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Solvent-free aromatic C–H functionalisation/halogenation reactions†‡

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The solvent-free, palladium-catalysed reaction of anilides with CuCl₂ in the presence or absence of copper acetate yields *ortho*-chlorinated anilides in good to excellent yields, even on a large scale (100 mmol). By contrast, the equivalent reactions with copper bromide, either solvent free or in 1,2-dichloroethane, in the presence or absence of palladium, under air or inert conditions, gave the products of simple electrophilic bromination. Mechanistic studies highlighted the involvement of palladacyclic intermediates, one of which was characterised crystallographically, which undergo subsequent reaction with copper(II) chloride to yield the chlorinated anilide products.

Introduction

Transition metal-catalysed cross-coupling reactions form the bedrock of many contemporary organic syntheses.¹ Whilst such reactions are extremely useful and versatile, they are rapidly being complemented and in some instances supplanted by catalytic C–H functionalisation processes,^{2,3} such as direct functionalisation of aromatics (Scheme 1), not least because these methodologies allow greater step-economy and atom efficiency than comparable cross-coupling reactions.



Scheme 1 Catalytic aromatic C-H functionalisation.

One class of reaction that has proved amenable to this protocol is selective aromatic halogenation, where product distribution can be controlled largely by the site of metal-mediated C–H activation (Scheme 2).⁴ Forty years ago Fahey reported the *ortho*-selective chlorination of azobenzene with chlorine.⁵ More recently Sanford and co-workers have designed elegant catalytic halogenation protocols that proceed *via* palladium-catalysed directed C–H functionalisation using *N*-halosuccinimides as milder halogen sources.⁶ Similarly Yu and co-workers used *in situ* prepared XOAc reagents.⁷



Scheme 2 Directed C-H functionalisation/halogenation.

Copper salts have also been exploited either as oxidative halogenating reagents or as oxidising agents in the presence of alternative halogen sources in palladium catalysed directed C–H functionalisation/halogenation reactions.⁸ They have even been shown to function as catalysts under appropriate conditions.⁹

A disadvantage with many C–H functionalisation processes, in particular halogenation reactions, is that they often require acidic (acetic acid or trifluoroacetic acid) or industrially disfavoured solvents such as 1,2-dichloroethane (DCE). We recently communicated our preliminary findings on the use of *solvent free* conditions for direct arylations and halogenations *via* C–H activation,¹⁰ and now report in detail our results for a range of direct halogenation reactions along with initial mechanistic findings.

Results and discussion

Palladium-catalysed chlorination reactions

A particularly useful C–H functionalisation/halogenation reaction is Shi's palladium-catalysed *ortho*-chlorination and bromination of anilides (Scheme 3) using a mixture of two equivalents each of $Cu(OAc)_2$ and CuX_2 in 1,2-dichloroethane.^{8a} In an attempt to circumvent the use of DCE we reinvestigated this reaction, *but under air without the use of solvent*.



Scheme 3 C-H functionalisation/halogenation of anilides.

We were delighted to find that under these conditions good to excellent activity was seen in the chlorination of a range of anilides using $CuCl_2/Cu(OAc)_2$ and 5 mol% palladium acetate¹¹ as catalyst with significantly reduced reaction time (2 h) compared to the 48 h required in 1,2-dichloroethane solution (Table 1). The reactions were very easily performed: the components were ground for ~ 30 s with a pestle and mortar and then the resultant powders heated in an open tube under air. Work-up was equally simple—the product mixture powder was poured directly onto a silica column and then subjected to flash chromatography. Using this method

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both acetyl and pivalyl *p*-toluides were *ortho*-chlorinated in high yields (entries 1 and 2). Unsubstituted acetanilide, **1d**, was cleanly chlorinated with complete *ortho*-selectivity in reasonable isolated yield (entry 4). By contrast, no reaction was observed with the 2-methyl, 2-bromo or 4-cyano-substituted acetanilides **1e**, **f** and **g** (entries 5–7), however when these acetanilides were replaced by their equivalent pivanilides **1h–j** then activity was restored (entries 8–10), although the yield obtained with **1j** was low.

