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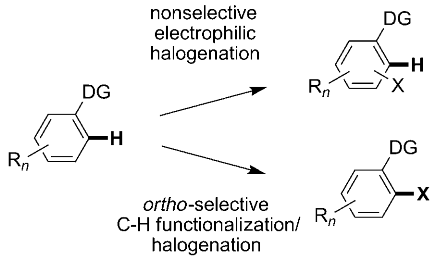
Mild C–H Halogenation of Anilides and the Isolation of an Unusual Palladium(I)–Palladium(II) Species**

Robin B. Bedford, Mairi F. Haddow, Charlotte J. Mitchell, and Ruth L. Webster*

Palladium-catalyzed C–H functionalization/halogenation is a particularly useful method for producing halogenated aromatic products with selectivity that would not ordinarily be obtained under simple electrophilic halogenation conditions (Scheme 1).[1] A significant advance in this area was reported by Shi and co-workers who demonstrated that anilides could be *ortho* chlorinated in good to excellent yields using Pd(OAc)$_2$ as the catalyst and a mixture of CuCl$_2$ and Cu(OAc)$_2$ as the chloride source and the oxidant.[2]



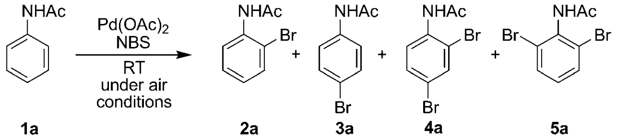
Scheme 1. Directed *ortho*-selective C–H functionalization/halogenation versus electrophilic halogenation. DG = directing group.

Unfortunately these reactions require the use of industrially disfavored 1,2-dichloroethane as a solvent and two days heating at 90 °C for completion. Furthermore, contrary to the original claims, we found that selective *ortho* bromination cannot be obtained under these reaction conditions and only *para*-selective electrophilic bromination is observed.[3] Since aryl bromides are significantly more reactive than their chloride congeners they represent profoundly more desirable targets, therefore the selective *ortho* bromination of anilides remained a synthetically highly important yet unmet goal.

Herein, we report that not only can *ortho*-selective bromination be achieved, but that the reactions can be performed under very mild reaction conditions: typically they are complete within 1–4 hours at room temperature, under air using a remarkably simple system. This mild, operationally simple methodology can also be readily extended to *ortho*-selective chlorination.[4] Furthermore we report the isolation of a highly intriguing, extremely fragile, mixed Pd^{I}–Pd^{II} species that is formed under reaction conditions comparable to those used in the catalytic reaction.

Inspired by de Vries and van Leeuwen's use of *p*-toluenesulfonic acid (PTSA) as an additive in the mild *ortho*-vinylation of anilides,[5] we were delighted to find that acetanilide, **1a**, reacts with *N*-bromosuccinimide (NBS) and 0.5 equivalents of PTSA in the presence of 5 mol% Pd(OAc)$_2$, at room temperature in toluene, to generate the 2-brominated anilide **2a** in 95% yield (spectroscopic) with no *para*-Br product **3a** and only trace amounts of the dibrominated products **4a** and **5a** (Table 1, entry 1). Other solvents, including 1,4-dioxane, also proved to be effective.[6] Lowering either the palladium or PTSA loading, or running the reaction without palladium gave significant electrophilic bromination (entries 2–4). The presence of acid was crucial, as neither the addition of NaOTs nor the use of the preformed tosylate complex [Pd(OTs)$_2$(MeCN)$_2$][7] alone were successful; while the addition of PTSA to this catalyst gave significant electrophilic bromination (Table 1, entries 5–7). Acetic acid showed no reactivity and trifluoroacetic acid poor reactivity, whereas

Table 1: Reaction optimization.[a]



