Synthesis of novel palladium OCN-pincer complexes: unprecedented sequential C(sp^3)–H activation and aerobic oxidation in the reaction of *N*,*N*-dialkyl-3-[(*N*,*N*-dimethylamino)methyl]-2-iodoanilines with $Pd_2(dba)_3$†

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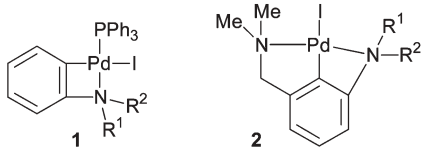
The reaction of *N*,*N*-dialkyl-3-[(*N*,*N*-dimethylamino)methyl]-2-iodoanilines with $Pd_2(dba)_3$ under O_2 gives palladium OCN-pincer complexes by means of an unprecedented process that involves the formal aerobic oxidation of C(sp^3)–H bonds at the α position of the aniline N atom.

Transition metal complexes containing ECE pincer-type ligands (where E is a neutral two-electron donor) have recently attracted considerable attention owing to their usefulness in different areas, including bond activation, catalysis, and the stabilisation of otherwise unstable compounds.[1] Consequently, many pincer complexes with a great variety of pendant ligands have been reported during the last years.[2]

In the context of our studies on the Pd(0)-catalysed coupling of aryl halides and ketones,[3,4a] we have recently described a new family of four-membered azapalladacycles of general structure **1**, which are obtained by reaction of *N*,*N*-dialkyl-2-iodoanilines with Pd(0) complexes.[4] Continuing our research on this chemistry, we were interested to see whether the introduction of an additional chelating group at the *ortho*-position of the palladated carbon was compatible with the four membered metallacycle and if so, whether palladium pincer complexes containing a four-membered ring such as **2** could be obtained.



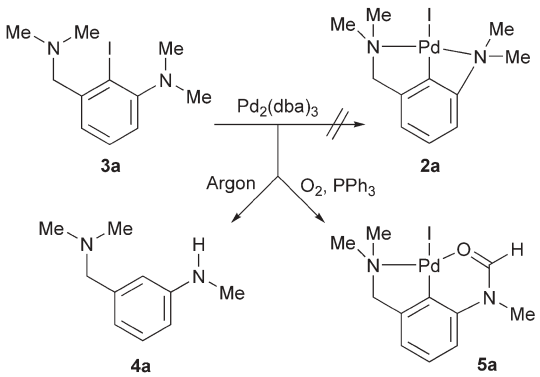
1 **2**

In this communication we report that the introduction of a (dimethylamino)methyl group at the *ortho*-position severely changes the reactivity of 2-haloanilines with $Pd_2(dba)_3$. This led us to obtain palladium OCN-pincer complexes by means of an unprecedented process involving sequential C(sp^3)–H activation at the α position of the aniline N atom, and aerobic oxidation of the transient palladium complex thus formed.

Instead of the expected palladium complex **2a**, the reaction of iodoaniline **3a** with $Pd_2(dba)_3$ (benzene, rt) under an argon atmosphere gave aniline **4a** (40%), resulting from the hydrodehalogenation and demethylation of the starting material (Scheme 1). After an unsuccessful survey of reaction conditions while trying to prepare our original target, we fortuitously found that treatment of **3a** with $Pd_2(dba)_3$ in the presence of PPh_3 (1 equiv.) in open air (benzene, rt, 9 h) afforded the palladium OCN-pincer complex **5a**, which was isolated in 43% yield by 'flash' chromatography. Some studies to optimise this unexpected oxidation process were performed and it was found that the addition of Et_3N under an O_2 atmosphere resulted in clean reaction mixtures and increased the yield of **5a** up to 53%. The structure of complex **5a** was confirmed by X-ray crystallography (Fig. 1).‡

To evaluate the scope of this unprecedented transformation, other differently substituted haloanilines were examined. As summarised in Table 1, substrates **3a–d** reacted under the optimised conditions to afford palladium OCN-pincer complexes **5a–d** in moderate yields. As expected, bromoaniline **3b** was less reactive than **3a** in the reaction with $Pd_2(dba)_3$. However, after heating a benzene solution of **3b** and $Pd_2(dba)_3$ at 50 °C for 3 days, palladium complex **5b** was obtained in 57% yield. Reaction of substrates **3c** and **3d** showed high selectivity for the functionalisation of primary C(sp^3)–H bonds in lieu of secondary carbon centres, as the only palladacycles we obtained were those resulting from the oxidation at the methyl group, **5c** and **5d** respectively.