The introduction of *meta*-fluoro, -methyl, or -ethoxy substituents onto the acetanilide (**1k–m**) led to some *para*- chlorination (entries 11–13, 15), presumably by a competitive electrophilic chlorination mechanism (entries 11–13). Indeed when the reaction with the electron-rich substrate **1m** was repeated in the absence of palladium then a very similar product mixture was obtained indicating that only electrophilic chlorination is operative in this case (entry 14). By contrast re-running the reactions in entries 1, 4 and 11 without palladium yielded no products.

We next briefly examined the *ortho*-chlorinations of benzamides and aryl carbamates and these results are summarised in Table 2.

In contrast to the palladium-catalysed *ortho*-C–H arylation of benzamides, which requires an N–H for success,¹² some—albeit very modest—activity was seen with N,N-dimethylbenzamide (entry 1). However the introduction of an N–H gave far superior performance, possibly indicating that the ability to form an anionic substrate is important. Good activity was seen with *para*- and *meta*-substituted anilides (entries 3–5), but again some competitive *para*-chlorination was seen with the 3-fluorobenzamide **3e** (entry 5). By contrast the *ortho*-substituted benzamides **3f** and **g** did not react. Certain aryl carbamates, **5**, were also found to react, however the success of the reactions was dependent on the aromatic substituents (entries 8–10).

We next examined the potential for reaction scale-up using toluide **1a** as the test substrate and the results from this study are summarised in Scheme 4. We found that with reactions performed on the 1 mmol scale, it was not always necessary to use copper acetate (see mechanistic section below for more details) and therefore we examined 10 mmol scale reactions in both the presence and absence of this salt. It can be seen that in a small diameter tube, optimal activity was obtained when using copper acetate, however, in a larger diameter beaker with a greater surface area in contact with the air, this extra oxidant proved unnecessary. Under these conditions we were able to get excellent conversion to product **2a** using 100 mmol (14.9 g) of **1a**. It should be noted that when a beaker was used it was necessary to cover it with an inverted filter funnel to capture any product that sublimed. Product work up consisted simply of extraction, washing and recrystallisation.



10 mmol scale, 13mm diameter tube, 66%^a

10 mmol scale, 13mm diameter tube, 2 equiv. Cu(OAc)₂ added, 89%^a

- 10 mmol scale, 55mm diameter beaker,^b 84%^a
- 100 mmol scale, 70mm diameter beaker,^b 89%^a (73)^c

Scheme 4 Large scale *ortho*-chlorination. ^{*a*} Spectroscopic yield (¹H NMR). ^{*b*} Covered with inverted filter funnel. ^{*c*} Isolated yield.

Solvent-free brominations

The results from an optimisation study on the *ortho*-bromination of toluide **1a** with $CuBr_2$ and $Cu(OAc)_2$ (Table 3) showed that reducing the palladium loading had no effect on the extent of bromination, even when palladium was omitted altogether (entries 1–5). This strongly suggests that the reactions proceeded *via* simple electrophilic substitution rather than C–H activation. Indeed under optimised, palladium-free conditions (Table 3, entry 5) a representative range of anilides all gave products consistent with electrophilic bromination, rather than *ortho*-C-functionalisation (Table 4).

The disparity between the chlorination reactions, which proceed predominantly through directed C–H activation, and the bromination reactions, which proceed through simple electrophilic processes, is in line with the results obtained recently by Stahl and coworkers who demonstrated different mechanisms of bromination and chlorination of electron-rich aromatics catalysed by copper salts in acetic acid solution.¹³

Specifically they showed that the copper-catalysed aerobic oxidation of bromide to bromine occurs under mild, acidic conditions and that it is the resultant bromine that is responsible for electrophilic bromination.

