

## Well-defined alkylpalladium complexes with pyridine-carboxylate ligands as catalysts for the aerobic oxidation of alcohols†‡

Cristóbal Melero,<sup>a</sup> Oleg N. Shishilov,<sup>b</sup> Eleuterio Álvarez,<sup>a</sup> Pilar Palma<sup>\*a</sup> and Juan Cámpora<sup>\*a</sup>

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Neophylpalladium complexes of the type  $[\text{Pd}(\text{CH}_2\text{CMe}_2\text{Ph})(\text{N}-\text{O})(\text{L})]$ , where N–O is picolinate or a related bidentate, monoanionic ligand (6-methylpyridine-2-carboxylate, quinoline-2-carboxylate, 2-pyridylacetate or pyridine-2-sulfonate) and L is pyridine or a pyridine derivative, efficiently catalyze the oxidation of a range of aliphatic, benzylic and allylic alcohols with oxygen, without requiring any additives. A versatile method is described which allows the synthesis of the above-mentioned complexes with a minimum synthetic effort from readily available materials. Comparison of the rates of oxidation of 1-phenylethanol with different catalysts reveals the influence of the structure of the bidentate N–O chelate and the monodentate ligand L on the catalytic performance of these complexes.

## Introduction

Oxidation of alcohols is one of the most important synthetic operations both in the organic chemistry laboratory and in the chemical industry.<sup>1</sup> Although classic oxidation reactions can be very efficient and selective, they often involve the use of stoichiometric reagents and halogenated solvents, resulting in the generation of large amounts of waste. The urgent need for more sustainable chemical processes has prompted the development of mild and selective oxidation methods based on the use of green reagents and solvents.<sup>2</sup> In this context, direct use of  $\text{O}_2$  as an oxidizing reagent is a very desirable feature for modern synthetic methodologies.<sup>3,4</sup> Therefore, new catalysts for aerobic oxidation of alcohols have received much attention in recent years.<sup>5</sup>

The ability of palladium compounds to oxidize organic compounds has been known for a long time.<sup>6</sup> In such reactions, palladium is reduced to palladium metal. In order to render such reactions catalytic they have to be coupled with a redox process that restores the metal to the divalent state.<sup>7</sup> Reduced palladium does not react directly with oxygen, but the discovery that Pd can be reoxidized with copper(II) chloride led to the development of one of the prime industrial applications of homogeneous catalysis, the Wacker process for the synthesis of acetaldehyde from ethylene.<sup>8</sup> In this process, Pd(0) is oxidized by Cu(II) to Pd(II),

and the resulting Cu(I) is brought back to Cu(II) by reaction with  $\text{O}_2$ . The aerobic oxidation chemistry developed in the Wacker process is an early example of what later came to be considered as green chemistry, but the elimination of toxic and highly corrosive copper salts would increase its efficiency and render palladium-catalyzed aerobic oxidations a more attractive tool in organic synthesis.<sup>5</sup> Stabilization of simple palladium catalysts such as palladium acetate with suitable ligands prevents the aggregation of Pd(0) into metal particles (palladium black) and enables direct re-oxidation of the reduced catalyst with oxygen, removing the need for redox co-catalysts.<sup>9</sup> In the late 1990s, Larock<sup>10</sup> discovered that, in the coordinating solvent dmsO and in the presence of a base ( $\text{Na}_2\text{CO}_3$ ), palladium acetate catalyzes the aerobic oxidation of allyl and benzyl alcohols. Shortly after, Uemura reported a new catalyst generated from palladium acetate, pyridine and molecular sieves.<sup>11</sup> Sigman developed a further example of a “modified palladium acetate” catalyst containing triethylamine, which oxidizes alcohols at the room temperature.<sup>12</sup>

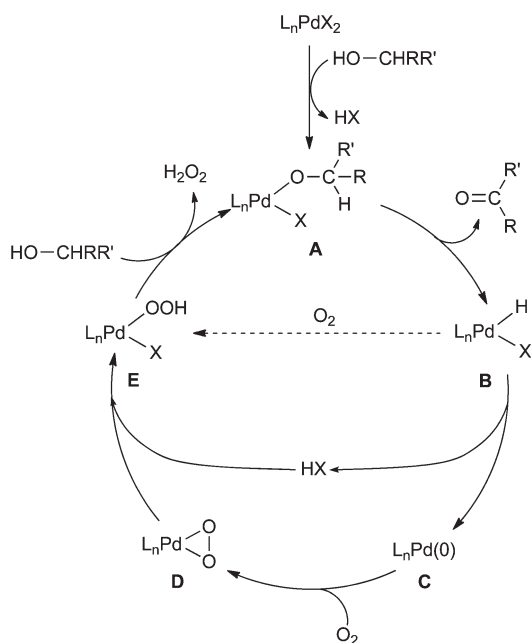
Palladium acetate catalysts modified with weak ligands such as dmsO or monodentate nitrogen bases are in fact equilibrium mixtures of species differing in the number of ligands attached to the metal. In addition, these systems require additives such as an external source of acetate (e.g.,  $\text{NaOAc}$ ,  $\text{NBu}_4\text{OAc}$ ), bases or molecular sieves. Therefore, careful optimization of the catalyst composition is required to obtain its maximum efficiency.<sup>13</sup> In 2000, independent reports by Bortolo<sup>14a</sup> and Sheldon<sup>14b</sup> showed that palladium acetate complexes with strongly binding phenanthroline-type ligands are very active catalysts for alcohol oxidation. The well-defined nature of the palladium-phenanthroline moiety is more amenable to systematic chemical modification, allowing rational optimization of the catalyst efficiency.<sup>15</sup> After this seminal discovery, a number of well-defined palladium catalysts have been discovered, for instance, chiral complexes with the bidentate nitrogen ligand (–)-sparteine, developed

<sup>a</sup>Instituto de Investigaciones Químicas, CSIC – Universidad de Sevilla. c/Americo Vespucio, 49. 41092, Sevilla, Spain. E-mail: ppalma@iiq.csic.es, campora@iiq.csic.es; Fax: +34 95460565; Tel: +34 954489555

<sup>b</sup>Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences (RAS), Leninsky Prospekt, 31, Moscow 119991, Russian Federation

†Dedicated to a good friend, Prof. David J. Cole-Hamilton on the occasion of his retirement, in warm recognition of his exceptional contribution to the field of homogeneous catalysis.

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Scheme 1

simultaneously by the Sigman<sup>16</sup> and Stoltz<sup>17</sup> groups. These catalysts selectively discriminate between alcohol enantiomers, and therefore perform the kinetic resolution of racemic mixtures. Sigman has also developed efficient catalysts containing non-dissociable *N*-heterocyclic ligands.<sup>12b,18</sup> Other well-defined systems based on cyclopalladated complexes<sup>19</sup> or pincer ligands<sup>20</sup> have also been reported. Very recently, Waymouth described new catalysts incorporating fluorinated phenanthrolines that are particularly resistant to severe oxidative conditions,<sup>21</sup> albeit their productivity is modest. In spite of the rapid progress of this field, the structural diversity of well-defined palladium oxidation catalysts is still rather limited because not many suitable ligands are known that also withstand the aggressive action of oxygen.

The mechanism of aerobic alcohol oxidation with palladium catalysts has been actively investigated.<sup>13,18,22–25</sup> Although some important details of the mechanism may change from one system to other, a number of essential features, outlined in Scheme 1, have been recognized. One of the key intermediates is the alkoxide complex **A**. This species is initially formed when the catalyst precursor (*e.g.*, an acetate complex) enters into the catalytic cycle. Intermediate **A** is unstable and undergoes  $\beta$ -hydrogen elimination, resulting in the formation of the oxidized product, an aldehyde or a ketone, and a hydride species, **B**. The next steps in the catalytic cycle eventually result in the transfer of the hydrogen atoms arising from alcohol oxidation to an O<sub>2</sub> molecule. This process may take place along two different pathways. In its classic version, the mechanism involves elimination of HX (usually acetic acid) from hydride **B**, with concomitant reduction of palladium to Pd(0) as intermediate **C**. This complex **C** reacts then with O<sub>2</sub> forming a palladium peroxide, **D**, which is subsequently attacked by the free acid, affording a Pd(II) hydroperoxide, **E**.<sup>26</sup> More recently, it has been suggested that in certain cases hydride **B** may not decompose, but instead it reacts

directly with O<sub>2</sub> affording the same hydroperoxide **E** without actually involving Pd(0) intermediates (dotted arrow).<sup>27</sup> Both pathways are supported by experimental and computational data, and any of them could prevail depending on the system considered.<sup>28</sup> Whatever the exact mechanism is, alkoxide **A** is brought back into the cycle when the hydroperoxide **E** undergoes protic exchange with the alcohol, releasing H<sub>2</sub>O<sub>2</sub>. Hydrogen peroxide can be recovered under specifically designed conditions,<sup>14a</sup> but more often it is disproportionated into water and oxygen by the catalase action of palladium complexes.<sup>29</sup> Therefore water is the only byproduct generated in the catalytic cycle, which contributes to increase its atom efficiency.