Substrates **6–8**, which contain two methylene carbons at the α position of the aniline N atom, provided further information about the oxidation reaction. Thus, under optimised conditions iodoanilines **6** and **7** afforded the palladium complexes **9** and **10**, respectively, both resulting from the oxidation at secondary



Scheme 1

† Electronic supplementary information (ESI) available: experimental details, characterization data of compounds **2c**, **4a,c–d**, **5a–d**, **9** and **10**, and crystallographic information. See http://www.rsc.org/suppdata/cc/b5/b502854j/

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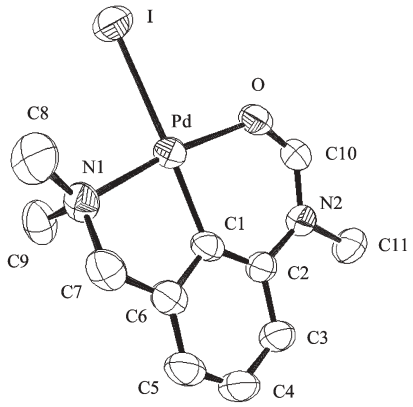
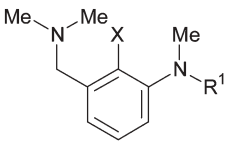
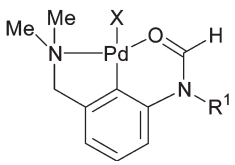
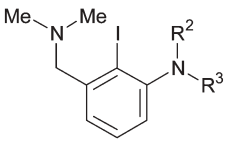
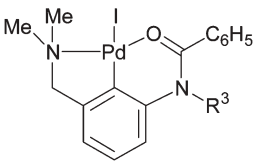
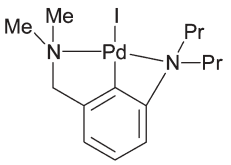


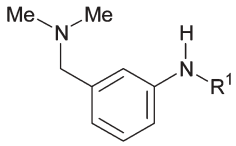
Fig. 1 Molecular structure of **5a** (ORTEP view). Selected bond distances (Å) and angles (°): Pd–C1 = 1.948(3), Pd–N1 = 2.083(2), Pd–O = 2.031(2), Pd–I = 2.7405(7), C1–Pd–N1 = 83.32(10), C1–Pd–O = 89.11(9), N1–Pd–I = 97.32(7), O–Pd–I = 90.04(6).

Table 1 Synthesis of palladium pincer complexes[a]

Entry	2-Haloaniline	Pd–pincer complex	Yield[b]
			
1	**3a**, X = I, R^1 = Me	**5a**, X = I, R^1 = Me	53%
2	**3b**, X = Br, R^1 = Me	**5b**, X = Br, R^1 = Me	57%[c]
3	**3c**, X = I, R^1 = Pr	**5c**, X = I, R^1 = Pr	60%
4	**3d**, X = I, R^1 = Bn	**5d**, X = I, R^1 = Bn	45%
			
5	**6**, R^2 = R^3 = Bn	**9**, R^3 = Bn	39%[d,e]
6	**7**, R^2 = Bn, R^3 = Pr	**10**, R^3 = Pr	46%[d,f]
7	**8**, R^2 = R^3 = Pr	 **2c**	40%[d]

[a] Reaction conditions: $Pd_2(dba)_3$ (0.55 equiv.), PPh_3 (1 equiv.), Et_3N (5 equiv.), benzene, rt, 9 h, O_2. [b] Yield refers to pure products isolated by 'flash' chromatography. [c] 50 °C for 3 days in open air. [d] 24 h. [e] **4d** (38%) was also isolated. [f] **4c** (35%) was also isolated.

benzylic positions. Especially interesting is the reaction of iodoaniline **7**, in which the oxidation took place regioselectively at the benzylic position. Additionally, it should be noted that significant amounts of the hydrodehalogenation–dealkylation by-products, **4d** and **4c** respectively, were also obtained.



4c (R^1 = Pr)
4d (R^1 = Bn)

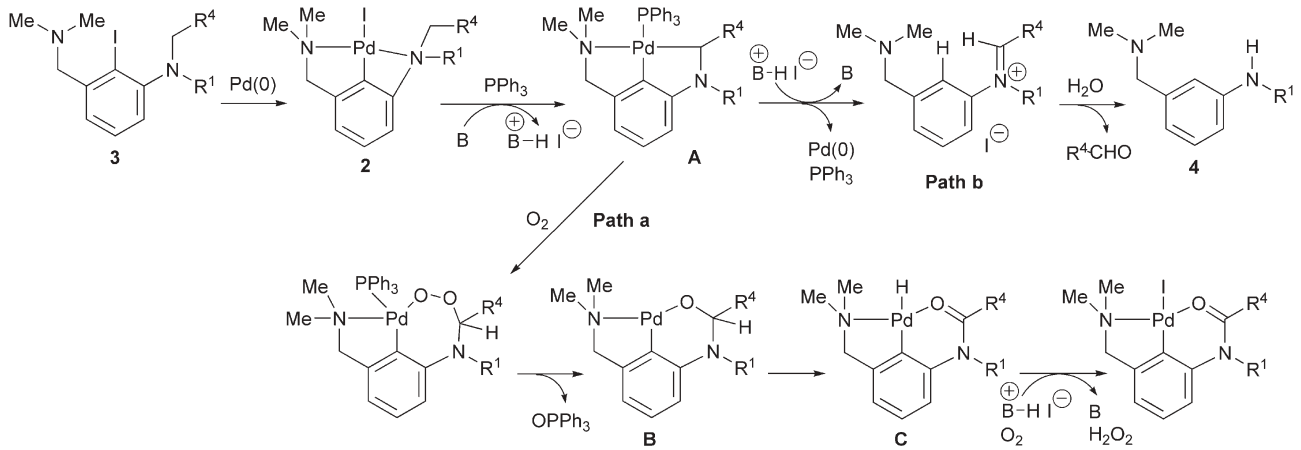
To our surprise, subjecting iodoaniline **8** to the same reaction conditions provided the NCN′-pincer derivative **2c** (40%) instead of the corresponding OCN-pincer complex. Longer reaction times resulted in the formation of the hydrodehalogenation–dealkylation product **4c** together with **2c**, the OCN-pincer complex still not being detected. The structure of the pincer complex **2c** was assigned from its spectroscopic data. Unfortunately, we failed to obtain a single crystal suitable for X-ray studies because of the instability of this palladium complex.