In Shi and co-workers study on the halogenation of anilides using copper(II) bromide,^{8a} it was concluded that bromination proceeds *via* directed C–H functionalisation. This is in contrast with both the results of bromination under solvent-free conditions obtained above and Stahl's studies on electron-rich aromatic substrates.¹³ We therefore conducted a comparison of bromination reactions in both DCE under Shi's conditions and in the absence of solvent and these results are summarised in Table 5.

With **1d** as substrate under solvent-free conditions in the absence of palladium we obtained *p*-brominated **7c** as the sole product (entry 1). When the reaction was repeated in the presence of palladium then substantial, competitive *ortho*-bromination was observed (products **7g** and **h**, entry 2) indicating that a C–H functionalisation/bromination is viable. In general, the reactions generate substantial amounts of acetic acid and when this reaction was repeated in a closed vial then much less *ortho*-bromination was observed (entry 3). This is consistent with Stahl's observation that acid is required for the copper-catalysed formation of bromine from bromide under mild conditions.¹³

In Shi's original report, all the brominations were conducted on para-substituted anilides, except for the reaction of 11. We found that under solvent- and palladium-free conditions only the para-brominated product 7b was produced to any great extent (entry 5). The same product was furnished when the reaction was repeated in the presence of palladium (entry 6), although in this case we also obtained 7i, again presumably via a competitive ortho-C-H functionalisation. Repeating the reaction under Shi's conditions in DCE solution either in the presence or absence of palladium (entries 7 and 8) in our hands yielded only 7b via electrophilic bromination. This was confirmed unequivocally by a single crystal X-ray structure (Fig. 1) of the isolated product from the reaction performed under Shi's conditions (entry 7). A reexamination of the 1H and 13C NMR spectroscopic data reported for the claimed ortho-brominated species 7j^{8a} showed them to be very close to those for $7b^{14,15}$ (with the exception of the NH peak in



^{*a*} Conditions: Anilide (1.0 mmol), Cu(OAc)₂ (2.0 mmol), CuCl₂ (2.0 mmol), Pd(OAc)₂ (5 mol%), ground then 120 °C, 2 h. ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR, 1,3,5-C₆H₃(OMe)₃ internal standard. ^{*d*} 2 mol% Pd(OAc)₂. ^{*c*} No Pd(OAc)₂. ^{*s*} 26 h.



Table 2 Solvent-free palladium-catalysed chlorination of benzamides and aryl carbamates



the ¹H NMR spectrum) and quite distinct from those of a genuine sample of **7**j.^{14,15} We therefore suggest that in both solution or solvent free, in the presence or absence of palladium, under inert or aerobic atmosphere, the predominant bromination products obtained from $Cu(OAc)_2/CuBr_2$ mixtures are those resulting from simple electrophilic bromination. This can be mitigated to some extent, allowing partial *ortho*-C–H bromination, by ensuring that the reactions are performed solvent free, in an open reaction vessel.

Mechanistic considerations

(a) Intermediation of palladacyclic species. Palladacycles are postulated to be intermediates in the *ortho*-halogenation of anilides with $CuX_2/Cu(OAc)_2$ in DCE solution^{8a} and it seemed likely that such species could also play a role in the solvent-free chlorination reactions described herein. Indeed the reactions of **1a** or **b** with palladium acetate under solvent-free conditions yielded a mixture of starting anilide and the palladacycles **8a** and

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 Table 3
 Optimisation of the bromination of anilide 1a^a

	\neg	—NHAc	m(Pd Cu(O	(OAc) ₂ Ac) ₂ , n MBr	\neg	→NHAc
		1a		con	ditions		Br 7a
Entry	Mol% Pd	MCl	т	n	Temp., °C	Time, h	Spec. Yield, %
1	5	CuBr ₂	2	2	120	1	>99 °
2	1	CuBr ₂	2	2	120	1	>99
3	0.1	CuBr ₂	2	2	120	1	93
4	0.01	CuBr ₂	2	2	120	1	>99
5	0	CuBr ₂	2	2	120	1	>99
6	0	CuBr ₂	2	2	100	15	87
7	0	LiBr	2	4	120	22	46
8	0	NaBr	2	4	120	1	0
9	0	KBr	2	4	120	1	0
10	0	CuBr ₂	0.1	2	120	1	65
11	0	CuBr ₂	0	2	120	1	50
12	0	CuBr ₂	2	1	120	1	50
13	0	CuBr ₂	1	2	120	1	64
14	0	$CuBr_2$	1	1	120	1	48