The catalytic cycle described above is a helpful guide to the rational design of new catalysts because it assigns a role to each of their components. To begin with, a base is essential in order to generate the palladium alkoxo intermediate. Some systems require an exogenous basic additive, such as Na<sub>2</sub>CO<sub>3</sub> in the Larock system,<sup>10</sup> or an excess of the same nitrogen base used as a ligand, as in the case of the (–)-sparteine system developed by Sigman and Stoltz.<sup>24b,30</sup> Oberhauser has recently shown that dicationic [PdL<sub>4</sub>]<sup>2+</sup> complexes (L = pyridine, 4-ethylpyridine) are efficient catalysts for the selective oxidation of diols in the presence of potassium carbonate.<sup>31</sup> In some other cases, acetate or other ligands can act as internal bases. It is now widely accepted that carboxylate ligands, present in most alcohol oxidation catalysts, play a double role as internal bases, assisting the deprotonation of the alcohol, and, more importantly, transferring the hydride generated in the alkoxide decomposition to the peroxide intermediate (**B** to **E** steps in Scheme 1).<sup>28b</sup> Another important feature for this catalytic process is the ability of intermediate **A** to generate a coordination vacancy in *cis* to the alkoxide ligand, in order to facilitate  $\beta$ -hydrogen elimination.<sup>13,24,32</sup> This is not strictly necessary, as palladium alkoxides are in general so prone to  $\beta$ -hydrogen elimination that this takes place even if 4-coordination is enforced by pincer-type ligands.<sup>33</sup> However, the presence of one or more readily dissociable ligands is an important feature of most Pd oxidation catalysts and probably contributes to accelerate this step. Finally, the presence of one or more reasonably good stabilizing ligands is mandatory to prevent the aggregation of reduced Pd species into a catalytically inactive bulk metal. Prominent examples of successful catalyst designs incorporating these three elements (internal base, labile co-ligands, and at least one strongly stabilizing ligand) are the carbene–carboxylate complexes introduced by Sigman,<sup>17,34</sup> and dimeric phenanthroline derivatives bridged by carboxylate or hydroxide ligands, described by Waymouth.<sup>21,35</sup>

As a further step in the rational design of palladium catalysts for the aerobic oxidation of alcohols, we decided to integrate the three above-mentioned key features required for catalytic activity into a single ligand. We reasoned that a bidentate ligand incorporating a heterocyclic donor unit and an anionic carboxylate fragment could stabilize the palladium centre throughout the different stages of the catalytic cycle, and at the same time behave similarly to acetate, playing the role of an internal base. Such a ligand leaves room for both the alkoxide group and a free coordination position in *cis* to the latter, creating the adequate environment for  $\beta$ -hydrogen elimination. Many simple heterocyclic molecules fulfil this design and, importantly, are stable towards oxygen, for example, pyridine-2-carboxylic acid

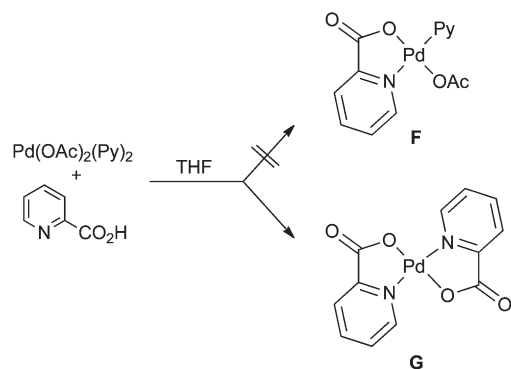
(picolinic acid) acid and its derivatives. A wide range of catalyst structures could be built from these molecules.

At the outset of this work, Muldoon reported that highly active oxidation catalysts can be generated when anionic N–O ligands, for example 2-heteroarylcarboxylic or 2-heteroarylsulfonic acids, are combined with palladium acetate, tetrabutylammonium acetate.<sup>36</sup> It was suggested that anionic carboxylate complexes  $[\text{Pd}(\text{N}-\text{O})(\text{OAc})_2]^-$  are responsible for the catalytic activity, although no evidence was provided to support this proposal. A number of well-defined palladium complexes with 2-pyridinecarboxylate and related ligands have been reported in the literature. In most cases, these are bis-ligand derivatives,  $[\text{Pd}(\text{N}-\text{O})_2]$ ,<sup>37</sup> or hybrid bis-chelate complexes<sup>38</sup> of the type  $[\text{Pd}(\text{N}-\text{O})(\text{L}-\text{L})]^+$  that, having no open coordination sites, are not expected to be catalytically active. However, several complexes with the general structure  $[\text{Pd}(\text{N}-\text{O})(\text{X})(\text{L})]$ , where X is an anionic ligand and L is a neutral donor, have been described, most notoriously a series of organometallic derivatives (X = Me) synthesized by Cavell.<sup>39</sup> Organopalladium compounds containing the very stable  $\eta^3$ -allylpalladium template have been recently used for the generation of active alcohol oxidation catalysts containing pyridine<sup>31</sup> or *N*-heterocyclic carbene ligands.<sup>40</sup> In our search for well-defined palladium complexes that could be used as precursors for this type of catalysts, we decided to prepare and investigate complexes of the type  $[\text{Pd}(\text{X})(\text{N}-\text{O})(\text{L})]$ , with N–O = picolinate and other related bidentate anionic ligands. In this paper we show that neophylpalladium derivatives (X = neophyl, 2-methyl-2-phenylpropyl) are well-defined precursors for aerobic alcohol oxidation catalysts. We describe a very convenient and versatile route for the synthesis for these complexes as well as their catalytic performance in the aerobic oxidation of alcohols.

## Results and discussion

### Synthesis of catalyst precursors

In a first attempt to prepare suitable catalyst precursors, we marked our target on a hybrid palladium carboxylate complex **F**, containing acetate, picolinate and pyridine ligands (Scheme 2). We hoped that this catalyst design would provide all essential elements required for catalytic activity without the need of any further component, anticipating that the chelate would enhance stability as compared to other carboxylate-based catalysts. In

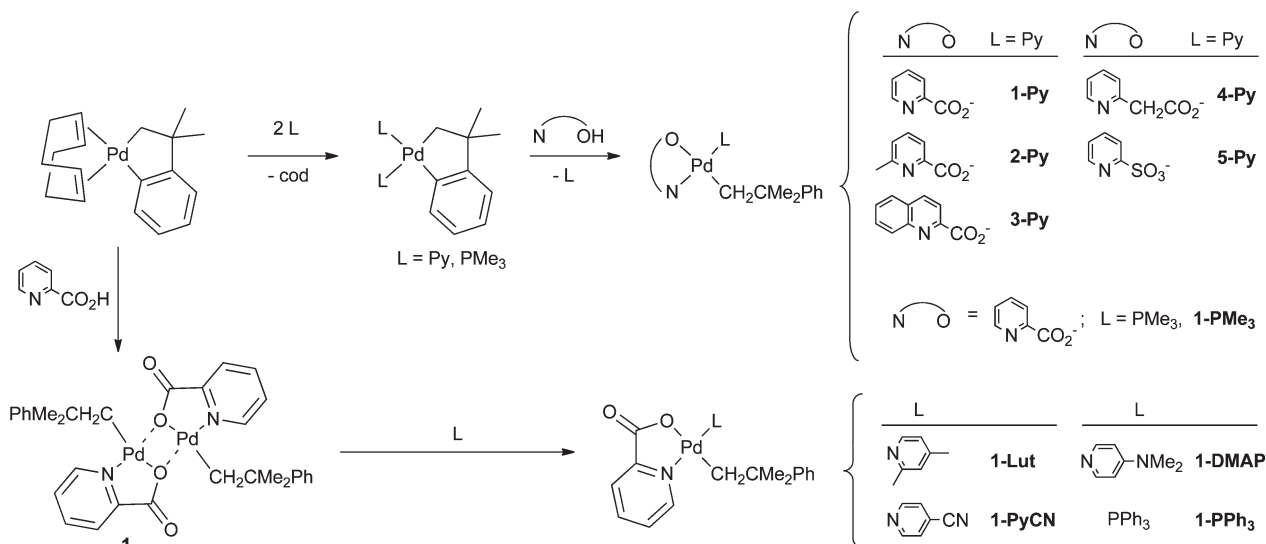


Scheme 2

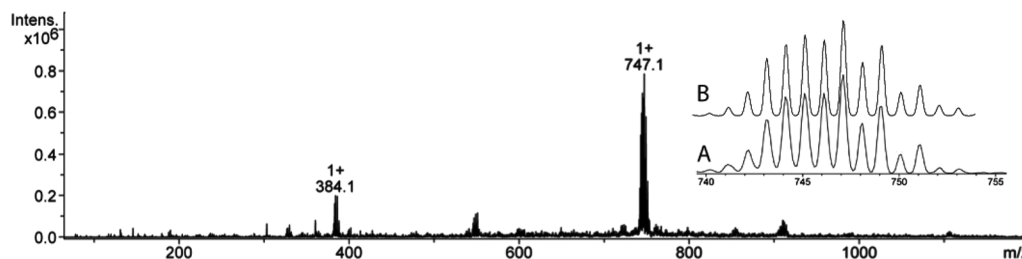
order to prepare such hybrid carboxylates, we reacted stoichiometric amounts of the palladium acetate pyridine adduct  $[\text{Pd}(\text{OAc})_2\text{Py}_2]$ <sup>12a</sup> and picolinic acid. However, this reaction does not afford the desired mixed carboxylate product, but a precipitate of the insoluble  $\text{Pd}(\text{N}-\text{O})_2$  complex **G**,<sup>37</sup> irrespective of the ligand ratio used. Compound **G** proved catalytically inactive.