The selectivity of the oxidation reaction can be rationalised on the basis of the requirements of C–H activation at Pd(II).[5] Thus, selective oxidation at primary *versus* secondary carbon centres (entries 3 and 4) probably results from a strong steric preference for the formation of less hindered primary Pd-alkyls. Additionally, the high regioselectivity for the oxidation at the benzylic position (entry 6) reflects that the dissociation energy of benzylic C–H bonds is lower than that of alkyl C–H bonds.

Although further studies will be necessary to determine the mechanistic features of the oxidation reported in this communication, the results obtained in the above reactions may be tentatively explained by considering the multi-step process shown in Scheme 2. Thus, the oxidative addition of Pd(0) to the carbon–halogen bond of the haloaniline gives rise to the corresponding NCN′-pincer complex (**2**), which would undergo activation at one of the C–H bonds at the α position of the aniline N atom[6] to give palladacycle **A**.[7–9] Palladium complex **A** could undergo reaction with O_2 to give an alkylperoxo palladium complex, which would then give alkoxo complex **B** and $OPPh_3$ (path a).[10] A control reaction with iodoaniline **3a** argues in favour of an active role of PPh_3 in this process, as no oxidation compound could be obtained when the reaction was carried out in the absence of PPh_3, although the starting material was consumed and significant amounts of **4a** were obtained. Finally, β-hydride elimination[11] from **B** would afford a hydrido-palladium complex **C**, which could react with O_2 and the acid formed *in situ*[12] to give the OCN-pincer complex.[13,14]

On the other hand, palladacycle **A** can undergo sequential reductive elimination and hydrolysis to give **4** (path b).[15] This process is the usual reaction pathway in the absence of O_2, and becomes a competitive reaction when the oxidation step is hampered by steric factors. The isolation of significant amounts of benzaldehyde together with the hydrodehalogenation–dealkylation by-products **4d** and **4c** in the reactions from **6** and **7** (entries 5 and 6) supports this sequence of events.

Finally, the isolation of the NCN′-pincer complex **2c** is a consequence of its greater stability, which is probably due to the propyl groups hampering the C(sp^3)–H activation that gives **A** (*vide supra*). On the other hand, although the formation of **4c** from the NCN′-pincer complex **2c** could also be explained by the steric hindrance that prevents the oxidation of intermediate **A** (R^1 = Pr, R^4 = Et) and forces path b, an alternative pathway (not



Scheme 2

represented) seems more likely, due to the presence of β hydrogens. It would involve β-hydride elimination from **A** to give an enamine, followed by reductive elimination of the Pd-hydride, and finally hydrolysis of the enamine.

In summary, we have shown that the palladium NCN′-pincer complexes that have simultaneously four- and five-membered metallacycles are not stable and undergo C–H activation at the α position of the aniline N atom. The sequential C(sp^3)–H activation and aerobic oxidation at this position led to the novel palladium OCN-pincer complexes. Further investigation will be conducted to gain deeper insight into the mechanism of the oxidation process and to expand the activation reaction to other substrates.

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Notes and references

‡ Crystal data for **5a**: $C_{11}H_{15}IN_2OPd$, M = 424.55, monoclinic, space group $P2_1/a$, a = 10.190(8), b = 11.219(3), c = 11.646(2) Å, β = 100.37 (3)°, V = 1309.6 (11) Å^3, Z = 4, T = 293 K, μ = 3.756 mm^{-1}; 3977 data, 3767 unique (R_{int} = 0.0509). R_1 = 0.0321 [$I > 2\sigma(I)$], wR_2 = 0.0705 on F^2. CCDC 265336. See http://www.rsc.org/suppdata/cc/b5/b502854j/ for crystallographic data in CIF or other electronic format.

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