^{*a*} Conditions: **1a** (1.0 mmol), Cu(OAc)₂, CuBr₂, Pd(OAc)₂, ground then 120 °C, time specified. ^{*b*} Determined by ¹H NMR, 1,3,5-C₆H₃(OMe)₃ internal standard. ^{*c*} Isolated yield.

Table 4	Bromination	ot	anilides"

Entry	Substrate	Product/s	Yield (%)
1			82 ^b
2	NHAc 1d	Br NHAC 7c	97
3	NHPiv 1h	Br-NHPiv 7d	84
4		Br	92
5		Br	75

 a Conditions: Anilide (1.0 mmol), Cu(OAc)_2 (2.0 mmol), CuBr_2 (2.0 mmol), ground then 120 $^\circ$ C, 1 h. b 0.5 mmol anilide scale.



Fig. 1 X-ray structure of 7b formed from reaction in DCE solution, thermal ellipsoids set at the 30% probability level.

R	NHAC $2 Cu(OAC)_2$ $120 \circ C$, conditions R R = H: $7c$	+ R Br 7g	+ R 7h	
	R = Me 7b	7i	7j	
Entry	Conditions	Spec. yield "		
	$\mathbf{R} = \mathbf{H} (\mathbf{1d})$			
		7c	7g	7h
1	Solvent free. Pd free	>99	0	0
2	Solvent free, 5 mol%	40	20	40
	Pd(OAc) ₂			
3	Solvent free, 5 mol%	85	15	0
	$Pd(OAc)_2$, closed tube			
4	Solvent free, 5 mol%	81	12	5
	Pd(OAc) ₂ , closed tube,			
	80 °C, 18 h			
	$\mathbf{R} = \mathbf{Me}(\mathbf{1l})$			
		7b	7i	7j
5	Solvent free, Pd free	82	trace	0
6	Solvent free, 5 mol%	78 ^b	21 ^b	0
	$Pd(OAc)_2$			
7	$Pd(OAc)_2$ (10 mol%),	80 ^b	trace	0
	DCE, 90 °C, 48 h,			
	argon			
8	Pd free, DCE, 90 °C,	80	trace	0
	48 h, argon			

 Table 5
 Comparison of bromination in DCE and under solvent-free conditions^a

^{*a*} Determined by ¹H NMR, 1,3,5-C₆H₃(OMe)₃ internal standard. ^{*b*} Isolated yields.



Scheme 5 Formation and reactivity of palladacycles. ^{*a*} Spectroscopic yield (determined by ¹H NMR, 1,3,5-C₆H₃(OMe)₃), remainder unreacted 1.

 b^{16} respectively after 2 h at 80 °C, as determined by ¹H NMR spectroscopy (Scheme 5). It is apparent that under these conditions the bulkier substrate **1b** was more reactive.

Both complexes could be prepared in better yield by the reaction of palladium acetate with **1a** or **b** in acetic acid. The structure of complex **8a** was determined by a single crystal X-ray diffraction study, the results of which are summarised in Fig. 2.

In order to determine whether palladacycle **8a** is indeed significant in catalysis we next compared the rates of *ortho*-chlorination of **1b** with either palladium acetate or **8a** (Fig. 3).



Fig. 2 X-ray structure of complex 8a (one of two similar molecules in asymmetric unit), thermal ellipsoids set at the 30% probability level.