As mentioned above, Cavell has reported a series of methylpalladium picolinate complexes  $[\text{PdMe}(\text{N}-\text{O})\text{L}]$ ,<sup>39</sup> with L = phosphine, phosphite or nitrogen bases, including a pyridine derivative.<sup>39a</sup> Therefore, we turned to palladium alkyls to prepare stable catalyst precursors containing a single picolinate ligand and a dissociable pyridine ligand. These compounds are stable in solution and their synthesis is straightforward, but requires the use of toxic reagents such as thallium(i) picolinate or dimethyl sulfide and the thermally sensitive complex  $[(\text{PdMe}(\text{SMe}_2)(\mu-\text{I}))_2]$ . Previously, we showed that the readily available palladium metallacycle  $[\text{PdCH}_2\text{CMe}_2\text{-o-C}_6\text{H}_4(\text{cod})]$ <sup>41</sup> is a versatile starting material for the synthesis of a wide range of  $\sigma$ -alkylpalladium complexes containing different types of ligands. Thus, we decided to use this compound for the synthesis of alkyl complexes containing picolinate and related anionic N–O ligands (Scheme 3). The cyclooctadiene ligand is easily displaced from the metallacyclic complex by monodentate ligands, *e.g.*, pyridine or phosphines, to afford the corresponding bis(ligand) derivatives. Picolinic acid selectively cleaves the Pd–aryl bond of the bis-pyridine or bis- $\text{PMe}_3$  metallacycles, and this is followed by loss of one monodentate unit to afford the *N,O* chelated complexes **1-Py** and **1-PMe<sub>3</sub>**, respectively, in essentially quantitative yield. This is a very general reaction, which allows the systematic synthesis of related derivatives varying the steric and electronic environment of the metal centre. Thus, complexes **2-Py** and **3-Py**, containing the bulkier 6-methylpyridine-2-carboxylate and quinoline-2-carboxylate ligands, respectively, were prepared analogously from the corresponding carboxylic acids. The size of the chelate ring was increased in the 2-pyridylacetate derivative **4-Py**, and the reaction of the pyridine-containing metallacycle with 2-pyridinesulfonic acid afforded complex **5-Py**, containing a less basic sulfonate group instead of the carboxylate unit.

The lower part of Scheme 3 describes a slight variation of the precedent methodology. Reacting the cyclooctadiene metallacycle with picolinic acid affords the co-ligand free compound **1**, as a greenish-yellow precipitate. This compound reacts rapidly and quantitatively with monodentate ligands (*e.g.*, pyridine derivatives or  $\text{PPh}_3$ ), yielding the corresponding adducts **1-L**. This modification avoids the unproductive use of a second equivalent of the monodentate ligand, and enables the preparation of derivatives of ligands such as 2,4-lutidine that fails to displace cyclooctadiene from  $[\text{PdCH}_2\text{CMe}_2\text{-o-C}_6\text{H}_4(\text{cod})]$ . The low solubility of compound **1** prevented us from growing X-ray quality crystals. This insolubility suggests that the apparent unsaturation of the Pd atom could be compensated with intermolecular interactions, probably by the formation of dimers bridged through the pyridinecarboxylate ligand. This is supported by the electrospray mass spectrum of **1**, which shows a signal cluster showing a base peak with  $m/z = 747$  and the isotopic pattern expected for the composition  $\text{M}_2\cdot\text{Na}^+$  (Fig. 1). The spectrum shows also a small signal centered at  $m/z = 384$ , corresponding to the monomeric species  $\text{M}\cdot\text{Na}^+$ .

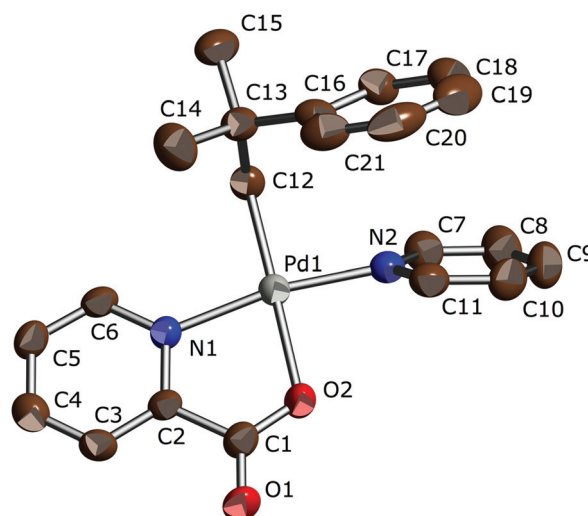


Scheme 3



**Fig. 1** ESI mass spectrum of compound **1** (from methanol). Inset: A, expansion of the signal centered at  $m/z = 747$ ; B, isotopic pattern calculated for the ion  $[M_2+Na]^+$ .

Palladium complexes **1–5** have been characterized by NMR, IR and elemental analysis. Although the non-symmetrical nature of the N–O donor allows for *cis/trans* isomerism, this is only observed for **1-PPh<sub>3</sub>**. The NMR spectra of the latter compound show two sets of signals in a 3 : 2 ratio, *e.g.*, two singlets at  $\delta$  39.0 (major) and 32.6 ppm in its  $^{31}\text{P}\{^1\text{H}\}$  spectrum. However, a single set of signals is observed in the spectra of all other complexes. This is fully consistent with the behaviour of the methyl derivatives described by Cavell, who observed *cis/trans* isomers only for bulky ligands, such as  $\text{PPh}_3$ , while smaller phosphine ligands (*e.g.*  $\text{P}(\text{CH}_2\text{Ph})_3$  or  $\text{PMe}_2\text{Ph}$ ), or pyridine give rise to a single species.<sup>39a</sup> Although the stereochemistry of the complexes cannot be directly deduced from their NMR spectra, it can be safely assumed that the most favourable isomer will have the strongest  $\sigma$  donor ligand, the alkyl group, and the weakest one, the carboxylate or sulfonate functionality, occupying mutually *trans* positions. The stereochemical preference is probably more marked for pyridine than for phosphine ligands, since the contrast between the  $\sigma$ -donor properties of R and L is less pronounced in the latter case. The *trans* arrangement of the alkyl ligand and the carboxylate fragment is confirmed in the X-ray diffraction structure of complex **1-Py** (Fig. 2). Bond lengths and angles are similar to those observed in the structures of phosphine-stabilized methylpalladium pyridine-2-carboxylate complexes,<sup>39b,d</sup> except for the Pd–N1 bond length, which is



**Fig. 2** ORTEP view of the molecular structure of compound **1-Py**. Selected bond distances (Å) and angles (°): Pd1–C12, 2.028(3); Pd1–N1, 2.054(3); Pd1–N2, 2.033(3); Pd1–O2, 2.130(3); N2–Pd1–C12, 91.78(13); N1–Pd1–O2, 80.92(10); N1–Pd1–C12, 98.23(13); N2–Pd1–O2, 89.20(1); O2–C1–C2–N1,  $-4.4(5)$ .

appreciably shorter (2.053(3) Å vs. *ca.* 2.12 Å in the  $\text{PPh}_3$  complexes), due to the lower *trans* influence of pyridine as compared

to phosphine. The aromatic rings of the pyridine and neophyl ligands of **1-Py** are almost aligned and lie at close distance (e.g., N2–C17 = 3.254(5) Å), evidencing an attractive  $\pi$ -stacking interaction, but this has no noticeable effects in other parts of the molecule.

### Catalytic performance

Catalysis experiments were carried out in magnetically stirred vials placed in a steel multireactor. Reaction volumes were limited to *ca.* 1 mL in order to facilitate oxygen diffusion and to minimize any hazards associated with the use of oxygen and organic solvents. Since we were interested in the ability of the heterocycle-carboxylate ligands to provide the essential elements for catalysis, the experiments were carried out in the absence of any additives other than the solvent.

1-Phenylethanol was taken as the reference substrate in order to screen catalysts and reaction conditions (Table 1). Under all the conditions tested, conversion of 1-phenylethanol to acetophenone was very clean with all of the catalysts, and no byproducts were detected by GC with FID or mass detectors. Although the complexes are not active at the room temperature and pressure, they catalyze the reaction at 80–100 °C under oxygen pressures of 3–4 bar. Under these conditions, 1 mol% of the picolinate catalyst **1-Py** quantitatively oxidizes the alcohol within 12 h (entries 1, 15 and 19). Oxygen pressures below 3 bar lead to

lower conversions (entry 20). Although this activity is low in comparison with some of the best catalysts known for alcohol oxidation, such as Sheldon's phenanthroline base catalysts<sup>14b,15a</sup> or Sigman's heterocyclic carbene complex,<sup>18</sup> it represents a clear improvement over palladium acetate catalysts modified with pyridine<sup>11</sup> or triethylamine,<sup>12a</sup> which require >3 mol% palladium catalyst to complete the oxidation of phenylethanol.

Using a solvent such as toluene is important to obtain best results, as only partial conversion is achieved in its absence (67%, entry 24). Interestingly, when the alcohol–catalyst mixture was suspended in water the yield was similar to that under solvent-free conditions (65%, entry 25), but much poorer yields were obtained in dmsO (20%, entry 26), in spite of the good solubility of reagents and products in the latter solvent. Although substrate conversion is not complete for catalyst loads below 1 mol%, catalyst performance improves with dilution in relative terms (entries 1–4). Thus, a 20-fold dilution of the catalyst, from 1% to 0.05%, causes only a 3-fold drop of conversion (from 100% to 32%). This means an increase of the total turnover number (TON) from 100 to 649, the latter figure being comparable with the absolute productivities achieved with phenanthroline-containing catalysts.<sup>15</sup>

Catalyst screening suggests that the parent complex **1-Py** gives rise to the best catalyst for the oxidation of 1-phenylethanol, and that modifications of the structure of the N–O ligand lead to similar or lower yields. For example, a comparison of entries 1, 5 and 6 suggests that the presence of substituents in the proximity of the metal center (a methyl group in complex **2-Py**, or a fused benzo ring in the quinoline-carboxylate derivative **3-Py**) causes a moderate decrease of the catalyst activity. The pyridinylacetate derivative **4-Py** performs similarly to **1-Py** (entry 8), achieving full conversion of the alcohol to ketone. Complex **5-Py**, in which a less basic sulfonate group replaces the acetate fragment, is considerably less active than **1-Py** (entry 9).

