Catalytic aerobic oxidation of substituted 8-methylquinolines in Pd^{II}-2,6-pyridinedicarboxylic acid systems†

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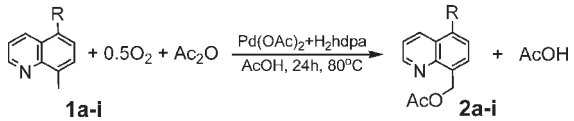
The ability of Pd^{II} complexes derived from 2,6-pyridinedicarboxylic acids to catalyze homogeneous regioselective aerobic oxidation of 5- and 6-substituted 8-methylquinolines in AcOH–Ac_2O solution to produce corresponding 8-quinolylmethyl acetates in high yield was demonstrated; corresponding 8-quinoline carboxylic acids are minor reaction products.

Selective CH functionalization of organic substrates is an important problem of synthetic chemistry.[1] A number of reports on heteroatom-directed catalytic CH functionalization have appeared recently.[2,3] The use of the Pd^{II} complexes in combination with strong oxidants such as $PhI(OAc)_2$, $NaHSO_5$, IOAc or alkyl peroxocarboxylates was especially fruitful.[2] Still, the use of dioxygen for selective CH functionalization remains challenging and constitutes an attractive practical goal.[3–5] Given the fact that facile aerobic conversion of monoalkyl platinum(II) complexes to corresponding alcohols[6,7] can be promoted by the dpms ligand[8] (Scheme 1), we were interested to find out whether the reactivity of the systems including monohydrocarbyl palladium(II) complexes and dioxygen can be enhanced with the help of suitable ligands. One of the useful routes to various organopalladium(II) species is *via* selective CH activation and cyclopalladation of suitable organic substrates with Pd^{II} complexes such as $Pd(OAc)_2$ or $Pd(acac)_2$ (acac = acetylacetonate) in AcOH or some other solvents.[9] The resulting palladacycles that contain Pd–C(sp^3) or Pd–C(sp^2) bonds are typically unreactive towards O_2,[10] and even H_2O_2.[10b] Therefore, the effect of added ligands on their reactivity towards O_2 could be readily established.

In this work, we report selective catalytic aerobic oxidation of various substituted 8-methylquinolines (HQ) in a $Pd(OAc)_2$ or $Pd(acac)_2$–4-hydroxopyridine-2,6-dicarboxylic acid (H_2hpda)–aceticacid–Ac_2O system leading to the corresponding 8-quinolylmethyl acetates in high yield (eqn (1)):

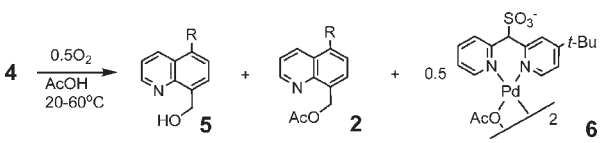


R = H(**a**), Me(**b**), MeO(**c**), F(**d**), Cl(**e**), Br(**f**), I(**g**), NO_2(**h**), 6-NO_2(**i**) (1)

Since the tridentate anionic pyridine-containing motif present in dpms turned out to be useful in promoting aerobic oxidation of various monoalkyl Pt^{II} complexes in water,[6,7] a lipophilic dpms ligand, *t*-Bu-dpms was tested in this work along with dianionic tridentate 2,6-pyridinedicarboxylates (L, Scheme 1). We anticipated that H_2pda-derived Pd^{II} carboxylates would be active in CH activation of HQ, similar to Pd^{II} acetate itself. A *tert*-butyl group present in some ligands was needed to increase solubility of the derived metal complexes in acetic acid. The ability of Li(*t*-Bu-dpms) and H_2hpda to promote aerobic oxidation of palladacycles **3a** and **3d** (Scheme 2) was tested first.

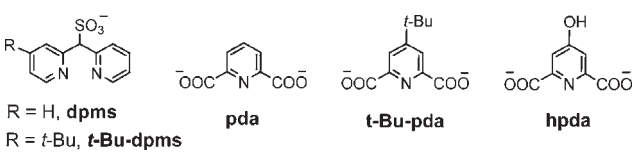
Complexes **3a** and **3d** were prepared according to standard procedures.† No reaction between **3a** and O_2 in acetic acid at 20 °C was seen after 1 day. Combination of yellowish complex **3a** with 1 equivalent of Li(*t*-Bu-dpms) in acetic acid quantitatively produced a ~1 : 1 mixture of colorless *cis*- and *trans*-**4a** that were characterized by NMR spectroscopy and elemental analysis.