Fig. 3 Varying palladium source and loading. Solid lines indicate best fit over linear regions used to determine maximum rates. Conditions: 1b (1.0 mmol), Cu(OAc)₂ (2.0 mmol), CuCl₂ (2.0 mmol), Pd catalyst (2.5 or 5 mol%), ground then 120 °C. Catalysts and loadings (trend line R²): ◆ 8a, 5 mol% Pd (0.995); ■ Pd(OAc)₂, 5 mol% Pd (0.994); ▲ 8a, 2.5 mol% Pd (0.989); ■ Pd(OAc)₂, 2.5 mol% Pd (0.993). ^b Conversion to 2b, determined by ¹H NMR.

There was essentially no difference observed between the rates of formation of **2b** using either **8a** or palladium acetate at 5 mol% Pd loading (7.2 (\pm 0.4) × 10⁻⁴ mmol s⁻¹ v. 7.1 (\pm 0.5) × 10⁻⁴ mmol s⁻¹ respectively).§ Reducing the palladium loading to 2.5 mol% led to an approximate halving of the rate in both cases indicating that the reactions are first order in palladium. Again there was no significant rate difference between the palladacycle and palladium acetate (3.3 (\pm 0.25) × 10⁻⁴ mmol s⁻¹ v. 3.0 (\pm 0.2) ×

 10^{-4} mmol s⁻¹ respectively).§ At both catalyst loadings **8a** showed shorter induction times than palladium acetate, consistent with the formation of the palladacycle *in situ* in these latter cases. The induction periods observed with **8a** were probably due to a lag in heat transfer through the stationary powder.

It is apparent from Scheme 5 that the formation of the palladacyclic intermediate from the smaller substrate **1a** was less efficient than with bulkier **1b**. Indeed a competition reaction revealed that the rate of formation of the palladacycle from **1b** is nearly twice that from **1a** (Scheme 5). The same size effect was noted above in the catalytic reactions, with pivanilides showing higher yields than equivalent acetanilides (compare Table 2 entries 1, 3–7 with entries 2, 8–10). This was further reflected in the rates of chlorination of **1a** and **1b** (Fig. 4), with the latter reaction over ~ 3 times slower (rate of starting material consumption: -0.55×10^{-4} mmol s⁻¹ v. $-2.4 (\pm 0.22) \times 10^{-4}$ mmol s⁻¹ respectively). Doubling the amount of pivanilide **1b** had no appreciable effect on the rate.



Fig. 4 Varying anilide substrate. Solid lines indicate best fit over linear regions used to determine maximum rates. Conditions: **1b** or **b** (1.0 or 2.0 mmol), $Cu(OAc)_2$ (2.0 mmol), $CuCl_2$ (2.0 mmol), $Pd(OAc)_2$ (5 mol%), ground then 120 °C. Substrate (trend line R²): \blacklozenge **1b**, 1.0 mmol (0.993); **a 1a**, 1.0 mmol (0.986); **b 1b**, 2.0 mmol (0.995).

(b) Roles of copper salts. Having established that palladium catalysis is essential for the directed chlorination reactions (although it plays little role in bromination reactions) and that the reaction proceeds *via* the formation of a palladacycle, we decided to investigate the roles of the copper salts in the chlorinations in more detail, in the first instance using **1a** as the substrate (Table 6).

Under aerobic conditions reducing copper acetate loadings had no affect on activity, even when the salt was omitted altogether (entries 1–3). By contrast when the reactions were repeated under an inert atmosphere (entries 4 and 5) then it is apparent that copper acetate can function as a reasonably efficient stoichiometric oxidant as can copper chloride alone, although to a more limited extent.

When the equivalent reactions where run in DCE solution under Shi's conditions but in the absence of copper acetate, either under air or argon, then the same modest performance resulted (entries 9 and 10) indicating that in solution $Cu(OAc)_2$ is required

 $[\]$ Note maximum rates cannot be expressed as [M]/s in the powder phase. Maximum rates in all cases are for reactions based on varying one component from 'standard' conditions of 1 mmol substrate, 2 mmol each of the copper salts and 5 mol% catalyst.