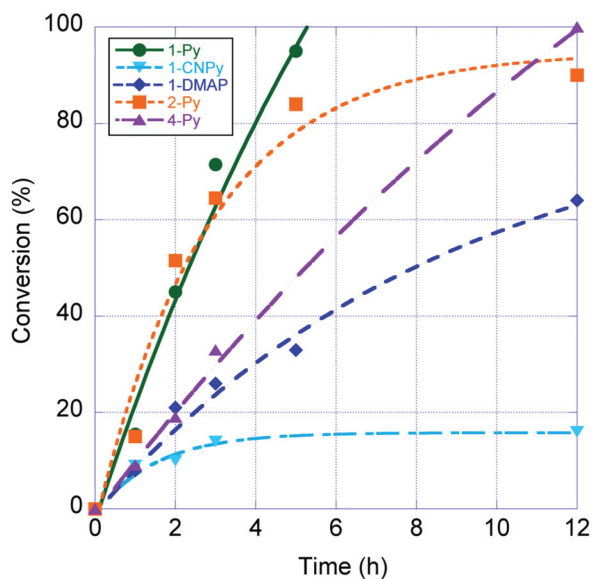
Far from being a mere spectator, the monodentate ligand L is an essential component of the catalyst. In fact, the coligand free dimer **1** is a rather poor catalyst, affording only 19% yield, and phosphine complexes **1-PPh<sub>3</sub>** and **1-PMe<sub>3</sub>** show little or no activity (entries 9 and 10). Pyridine itself is the best choice among the different co-ligands tested. Introduction of either electron-donating or withdrawing groups at position 4 of the pyridine ligand causes loss of activity. This loss much more pronounced for complex **1-CNPy**, containing the electron-poor 4-cyanopyridine ligand, than for the strongly basic 4-dimethylaminopyridine ligand **1-DMAP** (entries 11, 12 and 17). The activity of the latter is similar to that of **1-Lut**, which contains the bulkier ligand 2,4-dimethylpyridine (2,4-lutidine) (entries 14 and 19). Noteworthy, this complex performs slightly better at lower temperature, suggesting that its productivity may be limited by its thermal stability.

In order to gain a more precise understanding of factors that influence the catalysts performance, oxidation of 1-phenylethanol was studied at variable reaction times. Five catalysts, **1-Py**, **1-CNPy**, **1-DMAP**, **2-Py** and **4-Py**, were selected for this study as representative of the different electronic, steric and structural properties. A plot of conversion vs. time is presented in Fig. 3. As can be seen, complex **1-Py** completes the substrate

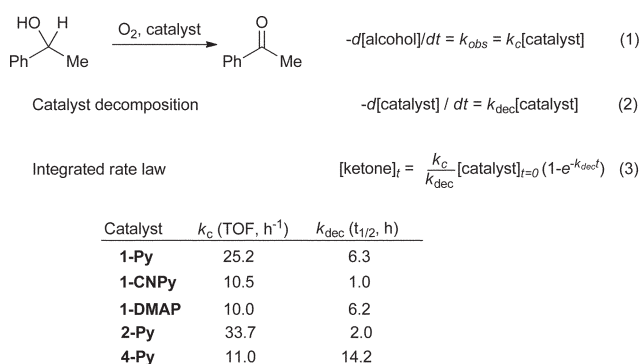
**Table 1** Aerobic oxidation of 1-phenylethanol with complexes **1–5<sup>a</sup>**

Entry	Catalyst	Cat. load (mol%)	Solv.	<i>p</i> O <sub>2</sub> (bar)	<i>T</i> (°C)	Yield
1	<b>1-Py</b>	1	Tol	4	100	100
2	<b>1-Py</b>	0.5	Tol	4	100	100
3	<b>1-Py</b>	0.1	Tol	4	100	41
4	<b>1-Py</b>	0.05	Tol	4	100	32
5	<b>2-Py</b>	1	Tol	4	100	75
6	<b>3-Py</b>	1	Tol	4	100	80
7	<b>4-Py</b>	1	Tol	4	100	100
8	<b>5-Py</b>	1	Tol	4	100	27
9	<b>1-PMe<sub>3</sub></b>	1	Tol	4	100	4
10	<b>1-PPh<sub>3</sub></b>	1	Tol	4	100	13
11	<b>1-CNPy</b>	1	Tol	4	100	16
12	<b>1-DMAP</b>	1	Tol	4	100	64
13	<b>1-Lut</b>	1	Tol	4	100	60
14	<b>1</b>	1	Tol	4	100	19
15	<b>1-Py</b>	1	Tol	4	80	100
16	<b>3-Py</b>	1	Tol	4	80	63
17	<b>1-CNPy</b>	1	Tol	4	80	11
18	<b>1-Lut</b>	1	Tol	4	80	73
19	<b>1-Py</b>	1	Tol	3	80	100
20	<b>1-Py</b>	1	Tol	2	100	65
21	<b>1-Py</b>	1	Tol	4	60	43
22	<b>1-Py</b>	1	Tol	4	60	16
23	<b>1-Py</b>	1	Tol	4	60	9
24	<b>1-Py</b>	1	—	4	100	67
25	<b>1-Py</b>	1	H <sub>2</sub> O	4	100	65
26	<b>1-Py</b>	1	dmsO	4	100	20

<sup>a</sup> Reaction conditions: 1-phenylethanol 60  $\mu$ L (0.45 mmol), toluene (0.5 mL), 12 h.



**Fig. 3** Oxidation of 1-phenylethanol with several catalysts at different conversion times. Lines represent fittings of data to eqn 3 (Scheme 4).



**Scheme 4** Kinetic model for the catalyzed alcohol oxidation, and values of the intrinsic activity and decay rate, expressed as turnover frequency ( $\text{h}^{-1}$ ) and catalyst half-life (h).

conversion in less than 6 h, while the rest of the catalysts only achieve partial conversion at this time. However, the initial rates of **1-Py** and **2-Py** are very similar, the latter decaying in the longer term. This suggests that the methyl group introduced in the structure of **2-Py** increases the catalyst activity, but also facilitates its deactivation. In contrast, although catalyst **4-Py** is substantially less active than **1-Py** or **2-Py**, it is also more stable and fully converts the substrate in the 12 h run. The low activity of **1-CNPy** is basically due to its low stability, becoming completely inactive in the initial stages of the experiment, whilst **1-DMAP** shows a rather good stability but lower activity than **1-Py**.

With **4-Py**, the oxidation rate holds nearly constant even when most of the alcohol has been converted. This indicates that, at least for this catalyst, the reaction rate does not depend on the substrate concentration, *i.e.*, the reaction is zero order on alcohol. This condition is incorporated in the simple kinetic model shown in Scheme 4, which combines zero and first order dependencies on the substrate and the catalyst, respectively, with unimolecular catalyst decay. Fits of the conversion data with the rate equation

deduced for this model (Eq. 3) are reasonably good for all catalysts, and extrapolation of the 0–3 h data is in good agreement with the final conversions after 12 h. Therefore it can be concluded that all catalysts exhibit zero order dependency on the alcohol. The kinetic model allows discriminating the influence of catalyst deactivation ( $k_{\text{dec}}$ ) from the intrinsic catalyst activity ( $k_c$ ). These parameters, intuitively presented as the catalyst half-life time ( $t_{1/2}$ , h) and catalyst turnover frequency (TOF,  $\text{h}^{-1}$ ) (see the table in Scheme 4), provide a more solid ground for the general conclusions deduced from the visual examination of Fig. 3. For example, the lower conversion achieved by **1-DMAP** as compared to **1-Py** is entirely due to differences in the intrinsic activities (TOF) of these catalysts, since their half-lives are virtually identical. In contrast, a poor ligand such as 4-cyanopyridine drastically reduces catalyst stability under the reaction conditions. Unfortunately, it is not possible at this point to judge how this ligand influences the intrinsic activity of the latter, because the estimation of the TOF is probably biased by the short lifetime of this catalyst. The intrinsic activity of pyridine-carboxylate complexes is probably similar to those of modified palladium acetate catalysts, but the overall performance of the former is improved by their much higher stability in solution. In comparison, the activity of the  $\text{Pd}(\text{OAc})_2/\text{Py}$  catalyst falls to negligible levels within 2 h at room temperature.<sup>13a</sup> However, the TOF numbers reported for catalysts containing some specific phenanthroline derivatives<sup>14,15</sup> or *N*-heterocyclic carbene<sup>12b,18</sup> ligands are *ca.* one order of magnitude higher than those reported in Scheme 4.

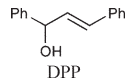
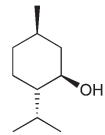
The aerobic oxidation of a range of alcohols was also investigated with catalysts **1-Py**, **1-CNPy**, **1-DMAP**, **2-Py** and **4-Py**. The alcohols studied included benzylic (benzyl alcohol), allylic ((*E*)-1,3-diphenylprop-2-en-1-ol (DPP)), (*E*)-hex-2-en-1-ol (2-hexenol), and aliphatic (1-decanol, menthol) derivatives. Table 2 collects yields and selectivity data obtained under the standard conditions (100 °C, 4 bar  $\text{O}_2$  and 12 h, at 1 mol% catalyst load). Benzyl alcohol and menthol (a secondary aliphatic alcohol with a substantial steric hindrance) produce very good results, comparable to those recorded with 1-phenylethanol both in terms of conversion and selectivity. These alcohols are also similar in their response to different catalysts, with **1-Py** and **4-Py** affording the best results, and **1-CNPy** the worst. Oxidation of other alcohols is not fully selective. GC-MS analysis of the reaction mixtures also shows the formation of small amounts of unidentified products in the case of DPP, and carboxylic acids (*i.e.*, overoxidation products) for the primary alcohols (1-decanol, 2-hexenol). Compared to secondary alcohols, the oxidation of primary alcohols is more difficult, and the selectivity is lower. The least satisfactory results are obtained for 1-decanol, for which 1-decanoic becomes the prevalent product. A similar result was obtained by Sheldon with a water-soluble phenanthroline catalyst, but this author showed that the selectivity for aldehyde is greatly improved if a radical scavenger (TEMPO) is added to the system.<sup>14b</sup> Interestingly, some remarkable specificities are observed in the oxidation of allyl alcohols, suggesting that the catalyst structure can be tuned to improve selectivity. For example, **1-CNPy** is surprisingly active in the oxidation of DPP, whilst **1-Py** consistently afforded low conversions with this alcohol. For both allyl alcohols, DPP and hex-2-en-1-ol, the best results are obtained with catalysts **2-Py** and **4-Py**. The peculiar behaviour of these substrates might be

due to the interaction of  $\alpha,\beta$ -unsaturated carbonyl products with the catalysts, leading to the formation of different active species. Displacement of weak co-ligands such as CNPy could actually contribute to improve the catalyst stability, explaining the unusually high activity observed in the **1-CNPy**–DPP system.

