl_2$[d]	2000 : 1	56	100 : 0
8	Palladacycle **1** + $NaBAr'_4$	2000 : 1	~40	N.D.
9	$(PhCN)_2PdCl_2$ + $NaBAr'_4$	2000 : 1	0	—

[a] See Scheme 3 for reaction conditions. [b] Determined by GC-MS; N.D. = not determined. [c] Reaction conducted at 140 °C (after 1 h). [d] Using MeOH (1.5 equiv.) as the nucleophile. [e] 1 equiv. of $NaBAr'_4$ per Pd.

illustrate the difference in reactivity of piperidine and methanol and also the catalytic performance of the palladacycle **1** against $(PhCN)_2PdCl_2$ (Fig. 2). Interestingly, addition of $NaBAr'_4$ (Ar′ = bis-3,5-trifluoromethylbenzene)[25] to both **1** and $(PhCN)_2PdCl_2$ *in situ* reveals a dramatic effect. Whilst, the additive clearly retards the rate of reaction for **1** (entry 8), it completely inhibits the carbonylation reactions mediated by $(PhCN)_2PdCl_2$ (entry 9).

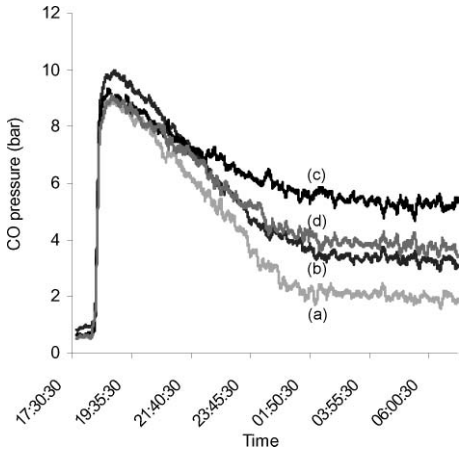


Fig. 2 CO consumption. Key: (a), Pd = **1**, Nu = piperidine; (b), Pd = **1**, Nu = MeOH; (c), Pd = $(PhCN)_2PdCl_2$, Nu = piperidine; (d), Pd = $(PhCN)_2PdCl_2$, Nu = MeOH.

Some other selected ligands were evaulated against dppf in parallel reactions of **5** to **6a**/**6b** to highlight the usefulness of this cheap and readily available ligand, when used in combination with **1** (Fig. 3). Whilst Xantphos proved as an effective ligand as dppf in terms of product conversion (88% *versus* 92%, respectively), product selectivity was slightly reduced (**6a** : **6b**, 91 : 9 *versus* 97 : 3, respectively). On the other hand, the *P*,*S*-ligands **8a** and **8b** exhibited conversions of only 10% (**6a** : **6b**, 1 : 1) and 9% (**6a** exclusively), respectively. A derivative of the ESPHOS class,

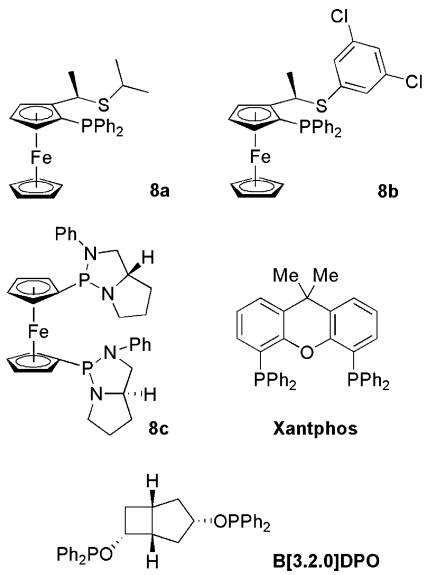
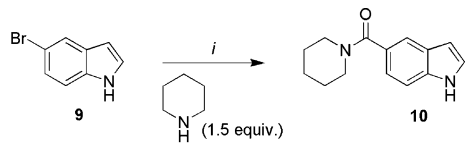


Fig. 3 Other ligands tested in the amidocarbonylation of **5** with piperidine.

namely **8c**, developed by Wills and co-workers,[26] also exhibited low conversion (5%) and poor selectivity (**6a** : **6b**, 1.7 : 1).