	-\	—NHAc		Pd(OAc) ₂ (5 mol%), m Cu(OAc) ₂ , n MCI air, conditions	► -{ 2a	
Entry	MCl	т	n	Temp., °C	Time, h	Spec. Yield, % ^a
1	CuCl ₂	2	2	120	2	97 ^{<i>b</i>}
2	CuCl ₂	0.5	2	120	2	96
3	CuCl ₂	0	2	120	2	98
4	$CuCl_2$	2	2	120	2	79 ^c
5	$CuCl_2$	0	2	120	2	28 ^c
6	LiCl	2	4	120	20	70
7	LiCl	0.5	4	120	20	23
8	LiCl	0	4	120	20	0
9	$CuCl_2$	0	2	120	2	49 ^{<i>d</i>,<i>e</i>}
10	CuCl ₂	0	2	120	2	$47^{d,c}$

^{*a*} Determined by ¹H NMR, 1,3,5-C₆H₃(OMe)₃ internal standard. ^{*b*} Isolated yield. ^{*c*} Under argon. ^{*d*} DCE, 90 °C, 48 h. ^{*e*} Under air.

for optimal performance. Comparing entries 3 and 9 it can be concluded that the oxidation step is more facile in the solid state.

 $CuCl_2$ could be replaced by LiCl under solvent-free conditions with reasonable results, provided that copper acetate was present. Reducing the amount of copper acetate in this case proved to be deleterious and no activity was seen in the absence of copper, demonstrating that copper must be present for the oxidative step to occur efficiently under air.

We next investigated the effect of removing the copper acetate from selected catalytic reactions described above. The reaction with acetanilide, **1c**, was largely unaffected (Table 1, entry 4) whilst the reactions of the 3-substituted substrates **1k** and **1l** showed no competitive electrophilic chlorination in the absence of copper acetate (Table 1, entries 11 and 12). The reactions of acetamides **3b** and **c** showed only a slight reduction in yield (Table 2, entries 2 and 3), by contrast leaving out copper acetate proved to be highly deleterious with the carbamate substrate **5a** (Table 2, entry 8).

Fig. 5 shows the effect of changing copper salt loadings on the rate of *ortho*-chlorination of **1b**. Doubling the amounts of either of the copper salts led to a significant reduction in rate, interestingly the new rates were essentially identical, irrespective of which copper salt was increased (4 equiv. $CuCl_2 = 4.9 \ (\pm 0.55) \ \text{mmol s}^{-1}$; 4 equiv. $Cu(OAc)_2 = 4.9 \ (\pm 0.3) \ \text{mmol s}^{-1}$).§ A likely explanation for this, given that copper acetate appears to play no role under aerobic conditions in the powder phase, is that the rate retardation was due to a lower rate of diffusion in the reaction mixture in each case.

The fact that copper acetate plays no role in the chlorination of **1b** in the absence of solvent under air enabled us to probe the intimate role of CuCl₂ further. Heating palladacycle **8a** with 4 equivalents of CuCl₂ under solvent-free conditions gave no reaction after 4 h, but when this was repeated with added acetic acid then quantitative liberation of **2b** was observed (Scheme 5). Presumably whilst the reaction mixture is still a powder, the addition of acetic acid allows sufficient diffusion to allow reaction to occur. In all the reactions reported here some acetic acid is produced, either from palladium or copper acetate.

While this data provides evidence for the formation of the product **2b** from the palladacycle **8a** by reductive elimination, it yields no information on the nature of the palladium intermediate



Fig. 5 Varying copper salt amounts. Solid lines indicate best fit over linear regions used to maximum determine rates. Conditions: 1b (1 mmol), Pd(OAc)₂ (0.05 mmol), CuCl₂ (2 or 4 mmol), Cu(OAc)₂ (2 or 4 mmol), ground then 120 °C, 2h. Copper salt loadings (trend line R²): ◆ CuCl₂ and Cu(OAc)₂, 2 mmol (0.994); ■ CuCl₂, 4 mmol, Cu(OAc)₂, 2 mmol (0.972); ▲ CuCl₂, 2 mmol, Cu(OAc)₂, 4 mmol (0.993).

that undergoes the elimination step. Reductive elimination of aryl chlorides from Pd(II) is rare, typically facilitated by very bulky phosphine ligands.¹⁷ Consequently alternative mechanisms have been invoked for *ortho*-halogenation that proceed *via* reductive elimination from palladacyclic intermediates in oxidation state IV or III.¹⁸ At present we do not have sufficient evidence to determine the likely oxidation state of intermediates in our case but are currently investigating this further.