When the solution of **4a** in AcOH was stirred under air at 20 °C, a fast reaction occurred, leading to the clean formation of a ~1 : 1 mixture of 8-quinolylmethanol (**5a**) : 8-quinolylmethyl acetate (**2a**) (86% combined NMR yield after 15 min), and complex [(*t*-Bu-dpms)Pd(OAc)]$_2$, **6** (eqn (2); R = H):



(2)

When the same reaction was carried out under O_2 in the presence of 5 equivalents of Ac_2O, a mixture of **2a** and **5a** that formed initially slowly produced **2a** as the only organic product (97% NMR yield after 8 h at 20 °C). Volumetric experiments allowed us to establish that 0.5 mol O_2 was consumed per mole of **4a**. Hence, no sacrificial substrate was required for dioxygen activation and oxidation of this palladacyclic complex.



Scheme 1 Anionic chelating pyridine-derived ligands.

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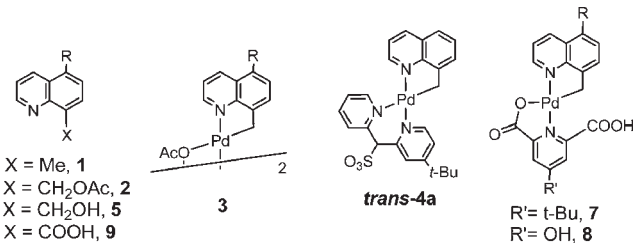
† Electronic supplementary information (ESI) available: Experimental and computational details. CCDC 679231. For ESI and crystallographic data for **7a** in CIF format see DOI: 10.1039/b803156h



Scheme 2 8-Methylquinoline derivatives.

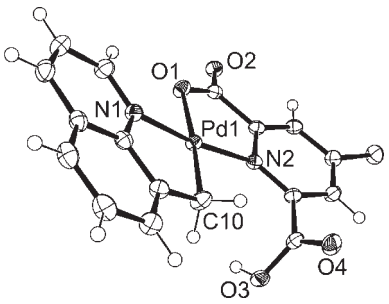


Fig. 1 ORTEP plots (50% probability ellipsoids) for complex **7a** (disordered methyl groups are omitted for clarity). Selected bond lengths (Å) and angles (°): Pd1–C10, 2.022(2); Pd1–N1, 2.003(1); Pd1–N2, 2.085(1); Pd1–O1, 2.132(1); N1–Pd1–N2, 172.51(5), O1–Pd1–C10, 176.45(6).

Fluoro analogue **4d** could also be oxidized with O_2 in AcOH–Ac_2O solution but due to its poorer solubility at ambient temperature a higher temperature of 60 °C was used. Solid **4d** dissolved after 5 h to produce **2d** as the only organic product detected by ^1H and ^{19}F NMR spectroscopy in 98% yield. No oxidation of **3d** could be observed under the same reaction conditions.

Similarly, palladacycles **7** and **8** derived from H_2-*t*-Bu-pda and H_2hpda, respectively (Scheme 2) were prepared in high yield by reacting **3** with 1 equivalent of the appropriate dicarboxylic acid, H_2-*t*-Bu-pda or H_2hpda, in DMF or AcOH. Complexes **7a** and **8a** were isolated in analytically pure form and the former was characterized by X-ray diffraction (Fig. 1).†

As in the case of complexes **4**, oxidation of **7a**, **8a** or **8d** with O_2 in AcOH–Ac_2O system was efficient, but it was less selective. For instance, in the reaction of **8d**, according to the ^{19}F NMR spectrum, after 5 h at 60 °C acetate **2d** formed in 87% yield along with 9% 5-fluoro-8-quinoline carboxylic acid **9d**. Since acetate **2d** was proven to be inert towards O_2 in the presence of 5% $Pd(OAc)_2$–H_2hpda under the conditions employed, we suggest that a Pd-catalyzed aerobic oxidation of alcohol **5d** contributed to the formation of **9d**.[11] Consistent with these observations, as established by volumetric measurements, oxidation of 1.0 mol **7a** at 20 °C required 0.6 mol of O_2 accounting for over-oxidation of a small part of alcohol **5a**. Importantly, the presence of Hg metal in the mixtures did not affect the rates of reaction above suggesting that they were homogeneous.[12]

With the results of aerobic oxidation of **3a** and **3d** in the presence of Li(*t*-Bu-dpms) and H_2hpda in hand, we tested the ability of the derived Pd^{II} complexes, **6** and Pd(hpda)(DMF),[13] to catalyze aerobic oxidation of free amines **1a**–**1i** (Table 1).