The bicyclo[3.2.0]heptanyl diphosphinate ligand, B[3.2.0]-DPO,[27] was also tested in several carbonylation reactions, however the results were not reproducible.[28]

We also evaluated the catalyst system **1**–dppf against $(PhCN)_2PdCl_2$–dppf, described as a versatile catalyst system for amidocarbonylation of unprotected 5-bromo-1*H*-indole **9** with piperidine by Beller and co-workers (Scheme 4 and Table 4).[29] Interest in this substrate stems from its potential application in the synthesis of ligands that interact with the serotonin (5-HT) subtype 2A receptor (a CNS target).[30]



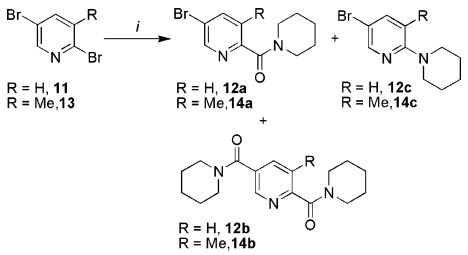
i, Pd source / dppf (1:3), Et_3N (1.5 equiv.), CO (25 Bar), toluene, 120-130 °C, 12 h.

Scheme 4 Amidocarbonylation of **9**.

We reproduced an experiment reported by Beller using PPh_3 as a ligand and $(PhCN)_2PdCl_2$ as the Pd source, as a benchmark (entry 1, Table 4)—under identical conditions (reagent quantities and ratios, temperature, CO pressure *etc.*) 30% conversion to compound **10** was recorded, compared to the reported 24% conversion.[29] Use of dppf was described under identical conditions in this report, except that the reaction time was 20 h. To maintain a fair comparison the conversion was analysed after 12 h for dppf (entry 2, Table 4), which showed a 50% conversion (reported[29] 92% after 20 h).

Lowering the Pd loading to 0.1 mol% served only to reduce product conversion (entry 3, Table 4). Use of Xantphos as a ligand gave an identical result to dppf (entry 4, Table 4; compare entry 2). Gratifyingly, with palladacycle **1** near quantative conversion for both dppf and Xantphos ligands was established (entries 5 and 6, Table 4); the temperature can also be lowered from 130 to 120 °C.

Having established an improved protocol for amidocarbonylation of **9**, regioselective amidocarbonylation of 2,5-dibromopyridines **11** and **13** with piperidine was tested (Scheme 5, Table 5).[31] In general, carbonylation/coupling is expected at the 2-position (the more electron-deficient carbon centre). Several products are possible in this reaction, *e.g.* the expected products **12a** and **14a**, and double functionalised products **12b** and **14b**. Under a range of conditions these products were formed (Table 5).



i, Pd **1** / dppf (1:3), base (3 equiv.), CO (9 Bar), dioxane, 14 h (see table for temp.)

Scheme 5 Amidocarbonylation of 2,5-dibromopyridines **11** and **13**.

However, for the first time we also detected the formation of the Hartwig–Buchwald amination[32] products **12c** and **14c**.

Using K_2CO_3 as the base at 70 °C and a S : C ratio of 2000 : 1 2,5-dibromopyridine **11** reacted with piperidine to afford products **12a**, **12b** and **12c** in a ratio of 12 : 8 : 1 (entry 1, Table 5). Increasing the temperature to 100 °C dramatically increased the formation of the amination product **12c** (entry 2, Table 5). Under these conditions, **12a** was the minor product. Reducing the temperature to 50 °C served to increase the selectivity for **12a**, providing that the Pd loading was increased to 0.08 mol% (S : C., 1250 : 1) (entry 3, Table 5).

Increasing the Pd loading to 0.33 mol% (S : C, ~300 : 1) improves the conversion to 96%, which moreover increases the selectivity for **12a**. Changing the base to NaOAc or DABCO results in lower conversions at 50 °C (compare entries 5 and 6 with 3, Table 5).