### Mechanism of catalytic oxidation

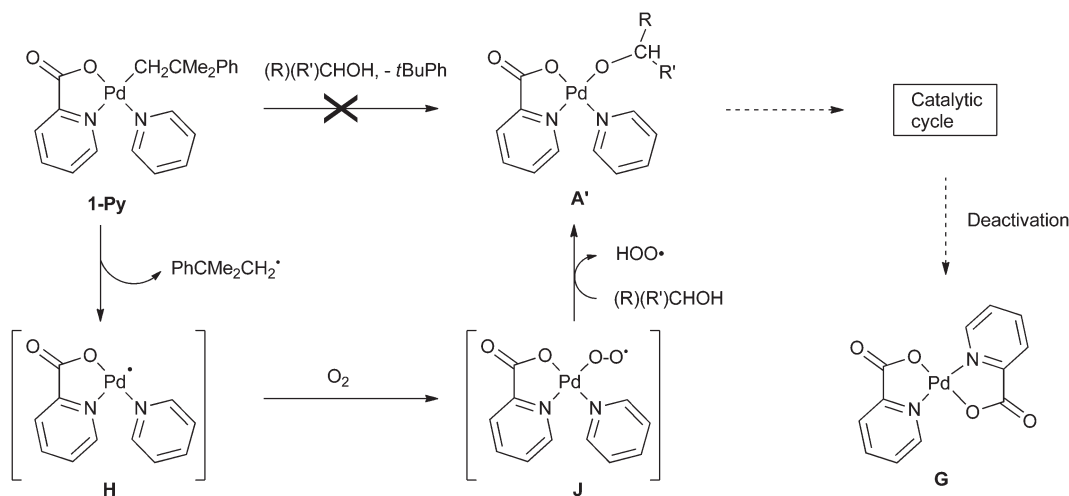
Although it can be reasonably assumed that the general mechanism shown in Scheme 1 also holds for pyridine-carboxylate

**Table 2** Oxidation of benzylic, allylic and aliphatic alcohols<sup>a</sup>

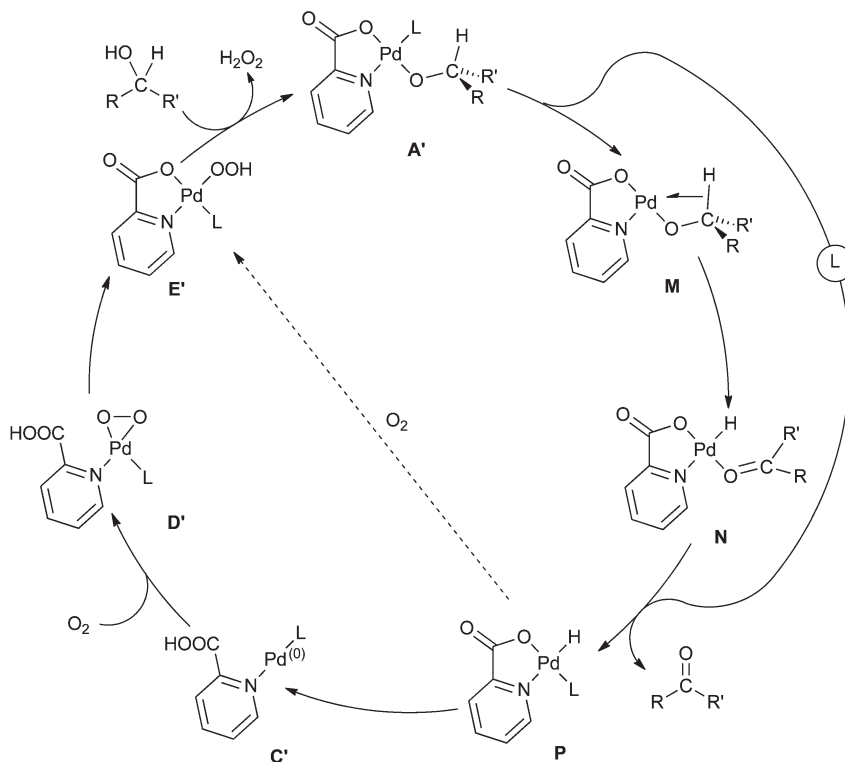
Alcohol	Catalyst	Convers.	Select.
PhCH <sub>2</sub> OH	<b>1-Py</b>	100	100
	<b>1-CNPy</b>	38	84
	<b>1-DMAP</b>	80	100
	<b>2-Py</b>	100	100
	<b>4-Py</b>	100	100
	<b>1-Py</b>	65	95
	<b>1-CNPy</b>	100	85
	<b>1-DMAP</b>	80	95
	<b>2-Py</b>	100	94
	<b>4-Py</b>	100	89
(E)-2-hexen-1-ol	<b>1-Py</b>	98	29
	<b>1-CNPy</b>	46	89
	<b>1-DMAP</b>	58	86
	<b>2-Py</b>	40	93
	<b>4-Py</b>	63	90
	<b>1-Py</b>	100	100
	<b>1-CNPy</b>	11	100
	<b>1-DMAP</b>	39	100
	<b>2-Py</b>	73	99
	<b>4-Py</b>	100	100
1-decanol	<b>1-Py</b>	90	17
	<b>1-CNPy</b>	57	23
	<b>1-DMAP</b>	83	20
	<b>2-Py</b>	92	21
	<b>4-Py</b>	86	22

<sup>a</sup> Catalyst loading 1 mol%. For other conditions see the foot of Table 1.

alkyl complexes, the specific features of this system raise a number of questions. One of them is how the alkyl precursor complex enters into the catalytic cycle. Presumably, the activation of this precursor requires the substitution of the alkyl group by an alkoxide ligand. Two different mechanisms, shown in Scheme 5, can be invoked to explain such a process. One of them involves the protonolysis of the Pd–C bond, leading to palladium alkoxide complex **A'** plus *t*-butylbenzene. Attempts to directly detect well-defined, Pd-containing species in this system by <sup>1</sup>H NMR were unsuccessful (see Experimental), but we observed that **1-Py** decomposes when CH<sub>3</sub>OH or CD<sub>3</sub>OD solutions are heated under an inert atmosphere, producing a dark precipitate. The decomposition process takes several hours to complete at 50 °C, but only a few minutes at 100 °C. Should this reaction involve protolytic cleavage of the Pd–C bond, an equivalent amount of *t*-butylbenzene would be generated. <sup>1</sup>H-NMR and GC-MS analysis of the methanol solutions confirmed the formation of *t*-butylbenzene, but the amount was much lower than expected (*ca.* 15% yield), and significant amounts of isomeric butenylbenzenes were detected as well. These are known products of decay of neophyl radicals,<sup>42</sup> therefore the decomposition of **1-Py** involves Pd–C bond homolysis rather than protolytic cleavage. It is also conceivable that the presence of O<sub>2</sub> could accelerate the transformation of the catalyst precursor. For example, Pd–C homolysis could be favoured if the Pd complex is previously oxidized by electron transfer to oxygen.<sup>43</sup> However, the fraction of **1-Py** that decomposes when a CD<sub>3</sub>OD solution is stirred for 50 min at 50 °C in a reactor under an O<sub>2</sub> atmosphere (4 bar) is very similar to that observed within the same time in NMR tube experiments under an inert atmosphere at the same temperature (*ca.* 50%), suggesting that oxygen has little effect on the reaction rate. GC-MS analysis of this reaction mixture revealed the formation of the same products detected when **1-Py** was heated under an inert atmosphere, together with minor amounts of oxygenated products tentatively identified as aldehydes or alcohols arising from autooxidation of neophyl or rearranged neophyl radicals (*i.e.* O<sub>2</sub> capture by radicals). This suggests that the mechanism of catalyst activation does not involve formal O<sub>2</sub> insertion into the Pd–C bond of the precursor, as this would lead exclusively to oxygenated organic products.<sup>44</sup>



**Scheme 5** Activation and deactivation pathways for catalyst **1-Py**.



**Scheme 6** Proposed mechanism for alcohol oxidation with pyridinecarboxylate catalysts.

Considering these observations, it seems likely that the activation of catalyst precursors involves first Pd–C bond homolysis, followed by the reaction of oxygen with **H**, the resulting Pd(I) species, to afford a Pd superoxide intermediate **J**, or a related peroxide species (Scheme 5, below). Recently, Ozerov and Thomas reported that the reaction of a pincer-based Pd(I) complex with O<sub>2</sub> affords superoxide or peroxide products.<sup>45</sup> The superoxide/peroxide intermediate would react with the alcohol to produce the required alkoxide **A'**. This step could involve proton exchange with the alcohol, releasing a hydroperoxide radical, although other routes to the alkoxide from the hydroperoxide intermediate are conceivable as well.