Heating **1a** with 5 equivalents of Ac_2O, 5 mol% **6** under ambient pressure of O_2 in AcOH solution at 80 °C for 24 h led to the formation of **2a** (4.5% by NMR, 24 h; Table 1, entry 1). A control experiment with $Pd(OAc)_2$ in the absence of Li(*t*-Bu-dpms) showed an only slightly lower yield of **2a**, 2.5%. The result observed in the presence of **6** is consistent with its poor ability to cyclopalladate HQ as established in a separate experiment.†

The use of Pd–pda complexes proved more effective. Pd^{II}(hpda)(DMF) dissolved in AcOH containing 5 equivalents of **1a** at room temperature produced, in the course of few hours, a palladacyclic product **8a**.

Importantly, catalytic oxidation of free 8-methylquinoline **1a** in the presence of 5 mol% of Pd(hpda)(DMF) at 80 °C was efficient (79%, entry 2). When the Pd(hpda) complex was prepared *in situ* from H_2hpda and $Pd(OAc)_2$ (entry 3), or $Pd(acac)_2$ (entry 4), virtually indistinguishable results were observed. Similar results were obtained with H_2-*t*-Bu-pda as a ligand (entry 5). Finally, the use of less lipophilic H_2pda resulted in a slightly lower yield of **2a** (66%, entry 6).

Oxidation of other quinolines **1b**–**1i** was performed in a $Pd(acac)_2$–H_2hpda system (Table 1, entries 7–14). Acetoxylation of 5,8-dimethylquinoline **1b** (entry 7) was regiospecific; no trace of a 5-acetoxymethyl derivative was detected by NMR spectroscopy. The electron-releasing MeO group (entry 8), halogens (entries 9–12), electron-withdrawing NO_2 group (entries 13–14) are all tolerated. Corresponding acetates **2** were obtained in moderate to high yield.

Along with acetates **2**, formation of poorly soluble Pd^{II} bis(8-quinolinecarboxylate)s was detected at the end of all reactions. As a result of catalyst degradation the reaction rates slowed and conversion of HQ could not be increased after 24 h.[14] In the case of fluorinated quinoline **1d** the yield of acid **9d** was 7%, according to the ^{19}F NMR spectrum. Importantly, catalytic oxidation of 2-*p*-tolylpyridine or pinacolone oxime,† substrates that form palladacycles as a result of C(sp^2)–H or non-activated C(sp^3)–H bond cleavage, respectively, was not successful. Though palladation of 2-*p*-tolylpyridine with Pd(hdpa)(DMF) in AcOH was facile, the product of its oxidation, 2-(2′-acetoxy-*p*-tolyl)pyridine was detected in low

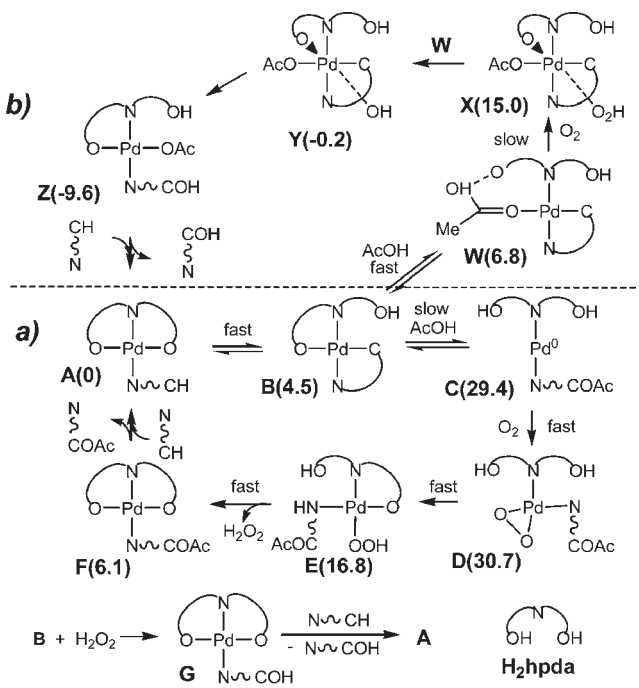
Table 1 Oxidation of **1** with O_2 in AcOH solution in the presence of 5 equivalents of Ac_2O and 5 mol% Pd^{II}–L (80 °C, 24 h) (NMR yields)