Interestingly, for 2,5-dibromo-3-methylpyridine **13** the formation of the amination product **14c** is less prevalent than was seen with **11** at 100 °C, which affords products **14a**, **14b** and **14c** in a 15 : 1.5 : 1 ratio (entry 7, Table 5). Lowering the temperature to 60 °C results in a better selectivity for **14a**, however lower

Table 4 Amidocarbonylation of 5-bromo-1*H*-indole **9**

Entry	Pd Source	Pd/mol%	Ligand	*T*/°C	Conv. (%)
1	$(PhCN)_2PdCl_2$	1	PPh_3	130	30
2	$(PhCN)_2PdCl_2$	1	dppf	130	50
3	$(PhCN)_2PdCl_2$	0.1	dppf	130	9
4	$(PhCN)_2PdCl_2$	1	Xantphos	130	50
5	Palladacycle **1**	1	dppf	120	>95
6	Palladacycle **1**	1	Xantphos	120	>95

[a] See Scheme 4 for reaction conditions.

Table 5 Amidocarbonylation of dibromopyridines **11** and **13**

Entry	Pd/mol%	R	*T*/°C	Base	Conv. (%)	Product ratio
1	0.05	H	70	K_2CO_3	100	**12a** : **12b** : **12c**, 12 : 8 : 1
2	0.05	H	100	K_2CO_3	100	**12a** : **12b** : **12c**, 1 : 5 : 12
3	0.08	H	50	K_2CO_3	75	**12a** : **12b** : **12c**, 11 : 1 : 0
4	0.33	H	50	K_2CO_3	96	**12a** : **12b** : **12c**, 30 : 1 : 0
5	0.08	H	50	NaOAc	15	**12a** : **12b** : **12c**, 3 : 2 : 0
6	0.08	H	50	DABCO	21	**12a** : **12b** : **12c**, 1 : 1 : 0
7	0.08	Me	100	K_2CO_3	89	**14a** : **14b** : **14c**, 15 : 1.5 : 1
8	0.08	Me	60	K_2CO_3	40	**14a** : **14b** : **14c**, 20 : 1 : 0

[a] See Scheme 5 for reaction conditions; piperidine (1.5 equiv.) used as the nucleophile.

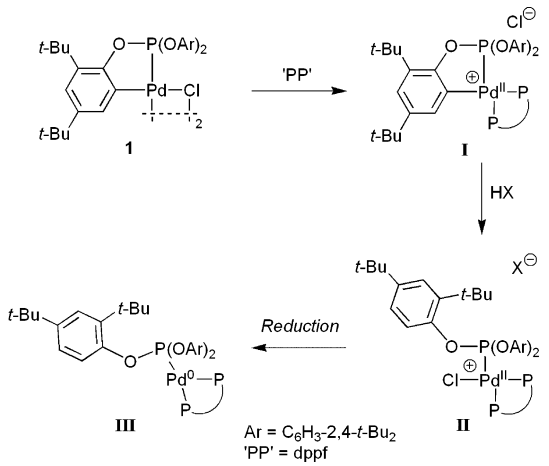
conversion is recorded (entry 8, Table 5), highlighting that **13** is a more deactivated substrate than **11**.

To explore the potential scope of **1** in mediating efficient amidocarbonylation, a series of other organohalide and amine substrates were evaluated (Table 6). 4-Methoxyphenyl bromide **5** reacted with cyclohexylamine **15** to afford mainly the monocarbonylated product **16a**; the bis-carbonylated product **16b** was also formed (entry 1, Table 6). Morpholine **17** was also found to be reactive towards **5**, however an equal mixture of both **18a** and **18b** were formed (entry 2, Table 6). The deactivated amine **19** (containing two electron-withdrawing *meta*-methoxy substituents) reacted well with **5**, which was highly selective for the monocarbonylation product **20a** (entry 3, Table 6). Piperazines **21** and **23** also reacted selectively with **5** to afford the monocarbonylation products **22a** and **24a**, respectively (entries 4 and 5, Table 6). Against a more activated aryl halide substrate **25** it was found that piperizine **21** showed a slightly lower conversion and selectivity than for the reaction with **5** (compare entries 4 and 6, Table 6). 4-bromoaniline **27**, a deactivated substrate which could also compete as a nucleophile in amidocarbonylation, showed good conversion but modest selectivity for the monocarbonylation product **28a** (entry 7, Table 6).