Entry	Conditions	Yield [%][b] 2a	 3a	 4a	 5a
1	5 mol% Pd, 1 h, 50 mol% PTSA	94	–	2.5	2.5
2	1 mol% Pd, 30 min, 50 mol% PTSA	21	66	–	–
3	0 mol% Pd, 1 h, 50 mol% PTSA	5	30	–	–
4	5 mol% Pd, 2 h, 10 mol% PTSA	68	22	7	0
5	5 mol% Pd, 1 h, 50 mol% NaOTs	0	0	0	0
6	5 mol% [Pd(OTs)$_2$(MeCN)$_2$], 2 h, no added acid	39	47	–	–
7	5 mol% [Pd(OTs)$_2$(MeCN)$_2$], 1 h, 50 mol% PTSA	54	26	4	6
8	5 mol% Pd, 1 h, 50 mol% CH$_3$CO$_2$H	0	0	0	0
9	5 mol% Pd, 1 h, 50 mol% CF$_3$CO$_2$H	26	0	0	0
10	5 mol% Pd, 1 h, 50 mol% H[BF$_4$][c]	67	17	–	–

[a] Reaction conditions: **1a** (0.5 mmol), NBS (0.52 mmol), additive as specified, catalyst (5 mol%), toluene (2 mL), RT. [b] Determined by ^{1}H NMR spectroscopy (1,3,5-C$_6$H$_3$(OMe)$_3$ internal standard). [c] Yields of isolated products. Ts = 4-toluenesulfonyl.

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[*] Prof. R. B. Bedford, Dr. M. F. Haddow, R. L. Webster
School of Chemistry, University of Bristol
Cantocks Close, Bristol, BS8 1TS (UK)
E-mail: r.bedford@bristol.ac.uk
C. J. Mitchell
GlaxoSmithKline
Stevenage, SG1 2NY (UK)

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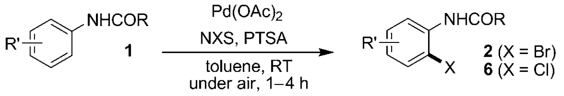
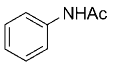
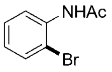
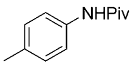
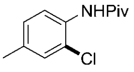
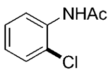
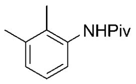
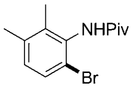
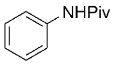
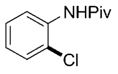
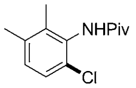
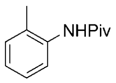
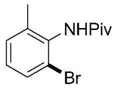
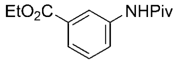
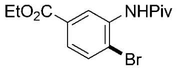
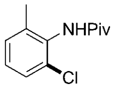
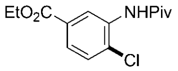
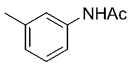
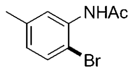
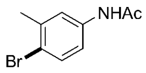
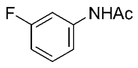
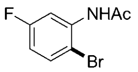
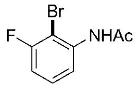
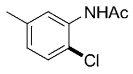
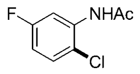
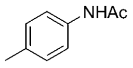
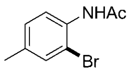
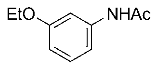
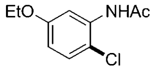
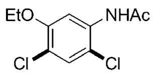
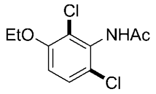
Table 2: Selected *ortho* bromination and chlorination of anilides.[a]



Entry	Anilide		Product(s)	Yield [%][b]	Entry	Anilide		Product(s)	Yield [%][b]
1		**1a**		**2a**: 80 (94)	9		**1f**		**6f**: 92
2		**1a**		**6a**: 73 (98)	10		**1g**		**2g**: 93
3		**1b**		**6b**: 52	11		**1g**		**6g**: 83
4		**1c**		**2c**: 93	12		**1h**		**2h**: 43[c,d]
5		**1c**		**6c**: 89	13		**1h**		**6h**: 80[c,d]
6		**1d**	 	**2d**: 68 **3d**: 16	14		**1i**	 	**2i**: 62 (81)[c] **7i**: 6 (11)[c]
7		**1d**		**6d**: 61 (82)	15		**1i**		**6i**: 50 (83)[c]
8		**1e**		**2e**: 94	16		**1j**	  	**6j**: 87[c] **8j**: 3[c] **9j**: (3)[c]