Entry	R	L	Pd source	**2**[a] (%)	Conversion of **1** (%)
1	H	*t*-Bu-dpms	$Pd(OAc)_2$	4.5 (2.5)	7.0
2	H	H_2hpda[b]	Pd(hpda)(DMF)	79 (2.5)	85
3	H	H_2hpda	$Pd(OAc)_2$	72 (2.5)	81
4	H	H_2hpda	$Pd(acac)_2$	78 (2.5)	85
5	H	H_2-*t*-Bu-pda	$Pd(acac)_2$	74 (2.5)	81
6	H	H_2pda	$Pd(OAc)_2$	66 (2.5)	75
7	Me	H_2hpda	$Pd(acac)_2$	73 (3)	82
8	OMe	H_2hpda	$Pd(acac)_2$	57 (3)	70
9	I	H_2hpda	$Pd(acac)_2$	48 (2.5)	70
10	Br	H_2hpda	$Pd(acac)_2$	79 (1)	89
11	Cl	H_2hpda	$Pd(acac)_2$	73 (1)	80
12	F	H_2hpda	$Pd(acac)_2$	63 (1.5)	69
13	NO_2	H_2hpda	$Pd(acac)_2$	70 (3.5)	80
14	6-NO_2	H_2hpda	$Pd(acac)_2$	53 (3.5)	60

[a] Yield determined in the absence of L is given in parentheses. [b] Pd(hpda)(DMF) was used as a catalyst.

5% yield only when the temperature of the reaction mixture was raised to 110 °C. Pinacolone oxime did not undergo CH activation with Pd(hdpa)(DMF). As in the case of stoichiometric oxidation, no Pd black was detected in either of these experiments; an additive of Hg metal in the mixtures did not affect the yields of the catalytic reactions. Hence, the reported catalytic aerobic CH functionalization is homogeneous and is currently limited to substrates with benzylic C–H bonds.[15]

Two plausible mechanisms of Pd(hpda)-catalyzed oxidation of HQ with O_2, involving Pd^0/Pd^{II} (Scheme 3a) or Pd^{II}/Pd^{IV} couple (Scheme 3b) were analyzed.[16] DFT calculations were used to estimate the thermodynamic accessibility of presumed key intermediates. According to the mechanism given in Scheme 3a, quinoline complex **A**[13] undergoes fast cyclometallation to give intermediate **B**, which was confirmed in this work. The slowest reaction step might be subsequent nucleophilic attack of acetic acid at the benzylic carbon in **B** leading to postulated Pd^0 transient **C**, which is consistent with the observed poor reactivity of arylpalladium intermediates. Very low steady-state concentration of **C** may be responsible for the lack of accumulation of palladium black in the reaction mixtures and for the remarkable tolerance of $C(sp^2)$–I and $C(sp^2)$–Br groups present in some substrates. An H_2hpda-enabled reaction of **C** with O_2 leading to a stable dichelate **F** *via* a Pd^{II} peroxo complex **D**[4a,c] and a hydroperoxo intermediate **E** might be the driving force for the CH functionalization reaction that does not occur under an inert gas atmosphere. Dichelate **F** liberates an acetoxy-functionalized quinoline ligand **2** and forms **A**. Finally, H_2O_2 formed in a reaction of **E** is responsible for the oxidation of **B** leading to an alcohol **5** which was established in separate experiments.† A Pd-mediated aerobic oxidation of **5** can lead to an acid **9**.[11]



Scheme 3 Two plausible mechanisms for the reaction in eqn (2).

An alternative oxidation mechanism in Scheme 3b involving Pd^{II}/Pd^{IV} couple is similar to that suggested for reaction of $(dpms)Pt^{II}(OH)Alk$ with O_2.[6] Reductive elimination of an alcohol **5** or an acetate **2** (not shown in Scheme 3b) from Pd^{IV} intermediate **Y** is responsible for the formation of these major reaction products. Though transient Pd^{IV} complexes **X** and **Y** are surprisingly low-energy, transformation of **W** to **X** might be a substrate dependent high-barrier reaction. More extensive computational study is required to theoretically support or rule out the viability of this Pd^{II}/Pd^{IV} couple mediated mechanism.

In summary, we have developed a simple homogeneous system that allows facile selective N-heteroatom directed organopalladium mediated aerobic benzylic CH acetoxylation of 8-methylquinolines. A detailed mechanistic study and work on other applications of the catalytic system developed are underway.

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