The appearance of the dark suspensions obtained after heating **1-Py** in the absence of oxygen is very different from the mixtures recovered after catalysis experiments. The latter are brownish suspensions containing a small amount of a pale solid. To identify this solid, a 1-phenylethanol oxidation experiment was carried out with an extra load of the catalyst, and the insoluble white material was separated by centrifugation. This was identified as palladium(II) bispicolinate **G** on the basis of its ESI-MS spectrometry and by comparison of its IR spectrum with that of an authentic sample of the same material (Scheme 5). Therefore, it can be concluded that catalyst deactivation involves a disproportionation process leading to catalytically inactive **G** and undisclosed “naked” palladium species, but not to the formation of palladium black.<sup>46</sup>

The low thermal stability of **1-Py** above 50 °C contrasts with the hours-long lifetimes of the catalyst at 100 °C. This indicates that the processes leading to catalyst activation are fast in comparison to the catalytic cycle itself. Thus, it is reasonable to

suppose that the effects of the ligands on catalytic activity can be interpreted on the basis of the fundamental steps of the previously described cycle (Scheme 1), adapted to the pyridine–carboxylate system as presented in Scheme 6. The zero-order dependency on the alcohol concentration implies that formation of the alkoxide complex **A'**, *i.e.*, the exchange between hydroperoxide **E'** and the free alcohol (*i.e.* **E'** → **A'**) is also fast with regard to the subsequent steps and has no influence on the catalytic rate (*k<sub>c</sub>* in Scheme 4).

One of the main differences between Schemes 1 and 6 is that the anionic ligand termed **X** in the former (usually **X** = acetate) becomes a structural component of the catalyst in the latter, therefore ligand **L** is the only one that can readily leave the coordination sphere of the metal. As mentioned in the Introduction, β-hydrogen elimination can take place in square-planar palladium complexes such as **A'**, but it is greatly enhanced if a coordination vacancy exists in the *cis* position to the alkoxo ligand. Since β-H elimination from the alkoxide is the key step for the alcohol oxidation, the activity of the catalyst will depend on the ability of the monodentate ligand **L** to dissociate from the metal center. The lack of activity of **1-PMe<sub>3</sub>** is probably due in part to the extremely good binding properties of the small and basic **PMe<sub>3</sub>** ligand. On the other hand, the ability to dissociate is not the only important property of **L**, otherwise base-free complex **1** would exhibit the highest catalytic activity when, in fact, it is a rather poor catalyst. Although **PPh<sub>3</sub>** is at the same time relatively labile and a good stabilizing ligand, complex **1-PPh<sub>3</sub>** has nearly the same activity as **1**, probably because **PPh<sub>3</sub>** is readily oxidized by O<sub>2</sub> under an oxygen atmosphere and this renders the catalyst essentially ligand-free. Very likely, the

stability of the catalytic system requires the presence of a reasonably good monodentate ligand L. Pyridines are similar to  $\text{PPh}_3$  in their good combination of leaving and stabilizing properties, but, in addition, they are resistant to oxygen. In fact, the  $k_c$  and  $k_{\text{dec}}$  data for different pyridines containing electron donating and withdrawing groups can be rationalized in terms of the ability to dissociate and at the same time stabilize the catalyst. For example, the low stability of the catalyst generated from **1-CNPy** is doubtless due to the decreased stabilizing capacity of the electron-poor ligand 4-cyanopyridine. Although the lability of this ligand should lead to a higher catalytic activity, the short catalyst life prevented an accurate measurement of  $k_c$ . On the other hand, the higher stability of catalyst **1-DMAP** is partially offset by its lower intrinsic activity, presumably due to the difficulty of the strongly basic ligand 4-dimethylaminopyridine to dissociate. Having properties intermediate between those of CNPy and DMAP, the parent pyridine ligand has better balance between lability and stabilizing capabilities, and this is probably the reason why **1-Py** gives rise to the most efficient catalyst.

A second aspect of Scheme 6 worthy of some comment is the *cis/trans* isomerism of the intermediates and its relationship with the geometric requirements of some elemental steps in the catalytic cycle. It can be foreseen that the favoured stereochemistry of **A'** is probably the same as for **1-Py**, for identical reasons. Hence, **A'** has been represented with the stronger donor, the alkoxide, placed in *trans* with regard to the weakest one, carboxylate. This configuration helps dissociation of L from **A'** because pyridine exerts a stronger *trans* effect than the carboxylate group. However,  $\beta$ -hydrogen elimination from **M** leads (once ligand L is recaptured) to hydride **P** with the hydride and pyridine fragments occupying mutually *trans* positions. This configuration is significantly higher in energy than the opposite one but, interestingly, it is the correct one for reductive O–H coupling. It could be argued that this geometrical coincidence would be meaningless if the mechanism turns out to involve direct oxygenation of the hydride **P** to hydroperoxide **E'** (dotted arrow in the scheme). However, the high energy of intermediate **P** would also contribute to the efficiency of the catalytic cycle by decreasing the energy barrier for the reaction of the hydride with oxygen. Note that no matter what the mechanism of oxygenation is, intramolecular proton transfer in the peroxide **D'** or direct reaction of **P** with  $\text{O}_2$ , the hydroperoxide intermediate **E'** is always formed in a configuration that is opposite to that of **A'** (i.e., with the carboxylate fragment and the pyridine ligand in *cis*). Thus, the last step in the cycle involves *cis/trans* isomerization in addition to the hydrogen peroxide–alcohol exchange.

The structure of the N–O chelating ligand has also a noticeable influence on the intrinsic activity and the decay rate of the catalysts. Comparison of the activities of **1-Py** and the related complex **2-Py** in Table 1 suggests that both complexes perform similarly. However, experiments at different reaction times show that the latter is somewhat more active, though the difference is compensated by a faster decay rate. This is strongly reminiscent of the boosting effect of methyl substituents on Sheldon's Pd-phenanthroline catalysts,<sup>15a</sup> and the facile oxidation of these substituents to afford catalytically inactive carboxylate complexes, discovered by Waymouth.<sup>35</sup> Although we have not investigated the final fate of the catalyst in alcohol oxidations with **2-Py**, oxidation of the methyl substituent to afford a catalytically

inactive pyridine 2,6-dicarboxylate complex also appears as a likely proposal in this particular case. The behaviour of complex **4-Py** can be considered opposite to that of **2-Py**. **4-Py** achieves lower TOF values than **1-Py** or **2-Py**, but the catalyst generated by the former is much more stable. The enhancement of the catalyst stability could be attributed to the higher basicity and better binding properties of the pyridineacetate ligand, as compared to pyridinecarboxylate derivatives. Considering this, it seems likely that the low activity of the pyridinesulfonate derivative **5-Py** could be due to rapid catalyst decay, since the binding capacity of the sulfonate ligand is relatively low.

## Conclusions and outlook

Well-defined palladium complexes of the type  $[\text{Pd}(\text{N}-\text{O})(\text{X})(\text{L})]$ , in which N–O is an anionic chelate, L is a monodentate base and X is a generic anionic ligand, are attractive as catalysts for aerobic alcohol oxidation because they contain within themselves the essential elements to generate catalytic activity. We have developed a versatile synthetic methodology that provides access to a wide variety of neophylpalladium complexes containing different combinations of chelating and monodentate ligands. These complexes promote the aerobic oxidation of benzylic, allylic and aliphatic alcohols by oxygen. Under the catalysis conditions, the Pd–C bond undergoes homolysis, giving rise to the actual active species. A drawback of our catalyst design is the tendency of chelate complexes to disproportionate to give catalytically inactive bis-ligand complexes  $[\text{Pd}(\text{N}-\text{O})_2]$ . This seems to be the main pathway to catalyst deactivation.

The chelating ligand N–O is the key element to ensure the stability of the catalyst, and controls the stereoelectronic properties of the active centre. We also believe that the anionic carboxylate group imparts bifunctional character to this ligand, facilitating the proton transfer from the substrate (alcohol) to the final electron acceptor (oxygen). Co-ligand L has also an important role. It has to be labile enough to generate the coordinative unsaturation required to enable catalytic activity, but at the same time it contributes to the system stability, preventing too rapid catalyst decay. Among the different co-ligands tested, pyridine itself showed the best balance of these two properties.

While the oxidation of benzyl and secondary aliphatic alcohols with pyridine–carboxylate catalysts is highly selective, carboxylic acids were produced in the case of the primary aliphatic and allyl alcohols. This problem is particularly severe for the aliphatic alcohol 1-decanol, which affords decanoic as the main product. However the oxidation of allyl alcohols can be performed with reasonable selectivity (>90%) with catalysts **2-Py** or **4-Py**. The causes for this specificity are still unclear, but could be related to the ability of the oxidation products to interact with the catalytic species.

Neophylpalladium pyridinecarboxylate complexes are modular. Their synthesis is straightforward and can be readily extended to other complexes containing different chelates and monodentate ligands. Since the activity and selectivity of these catalysts are ligand-controlled, it is foreseen that the catalyst design can be tuned to improve activity, selectivity and resistance to the aggressive oxidation conditions, or to generate desirable properties such as compatibility with water or other

environmentally friendly solvents. Another useful property of this system is that the catalysts perform without additives, facilitating product separation and purification. Although this work has focused on general aspects of a new type of palladium oxidation catalysts, such as their synthesis, activity and selectivity, we have been able to come to some relevant mechanistic conclusions. We are continuing this work with new experimental and computational studies in order to gain a better understanding of these mechanisms, and to develop new and improved catalyst designs.