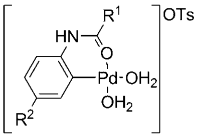
[a] Selected data; see Table S1 for more comprehensive data,[8] Reaction conditions: Anilide (0.5 mmol), NXS (0.52 mmol), PTSA (0.25 mmol), $Pd(OAc)_2$ (5 mol%), toluene (2 mL), RT 1–4 h. [b] Yield of isolated products; yield determined by ^1H NMR spectroscopy in parentheses (1,3,5-$C_6H_3(OMe)_3$ internal standard). [c] Run at 50°C. [d] Run for 24 h. Piv = pivaloyl.

tetrafluoroboric acid gave some competitive electrophilic bromination (entries 8–10).

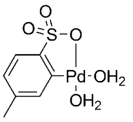
With optimized reaction conditions in hand we next examined the scope of the reaction (see selected results in Table 2; full results in Table S1 of the Supporting Information).[8] Good to excellent yields of both *ortho* brominated and chlorinated anilides were obtained under very mild reaction conditions and short reaction times with little or no competitive electrophilic halogenation apparent in most cases.

We next turned our attention to the possible mechanism of the reaction. The function of the acid is presumably to protonate a carbonyl group of the *N*-halosuccinimide (NXS), thus rendering it a more effective source of X^+.[9] The halonium (or possibly HOX formed in situ) might be expected to oxidatively add to an orthopalladated anilide intermediate which then liberates the product by reductive elimination. Such anilide-based palladacyclic intermediates have been proposed in a range of related oxidative C–H functionalization reactions.[10] Accordingly we prepared the complexes **10a** and **b** under reaction conditions that mimic the catalytic process, but in the absence of NXS. Detailed kinetic comparison of reactions catalyzed by $Pd(OAc)_2$ or **10a** proved to be difficult because of the low solubility of PTSA. However, in each case protracted induction periods of at least 20 minutes were observed (see Figure S3 in the Supporting Information),[8] thus militating against direct intermediacy of **10a** in the catalytic cycle. Meanwhile reaction of $Pd(OAc)_2$ with PTSA alone gave the fragile palladacyclic complex **11**. This complex was not only catalytically competent, but showed no induction period in the *ortho* chlorination of **1a** (Figure S3).[8]

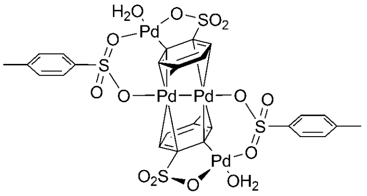
To the best of our knowledge complex **11** represents the first example of a C–H activated arylsulfonate ligand. Crystals of **11** were subjected to X-ray analysis, the results of which supported the indicated connectivity (Figure S1);



10a: R^1 = Me; R^2 = H
b: R^1 = *t*Bu; R^2 = Me



11



12

however whole-molecule disorder meant that the data were too poor in quality to comment on the structure further.[8]