Conclusions

In this paper we have established that palladacycle **1**, originally developed by Bedford and co-workers for use in cross-coupling reactions, is useful for both amidocarbonylation and methoxycarbonylation processes. It has been demonstrated that **1** is generally *a superior source of Pd* over other primary sources of Pd such as $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$. Although it is evident that $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$ are useful Pd sources, generally higher temperatures are required for equivalent conversions and product selectivities seen using **1**.

Based on previous literature precedent, and the results detailed herein, it can be proposed that the palladacyclic structure slowly breaks down under the reaction conditions releasing Pd^0 into the catalytic cycle, particularly given that relatively high temperatures and modest CO pressures were used. The importance of the Pd : dppf ratio of 1 : 3 suggests that "$(dppf)Pd^0$" is a potential catalytically active species. However, $(dppf)_2Pd^0$ or $(dppf)Pd^0P(OAr)_3$ ($Ar = C_6H_3$-2,4-t-Bu_2) complexes could also be important as catalyst resting states. Bedford and co-workers[14c] have previously shown that the Pt variant of **1** reacts cleanly with dppf to generate $[(dppf)Pt^{II}P(OAr)_3]X$ complexes. Reaction of **1** with 2 equiv. of HCl was also shown to result in de-orthometallation. It is therefore not unresonable to suggest that **1** reacts with dppf to give intermediate **I**, followed by de-orthometallation to give **II**, which can then be reduced *in situ* to **III** (Scheme 6). The π-acidic phosphite ligand, as well as CO, would readily coordinate to and stabilise "$(dppf)Pd^0$" both kinetically and thermodynamically—reversible decoordination of either ligand would release "$(dppf)Pd^0$" back into the catalytic cycle. The differences seen between **1**, $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$, suggest that the phosphite ligand is associated with the catalytic cycle. In keeping with the proposal that mixed phosphite–phosphine palladium complexes derived from **1**, *e.g.* "$Pd(P(OAr)_3)PCy_3$", increase catalyst longevity in Suzuki cross-couplings of deactivated aryl halides,[14c] the phosphite ligand would



Scheme 6 Degradation of **1** in the presence of dppf.

be expected to ameliorate catalyst stability in the carbonylation reactions.

Clearly for some aryl halide substrates, *e.g.* 2,5-dibromopyridine **11**, a Pd^{II} catalyst resting state could equally be as important.[33] Indeed, the dramatic differences in product selectivity observed for this substrate on changing the reaction temperature from 70 to 100 °C suggests that there is a higher concentration of the Pd^{II} intermediate at higher temperatures.