## Experimental section

All procedures and chemical manipulations were carried out under an Ar or N<sub>2</sub> atmosphere using Schlenk or glovebox techniques. Solvents were rigorously dried and degassed before use. Commercially available reagents were used as received. The metallacycle [PdCH<sub>2</sub>CMe<sub>2</sub>-o-C<sub>6</sub>H<sub>4</sub>(cod)] was prepared according to literature methods.<sup>41</sup> NMR spectra were recorded on Bruker DRX 300, 400 and 500 MHz spectrometers. Assignment of signals was assisted by combined one-dimensional and two-dimensional techniques (HSQC, HMBC and COSY). Chemical shifts ( $\delta$ ) are given in ppm. The resonances of the solvent were used as internal standards for <sup>1</sup>H and <sup>13</sup>C spectra, but chemical shifts are reported with respect to TMS. <sup>31</sup>P spectra are referenced to external PPh<sub>3</sub> in C<sub>6</sub>D<sub>6</sub> ( $\delta$  –6 ppm). Abbreviations for multiplicities are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; ddd, doublet of doublet of doublet. Assignments of NMR signals are indicated according to the atom numbering scheme given in Fig. 4. IR spectra were recorded in Nujol mulls on Bruker Vector 22 and Tensor 27 spectrophotometers. GC analyses were carried out in an Agilent 7820A equipped with an FID detector, an automatic liquid sampler and an HP-5 column (30 m, 0.32 mm diam.) using helium gas as a carrier,  $T_{\text{injector}} = 275$  °C;  $T_{\text{detector}} = 300$  °C;  $T_{\text{column}} = 60$  °C (3 min) and 270 °C (15 min). GC-MS analyses were carried out in Thermoquest Trace CG Chromatographs equipped with an AutomassMulti mass spectrometer. ESI-MS spectra were measured with a Bruker Esquire 6000 equipped with electrospray ionization (ESI) with an ion trap mass analyzer. Microanalyses were performed by the Micro-analytical Service of the Instituto de Investigaciones Químicas.

### Reaction of Pd(OAc)<sub>2</sub>(Py)<sub>2</sub> with pyridine-2-carboxylic acid

To a solution of Pd(OAc)<sub>2</sub>(Py)<sub>2</sub> (0.101 g, 0.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added a solution of pyridine-2-carboxylic acid (0.035 g, 0.28 mmol) in the same solvent (3 mL) at room temperature. After 3 h stirring, a white precipitate of palladium(II)

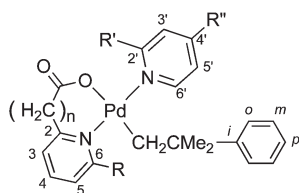


Fig. 4 Atom numbering scheme for complexes 1–5.

bispycolinate, **G**,<sup>37a</sup> was formed. The reaction mixture was centrifuged and the product was washed with hexane (2 × 3 mL) and dried under vacuum. IR (nujol mull, cm<sup>–1</sup>): 3069 w, 2953 st, 1924 st, 2854 st, 1690 st ( $\nu$ (C=O, C=N)), 1607 m ( $\nu$ (C=C) arom), 1573 w, 1494 m, 1462 m, 1332 st ( $\nu$ (O–CO)), 1281 st; 1268 m, 1166 m, 1156 m, 1060 m, 858 m, 818 w, 762 st, 724 w, 719 m. ESI-MS: M·Na<sup>+</sup>,  $m/z$  372.95 calcd for C<sub>12</sub>H<sub>8</sub>N<sub>2</sub>O<sub>4</sub>Pd; found 372.9.

**Synthesis of 1.** A solution of pyridine-2-carboxylic acid (0.037 g, 0.3 mmol) in 10 mL of a 1 : 1 mixture of Et<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> was added to a solution of [PdCH<sub>2</sub>CMe<sub>2</sub>-o-C<sub>6</sub>H<sub>4</sub>(cod)] (0.104 g, 0.3 mmol) in Et<sub>2</sub>O (10 mL) at room temperature. After stirring for 2 h, a green precipitate of complex **1** was formed. The liquid was filtered out and the product was washed with hexane (2 × 5 mL) and Et<sub>2</sub>O (2 × 5 mL) and dried under vacuum. Yield 91%. <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.08–7.95 (m, 2H, CH<sup>3</sup>, CH<sup>2</sup>), 7.95–7.83 (m, 2H, CH<sup>4</sup>, CH<sup>5</sup>), 7.81–7.69 (m, 4H, *o,m*-Ph), 7.37 (m, 1H, *p*-Ph), 1.33 (s, 6H, CMe<sub>2</sub>), 1.26 (s, 2H, CH<sub>2</sub>). IR (KBr, cm<sup>–1</sup>): 3083 w, 3055 w, 2950 st, 2919 st, 1615 st ( $\nu$ (C=O, C=N)), 1591 st ( $\nu$ (C=C) arom), 1494 m, 1472 m, 1445 m, 1398 st ( $\nu$ (O–CO)), 1333 st ( $\nu$ (O–CO)), 1239 w, 1120 w, 1093 m, 1057 m, 1030 m, 849 m, 758 st, 696 st, 555 w, 460 w. ESI-MS (methanol solution): M·Na<sup>+</sup>,  $m/z$  calcd for C<sub>32</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>Pd<sub>2</sub>, 747.1; found 747.1.

**General procedure for the synthesis of 1-Py, 2-Py, 3-Py and 5-Py.** To a solution of [PdCH<sub>2</sub>CMe<sub>2</sub>-o-C<sub>6</sub>H<sub>4</sub>(cod)] (0.104 g, 0.3 mmol) in Et<sub>2</sub>O (20 mL) was added pyridine (0.6 mmol) at –30 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was evaporated under reduce pressure and the solid residue was washed with hexane (2 × 10 mL) and dried under vacuum. This was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and cooled to –50 °C. A solution of 0.3 mmol of the appropriate bidentate ligand in acidic form (picolinic acid, 6-methyl-2-pyridinecarboxylic acid, 2-quinolinecarboxylic acid or 2-pyridinesulfonic acid) was added, and the resulting mixture was stirred at the same temperature. After 30 min stirring, the cooling bath was removed and the mixture was stirred for 2 h at room temperature. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was washed with hexane (2 × 5 mL) and Et<sub>2</sub>O (2 × 5 mL) to afford the corresponding product after drying under vacuum.

**1-Py:** colourless solid, 92% yield. <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  8.55 (d, <sup>3</sup>*J*<sub>HH</sub> = 4.7 Hz, 2H, CH<sup>2</sup>), 8.22 (d, <sup>3</sup>*J*<sub>HH</sub> = 5.6 Hz, 1H, CH<sup>6</sup>), 8.07 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.8, *J*<sub>HH</sub> = 1.5 Hz, 1H, CH<sup>3</sup>), 7.89 (td, <sup>3</sup>*J*<sub>HH</sub> = 7.7, *J*<sub>HH</sub> = 1.5 Hz, 1H, CH<sup>4</sup>), 7.76 (td, <sup>3</sup>*J*<sub>HH</sub> = 7.7, *J*<sub>HH</sub> = 3.8 Hz, 1H, CH<sup>4</sup>), 7.43 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.7 Hz, 2H, *o*-Ph), 7.34 (ddd, <sup>3</sup>*J*<sub>HH</sub> = 7.4, *J*<sub>HH</sub> = 5.5, 1.6 Hz, 1H, CH<sup>5</sup>), 7.28 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.0 Hz, 2H, CH<sup>3</sup>), 6.99 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.7 Hz, 2H, *m*-Ph), 6.90 (t, <sup>3</sup>*J*<sub>HH</sub> = 7.3 Hz, 1H, *p*-Ph), 2.10 (s, 2H, CH<sub>2</sub>), 1.37 (s, 6H, CMe<sub>2</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  169.4 (COOPd), 156.4 (C<sup>2</sup>), 152.4 (2 × CH<sup>2</sup>), 151.2 (*ipso*-Ph), 147.5 (CH<sup>6</sup>), 138.8 (CH<sup>4</sup>), 138.0 (CH<sup>4</sup>), 127.9 (*m*-Ph), 127.1 (CH<sup>3</sup>), 126.4 (CH<sup>5</sup>), 126.2 (*o*-Ph), 125.4 (3C, CH<sup>3</sup> and *p*-Ph), 42.6 (CH<sub>2</sub>), 42.1 (CMe<sub>2</sub>), 31.20 (CMe<sub>2</sub>). IR (nujol mull, cm<sup>–1</sup>): 1637 st ( $\nu$ (C=O, C=N)), 1596 m ( $\nu$ (C=C) arom), 1376 st ( $\nu$ (O–CO)). Elemental analysis: calc. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>Pd: C 57.22, H 5.03, N 6.35; found: C 57.22, H 5.32, N 6.15.

**2-Py:** colourless solid, 90% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  8.26 (d,  $^3J_{\text{HH}} = 5.4$  Hz, 2H,  $\text{CH}^2$ ), 8.01 (d,  $^3J_{\text{HH}} = 7.8$  Hz, 1H,  $\text{CH}^3$ ), 7.74 (t,  $^3J_{\text{HH}} = 7.7$  Hz, 1H,  $\text{CH}^4$ ), 7.61 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H,  $\text{CH}^4$ ), 7.27 (d,  $^3J_{\text{HH}} = 7.2$  Hz, 2H, *o*-Ph), 7.12 (d,  $^3J_{\text{HH}} = 7.7$  Hz, 1H,  $\text{CH}^5$ ), 7.08–6.97 (m, 5H,  $\text{CH}^3$ , *m,p*-Ph), 2.38 (s, 2H,  $\text{CH}_2$ ), 1.51 (s, 3H, R = Me), 1.46 (s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  162.1 (COOPd), 158.1 ( $\text{C}^2$ ), 153.7 ( $\text{CH}^2$ ), 152.4 ( $\text{C}^6$ ), 152.2 (*i*-Ph), 138.7 ( $\text{CH}^4$ ), 137.3 ( $\text{CH}^4$ ), 128.1 (*m*-Ph), 127.6 ( $\text{CH}^5$ ), 126.0 (*o*-Ph), 125.7 ( $\text{CH}^3$ ), 125.1 (*p*-Ph), 123.9 ( $\text{CH}^3$ ), 42.3 ( $\text{CMe}_2$ ), 35.7 ( $\text{CH}_2$ ), 31.1 ( $\text{CMe}_2$ ), 23.1 (R = Me). IR (nujol mull,  $\text{cm}^{-1}$ ): 1643 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1599 m ( $\nu(\text{C}=\text{C})$  arom), 1352 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2\text{Pd}$ : C 58.09, H 5.32, N 6.16; found: C 58.19, H 5.23, N 5.91.