Complex **11** was briefly stable in THF and DMSO, but in most other donor solvents underwent rapid loss of PTSA, even under anhydrous conditions, thus suggesting that decomposition occurred by intramolecular protonolysis of the Pd–C bond by an aquo ligand. Solutions of **11** in 1,4-dioxane under air gradually (hours) turned brown, thus taking on the same coloration observed in the majority of the catalytic reactions, which were performed under similar conditions. In contrast, and somewhat surprisingly, the brown solutions formed faster yet were far less stable under a nitrogen atmosphere: the reactions deposited palladium black within 45 minutes. NMR spectroscopic analysis of a brown solution formed under air showed peaks for a mixture of free PTSA and a new species **12**, which is consistent with an orthopalladated PTSA complex.[8] A crystal structure of **12** showed it to be a highly unusual complex wherein half of the palladium had been reduced to give a Pd^I dimer supported by π coordination of two Pd^{II} palladacycles (Figure 1).[8] The Pd–Pd bond length (2.538(6) Å) is typical of aryl-stabilized Pd^I dimers where the ligand *trans* to the Pd–Pd bond is a moderately weakly coordinating anion.[11] Longer distances (up to 2.727(4) Å)[12] are seen for structures with phosphine ligands in this position. The distance from the centroid of the Pd–Pd bond to the plane of the phenyl ring is 2.125(12) Å, which is also typical for these systems. The structure contains four 1,4-dioxane solvate molecules per molecule of dimer, two of which are hydrogen bonded to the water ligand. This solvation appeared to play a key role in the stability of the complex: crystals of **12** underwent rapid decomposition in the absence of extraneous 1,4-dioxane.

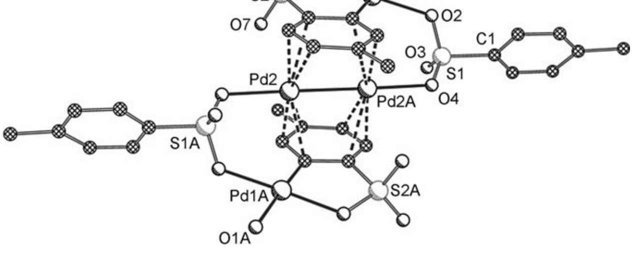


Figure 1. X-ray crystal structure of **12** (1,4-dioxane solvate omitted for clarity).

The formation of complex **12** is extraordinary in two regards. Firstly **12** is a very rare example of a π-arene complex where the arene is itself part of a metallacycle; indeed to the best of our knowledge this is the first example of a metallacycle supporting a Pd^I dimeric core. More importantly though, the results show that a palladacycle can undergo facile reduction to Pd^I under mild reaction conditions—even under air![13] There has been considerable discussion as to whether catalytic oxidative C–H functionalization proceeds by oxidation of Pd^{II}-based metallacycles to Pd^{IV} or Pd^{III} intermediates.[14] In contrast, the potential role(s) of Pd^I in C–H functionalization has yet to be established, an area that we are currently exploring.[15]

In conclusion *ortho*-selective halogenation of anilides can be achieved under very mild, aerobic conditions. An anilide-based palladacycle isolated under comparable conditions does not appear to be directly involved in the catalytic manifold. Conversely an unusual palladacycle based on orthometalated PTSA, formed under conditions similar to those employed in the catalytic reactions, is active and shows no induction period. Furthermore this species can undergo a facile reduction, under conditions similar to those used in the catalysis, to generate a highly unusual Pd^I–Pd^{II} tetrameric complex. PTSA is used as an additive in a range of C–H functionalizations,[16] accordingly we are probing the potential roles of these unique orthometalated PTSA complexes in such processes.

Experimental Section

General procedure for the halogenation of anilides: A mixture of anilide (0.5 mmol), $TsOH{\cdot}H_2O$ (0.25 mmol), NXS (0.52 mmol), and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) in toluene (2 mL) was stirred under air for the 1–4 h. The solution was then diluted with Et_2O, washed with $NaHCO_3$ (aq) (10 mL) and then H_2O (2 × 10 mL), after which the organic extracts were dried over $MgSO_4$ and the volatiles removed under reduced pressure. The crude reaction mixture was then purified by column chromatography (silica gel) eluting with EtOAc/hexanes (1:1).

Preparation of palladacycle **11:** $TsOH{\cdot}H_2O$ (1 mmol) and $Pd(OAc)_2$ (1 mmol) in toluene (2 mL) was stirred at RT for 1 h under air. The supernatant was removed and the residue washed with cold anhydrous EtOAc (4 × 2 mL) to give **11** as a yellow solid (66 %).