Conclusions

In summary we have demonstrated that a range of anilides, benzamides and carbamates can be *ortho*-chlorinated under solvent free conditions using palladium catalysis and copper chloride under air and that the process can be readily scaled to 100 mmol of substrate. In contrast to equivalent reactions performed in DCE solution, the use of copper acetate as a co-oxidant is not required in most instances. Bromination reactions in either the solid state or DCE solution proceed *via* electrophilic bromination rather than sequential C–H activation/bromination. Mechanistic studies reveal that the chlorination reactions proceed *via* the formation of Pd(II) metallacycles followed by reductive elimination from as yet uncharacterised intermediates.

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Experimental

General procedure for the preparation of 2-chloroarenes using $\ensuremath{\text{CuCl}}_2$

To a mortar was added the substrate (1.0 mmol), copper acetate (363 mg, 2.0 mmol), copper chloride (266 mg, 2.0 mmol) and $Pd(OAc)_2$ (0.05 mmol). The reagents were ground with a pestle to form a homogenous powder. The reaction mixture was transferred

to a thick walled glass vial. The vessel was then heated at $120 \,^{\circ}$ C for the appropriate length of time, under an atmosphere of air without stirring. The vial was then allowed to cool to room temperature, mixed with a spatula to form a free-flowing homogenous powder, and added directly to the top of a chromatography column. The product was purified by flash chromatography, eluting with ethylacetate/hexanes.

General procedure for the preparation of bromoanilides using $\ensuremath{\text{CuBr}}_2$

To a mortar was added anilide (1 mmol), copper acetate (363 mg, 2 mmol) and copper bromide (447 mg, 2 mmol). The reagents were ground with a pestle to form a homogenous powder. The reaction mixture was transferred to a thick walled glass vial. The vessel was then heated at 120 $^{\circ}$ C for the appropriate length of time, under an atmosphere of air without stirring. The vial was then allowed to cool to room temperature, mixed with a spatula to form a free-flowing homogenous powder, and added directly to the top of a chromatography column. The product was purified by flash chromatography, eluting with ethylacetate/hexanes.

Procedure for the preparation of palladacycle 8a

The appropriate anilide (4 mmol) was added to a round-bottom flask along with $Pd(OAc)_2$ (4 mmol) and acetic acid (3.5 ml). The reaction mixture was heated to 80 °C and stirred under air at this temperature for 2 h. The solvent was removed in vacuo and chloroform (15 ml) was added. The vessel was cooled to 0 °C to allowed complete precipitation of the product. The mother liquor was removed by cannula filtration through glass paper. The precipitate was washed a further 3 times with cold chloroform. The precipitate was dried in vacuo. 8a: Green solid, 1.27 g (89%); ¹H NMR (400 MHz; CD_2Cl_2) δ 7.71 (br. s, 1H), 7.04 (s, 1H), 6.81 (dd, J 7.9, 1.3 Hz, 1H), 6.48 (d, J 7.9 Hz, 1H), 2.24 (s, 3H), 2.09 (s, 3H), 0.87 (s, 9H); ¹³C NMR (100 MHz; CD₂Cl₂) δ 180.7, 173.3, 134.7, 132.3, 128.9, 125.3, 118.1, 114.5, 38.2, 26.6, 24.0, 20.7; IR neat, v/cm⁻¹ 3436, 2971, 1611, 1571, 1532, 1471, 1410, 746, 688, 666; m.p. (decomp.) 197.0 °C; Anal. calcd. for C₂₈H₃₈N₂O₆Pd₂: C, 47.3; H, 5.4; N, 3.9. Found: C, 47.3; H, 5.0; N, 3.5.