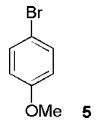
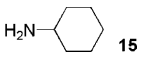
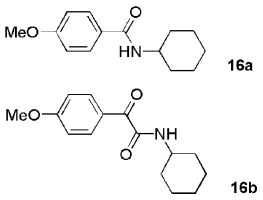
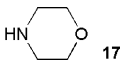
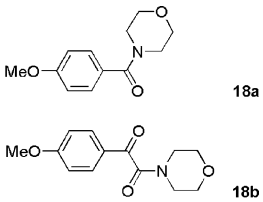
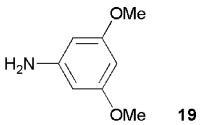
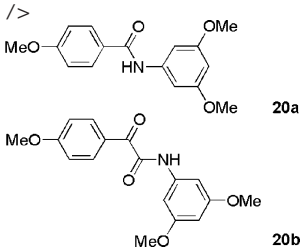
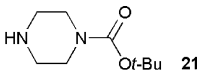
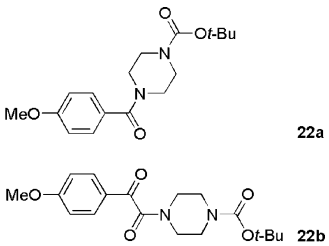
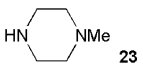
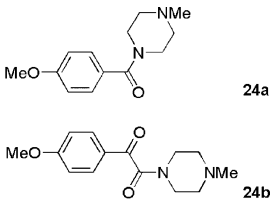
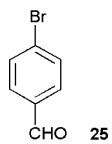
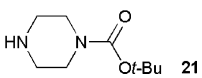
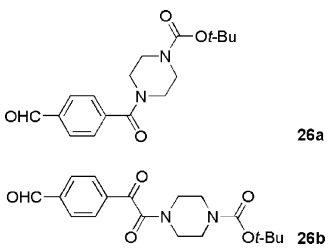
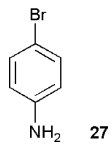
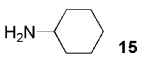
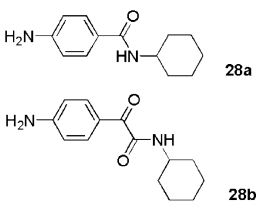
Experimental

General procedure for carbonylation

Carbonylation reactions were carried out at 120 °C, unless otherwise stated, in a stainless steel Parr-Multi channel reactor with a stirrer rate of 1000 rpm. Carbon monoxide pressure of 9–10 bar was applied to the reactions which were monitored by following CO consumption. For analytical purposes, samples from reactions were combined and purified by column chromatography on silica-gel eluting with ethyl acetate–hexane mixtures.

Using a substrate : catalyst ratio of 2000 : 1. To oven-dried stainless steel bombs containing a "propeller" magnetic stirrer bar was added aryl halide (15 mmol, 1 equiv.), K_2CO_3 (45 mmol, 3 equiv.), palladium source (0.05 mol%), dppf (0.15 mol%). The stainless steel vessels were evacuated and back-filled with argon gas (5 to 7 times) and sealed using a rubber septum, before addition of a solution of dried degassed dioxane (by three freeze–pump–thaw cycles). A solution containing the desired quantity of nucleophile in 14 mL of solvent was then added. The bombs were assembled and pressurised, then depressurised with argon (4 times), followed by CO (5 to 7 times). Reactions were worked-up by filtration through a silica-gel plug washed with EtOAc or CH_2Cl_2, which were analysed directly by GC-MS against hexadecane (as the internal standard). All products, and ratios of mono- and bis-carbonylated products, were characterised and calculated principally by GC-MS. Product purity was determined by ^1H and ^{13}C NMR spectra. Spectroscopic data were in agreement with those reported (see citations indicated in the text against specific benchmark reactions).

Table 6 Substrate scope in amidocarbonylation

Entry	ArX	Amine	Products	*T*/°C	Conv. (%)	Product ratio
1	 **5**	 **15**	 **16a** **16b**	130	93	**16a** : **16b**, 84 : 16
2	**5**	 **17**	 **18a** **18b**	120	58	**18a** : **18b**, 1 : 1
3[b]	**5**	 **19**	 **20a** **20b**	120	100	**20a** : **20b**, 98 : 2
4	**5**	 **21**	 **22a** **22b**	130	92	**22a** : **22b**, 96 : 4
5		 **23**	 **24a** **24b**	130	100	**24a** : **24b**, 98 : 2
6	 **25**	 **21**	 **26a** **26b**	100	84	**26a** : **26b**, 92 : 8
7	 **27**	 **15**	 **28a** **28b**	130	64	**28a** : **28b**, 66 : 34

[a] For general reaction conditions: Pd **1** (0.05 mol%), dppf (0.15 mol%), aryl halide (1 equiv.), amine (1.5 equiv.), K_2CO_3 (3 equiv.), CO (9 bar), dioxane, 130 °C, 14 h; unless otherwise stated the substrate : catalyst ratio = 2000 : 1. [b] Substrate : catalyst = 1000 : 1.

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