Preparation palladacycle **12:** A solution of **11** (ca. 10 mg) in anhydrous 1,4-dioxane (1 mL, under air) in an NMR tube was layered with anhydrous hexanes to give **12** as a brown, crystalline solid which was characterized by X-ray analysis.[11] Solutions prepared in $[D_8]$1,4-dioxane were analyzed by NMR spectroscopy and showed mixtures of **12** and free PTSA in a 1:8 ratio within 3 h with an increase to 1:4 after 20 h. Pure samples of **12** could not be isolated as the crystals were unstable in the absence of 1,4-dioxane, and decomposed rapidly (min) into palladium black. In the presence of air and 1,4-dioxane, the crystals were stable for approximately 1 week. When formed or stored under nitrogen (in the presence of 1,4-dioxane), they decomposed into palladium black within 2 h.

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Keywords: arenes · catalysis · C–H functionalization · halogenation · palladium

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[1] Selected recent examples: a) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300; b) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem.* **2005**, *117*, 2150; *Angew. Chem. Int. Ed.* **2005**, *44*, 2112; c) R. Giri, X. Chen, X.-S. Hao, J.-J. Li, J. Liang, Z.-P. Fan, J.-Q. Yu, *Tetrahedron: Asymmetry* **2005**, *16*, 3502; d) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134; e) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483; f) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, *8*, 2523; g) J.-J. Li, R. Giri, J.-Q. Yu, *Tetrahedron* **2008**, *64*, 6979; h) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 5293; *Angew. Chem. Int. Ed.* **2008**, *47*, 5215; i) X. Zhao, E. Dimitrijević, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466; j) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama, T. Tanabe, *J. Am. Chem. Soc.* **2009**, *131*, 11310; k) B. Song, X. Zheng, J. Mo, B. Xu, *Adv. Synth. Catal.* **2010**, *352*, 329.

[2] X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416.

[3] a) R. B. Bedford, C. J. Mitchell, R. L. Webster, *Chem. Commun.* **2010**, *46*, 3095; b) R. B. Bedford, J. U. Engelhart, M. F. Haddow, C. J. Mitchell, R. L. Webster, *Dalton Trans.* **2010**, *39*, 10464.

[4] For two examples of chlorination of anilides using NCS under far more forcing conditions (100 °C, 12 h) see Ref. [1f].

[5] M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586.

[6] Using THF, diethyl ether, or dichloromethane as the solvent led to modest (11–14 %) levels of competitive *p*-bromination. 1,4-Dioxane gave 61 % of **2a** and 16 % of **3a**, whereas toluene/1,4-dioxane (1:1) gave 73 % of **2a**, 14 % of **3a**, and 5 % of **4a**.

[7] C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.* **2009**, *121*, 1862; *Angew. Chem. Int. Ed.* **2009**, *48*, 1830.

[8] See the Supporting Information for details.

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[10] For selected recent examples see: a) R. Giri, J. K. Lam, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 686; b) M. Tobisu, Y. Ano, N. Chatani, *Org. Lett.* **2009**, *11*, 3250; c) W. Rauf, A. L. Thompson, J. M. Brown, *Chem. Commun.* **2009**, 3874.

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[13] As yet, we do not know what acts as the reductant in this reaction.

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[15] Attempts to explore the precise role of **12** have so far been hampered by the fact that it is not stable in the solid state in the absence of 1,4-dioxane, but rather undergoes rapid (min) decomposition. Conversely, 1,4-dioxane solutions of **12** contain varying amounts of free PTSA and therefore must also contain concomitant amounts of unidentified Pd species.

[16] For examples see: a) W. Rauf, J. M. Brown, *Synlett* **2009**, 3103; b) C. E. Houlden, C. D. Bailey, G. Ford, M. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066 and Refs. [7], [9a], and [9c].