Procedure for kinetic studies

The appropriate quantity of anilide, $CuCl_2$, $Cu(OAc)_2$ and palladium source were mixed to form a homogeneous powder using a pestle and mortar. The mixture was transferred to a thickwalled vial and placed in an oil bath, pre-heated to 120 °C. A small quantity of the mixture was removed using a spatula at the appropriate time interval and dissolved in EtOAc. The solution was passed through a plug of glass paper, the solvent removed under reduced pressure and the sample analysed by ¹H NMR (CDCl₃).

X-Ray structure determination of complex 7b

Crystals of **7b** suitable for X-ray analysis were grown by slow diffusion of a dichloromethane solution layered with cyclohexane. The X-ray diffraction was carried out at 100 K on a Bruker APEX II diffractometer using Mo-K α radiation ($\lambda = 0.71073$ Å). Data collections were performed using a CCD area detector

	7b	8a
Size/mm	$0.48 \times 0.22 \times 0.12$	$0.36 \times 0.18 \times 0.18$
Empirical Formula (excluding unknown solvent molecules)	$C_9H_{10}BrNO$	$C_{189}H_{270}Cl_6N_{12}O_{37}Pd_{12}$
M	228.09	4791.67
Crystal system	Monoclinic	Trigonal
Space group	$P2_{1}/c$	RĪ
a/Å	4.0401(10)	44.9022(6)
b/Å	23.7100(5)	44.9022(6)
c/Å	9.7444(2)	25.3871(7)
α (°)	90.00	90.00
β (°)	100.007(1)	90.00
γ (°)	90.00	120.00
V/A^3	919.22(4)	44328.1(15)
Z	4	6
μ/mm^{-1}	4.422	0.814
T/K	100	100
$\theta_{\min,\max}$	1.72,32.94	0.91,27.49
Completeness	0.998 to $\theta = 27.50^{\circ}$	0.998 to $\theta = 27.49^{\circ}$
Reflections: total/independent	10973/3192	22570/167944
R _{int}	0.0320	0.0439
Final <i>R</i> 1 and <i>wR</i> 2	0.0291, 0.0694	0.0465, 0.1254
Largest peak, hole/e A ⁻³	0.938, -0.738	1.097, -0.875

from a single crystal mounted on a glass fibre. Intensities were integrated¹⁹ from several series of exposures measuring 0.5° in ω or φ . An absorption correction was applied based on equivalent reflections using SADABS.²⁰ The structure was solved using ShelXS and refined against all F_o^2 data with hydrogen atoms riding in calculated positions using SHELXL.²¹ Crystal structure and refinement data are given in Table 7.

X-Ray structure determination of complex 8a

Crystals of 8a suitable for X-ray analysis were grown by slow diffusion of a dichloromethane solution layered with cyclohexane. The X-ray diffraction was carried out at 100 K on a Bruker APEX II diffractometer using Mo-K α radiation ($\lambda = 0.71073$ Å). The data collection was performed using a CCD area detector from a single crystal mounted on a glass fibre. Intensities were integrated¹⁹ from several series of exposures measuring 0.5° in ω or φ . An absorption correction was applied based on equivalent reflections using SADABS,²⁰ and structures were refined against all F_0^2 data with hydrogen atoms riding in calculated positions using SHELXL.²² Crystal structure and refinement data are given in Table 7. The structural model was found to contain residual electron density which could not be satisfactorily resolved, and so the data were modelled using the SQUEEZE algorithm, as implemented in PLATON.²¹ The estimate of the number of extra electrons in the unit cell is 6606, which approximately equates to an extra 184 electrons per molecule of complex in the crystal. Since there is also ordered cyclohexane and dichloromethane in the structure, it is difficult to say with certainty to what the residual electron density relates.

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