**3-Py:** colourless solid, 93% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  8.40–8.23 (m, 4H, 2  $\text{CH}^{\text{quin}}$  and  $\text{CH}^2$ ), 7.85 (d,  $^3J_{\text{HH}} = 8.2$  Hz, 1H,  $\text{CH}^{\text{quin}}$ ), 7.71 (t,  $^3J_{\text{HH}} = 7.7$  Hz, 1H,  $\text{CH}^4$ ), 7.44 (t,  $^3J_{\text{HH}} = 7.6$  Hz, 1H,  $\text{CH}^{\text{quin}}$ ), 7.26 (m, 2H, *o*-Ph), 7.17–7.05 (m, 3H,  $\text{CH}^{\text{quin}}$  and 2  $\text{CH}^3$ ), 7.04–6.91 (m, 3H, *m,p*-Ph), 6.37 (s, 1H,  $\text{CH}^{\text{quin}}$ ), 2.52 (s, 2H,  $\text{CH}_2$ ), 1.46 (s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  161.1 (COOPd), 153.8 ( $\text{CH}^2$ ), 152.5 (*i*-Ph), 146.0 ( $\text{C}^{\text{quin}}$ ), 139.2 ( $\text{CH}^{\text{quin}}$ ), 138.7 ( $\text{C}^2$ ), 137.6 ( $\text{CH}^4$ ), 130.5 ( $\text{C}^{\text{quin}}$ ), 130.3 ( $\text{CH}^{\text{quin}}$ ), 128.7 ( $\text{CH}^{\text{quin}}$ ), 128.1 (*m*-Ph), 128.0 ( $\text{CH}^{\text{quin}}$ ), 126.6 ( $\text{CH}^{\text{quin}}$ ), 126.0 ( $\text{CH}^3$  and *o*-Ph), 125.1 (*p*-Ph), 122.94 ( $\text{CH}^{\text{quin}}$ ), 42.3 ( $\text{CMe}_2$ ), 36.89 ( $\text{CH}_2$ ), 31.1 ( $\text{CMe}_2$ ). IR (nujol mull,  $\text{cm}^{-1}$ ): 1670 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1601 m ( $\nu(\text{C}=\text{C})$  arom), 1377 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_2\text{Pd}$ : C 61.17, H 4.93, N 5.71; found: C 61.08, H 5.07, N 5.58.

**5-Py:** colourless solid, 89% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  8.55 (s, 2H,  $\text{CH}^2$ ), 8.19 (d,  $^3J_{\text{HH}} = 5.5$  Hz, 1H,  $\text{CH}^6$ ), 8.00–7.87 (m, 2H,  $\text{CH}^4$  and  $\text{CH}^3$ ), 7.79 (t,  $^3J_{\text{HH}} = 7.8$  Hz, 1H,  $\text{CH}^4$ ), 7.44 (d,  $^3J_{\text{HH}} = 7.8$  Hz, 2H, *o*-Ph), 7.39–7.25 (m, 3H,  $\text{CH}^5$ ,  $\text{CH}^3$ ), 7.00 (t,  $^3J_{\text{HH}} = 7.5$  Hz, 2H, *m*-Ph), 6.90 (t,  $^3J_{\text{HH}} = 7.2$  Hz, 1H, *p*-Ph), 2.40 (s, 2H,  $\text{CH}_2$ ), 1.34 (s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  163.0 ( $\text{C}^2$ ), 152.6 ( $\text{CH}^2$ ), 150.1 (*i*-Ph), 148.0 ( $\text{CH}^6$ ), 140.0 ( $\text{CH}^4$ ), 138.5 ( $\text{CH}^4$ ), 128.1 (*m*-Ph), 126.3 (3C,  $\text{CH}^5$ , *o*-Ph), 125.7 (3C, *p*-Ph and  $\text{CH}^3$ ), 123.85 ( $\text{CH}^3$ ), 44.68 ( $\text{CH}_2$ ), 42.29 ( $\text{CMe}_2$ ), 30.7 ( $\text{CMe}_2$ ). IR (nujol mull,  $\text{cm}^{-1}$ ): 1601 m ( $\nu(\text{C}=\text{C})$  arom), 1274–1182 (many strong bands associated with the sulfonyl group ( $\nu(\text{S}=\text{O})$ )). Elemental analysis: calc. for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3\text{PdS}$ : C 50.37, H 4.65, N 5.87, S 6.72; found: C 50.58, H 4.65, N 5.53, S 7.03.

**Synthesis of 4-Py.** To a solution of  $[\text{PdCH}_2\text{CMe}_2\text{-o-C}_6\text{H}_4\text{(cod)}]$  (0.346 g, 1 mmol) in  $\text{Et}_2\text{O}$  (40 mL) was added pyridine (77 mg, 81  $\mu\text{L}$ , 3 mmol) at  $-30^\circ\text{C}$ . The mixture was allowed to warm to room temperature and stirred for 2 h. After evaporating the solvent under reduced pressure, the residue was washed with hexane (2  $\times$  10 mL) and dried under vacuum to afford the pyridine-ligated metallacycle as a white solid. A solution of 2-pyridylacetic acid was prepared by mixing MeOH solutions of NaOMe (0.17 M, 5.9 mL, 1 mmol) and 2-pyridylacetic acid hydrochloride (0.137 g, 1 mmol) and stirring the resulting mixture for 30 min at room temperature. This was added to a solution of the previously prepared pyridine complex in THF (20 mL), stirred at  $-30^\circ\text{C}$ . After 30 min, the mixture was allowed to warm to the room temperature and the stirring was continued for 2 h. The solids were removed by centrifugation

and the solution was concentrated under vacuum to 3–4 mL. Toluene was added (10 mL) and the solution was evaporated to dryness, leaving **4-Py** as a grey solid, which was washed with  $\text{Et}_2\text{O}$  (3  $\times$  20 mL) and dried under vacuum. Yield 88%.  $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 500 MHz)  $\delta$  8.54 (d,  $^3J_{\text{HH}} = 5.7$  Hz, 1H,  $\text{CH}^6$ ), 8.49 (d,  $^3J_{\text{HH}} = 5.5$  Hz, 2H,  $\text{CH}^2$ ), 7.77 (t,  $^3J_{\text{HH}} = 7.7$  Hz, 1H,  $\text{CH}^4$ ), 7.72 (t,  $^3J_{\text{HH}} = 7.7$  Hz, 1H,  $\text{CH}^4$ ), 7.34–7.21 (m, 4H,  $\text{CH}^3$ ,  $\text{CH}^5$ ,  $\text{CH}^3$ ), 7.18 (d,  $^3J_{\text{HH}} = 7.5$  Hz, 2H, *o*-Ph), 6.99–6.87 (m, 3H, *m,p*-Ph), 2.95 (s, 2H,  $\text{CH}_2\text{COOPd}$ ), 2.07 (s, 2H,  $\text{PdCH}_2$ ), 1.14 (s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ , 126 MHz)  $\delta$  171.6 (COOPd), 159.3 ( $\text{C}^2$ ), 152.3 ( $\text{CH}^2$ ), 151.3 (*i*-Ph), 151.0 ( $\text{CH}^6$ ), 138.5 ( $\text{CH}^4$ ), 138.0 ( $\text{CH}^4$ ), 127.9 (*m*-Ph), 125.5 (*o*-Ph), 125.4 ( $\text{CH}^3$ ), 125.3 ( $\text{CH}^3$ ), 125.2 (*p*-Ph), 122.8 ( $\text{CH}^5$ ), 51.4 ( $\text{CH}_2\text{COOPd}$ ), 43.2 ( $\text{PdCH}_2$ ), 42.1 ( $\text{CMe}_2$ ), 31.1 ( $\text{CMe}_2$ ). R (nujol mull,  $\text{cm}^{-1}$ ): 1636 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1598 m ( $\nu(\text{C}=\text{C})$  arom), 1340 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{22}\text{H}_{24}\text{-N}_2\text{O}_2\text{Pd}$ : C 58.09, H 5.32, N 6.16; found: C 58.08, H 5.42, N 6.11.

**Synthesis of 1-PMe<sub>3</sub>.** To a solution of  $[\text{PdCH}_2\text{CMe}_2\text{-o-C}_6\text{H}_4\text{(cod)}]^{41}$  (0.195 g, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was added a solution of pyridine-2-carboxylic acid (0.062 g, 0.5 mmol) at  $-50^\circ\text{C}$  and the reaction mixture was stirred for 30 min. The mixture was allowed to reach room temperature and stirred for 2 h. Then it was filtered and the solvent evaporated under reduced pressure. The residue was washed with hexane (2  $\times$  15 mL) and  $\text{Et}_2\text{O}$  (2  $\times$  15 mL). Yield 60%. **1-PMe<sub>3</sub>** was obtained as yellow solid, in 95% yield:  $^1\text{H}$  NMR (300 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  8.16–8.07 (m, 2H,  $\text{CH}^6$  and  $\text{CH}^2$ ), 7.88 (td,  $^3J_{\text{HH}} = 7.6$ ,  $J_{\text{HH}} = 1.6$  Hz, 1H,  $\text{CH}^4$ ), 7.63 (d,  $^3J_{\text{HH}} = 7.3$  Hz, 2H, *o*-Ph), 7.35 (t,  $^3J_{\text{HH}} = 6.0$  Hz, 1H,  $\text{CH}^5$ ), 7.15 (t,  $^3J_{\text{HH}} = 7.7$  Hz, 2H, *m*-Ph), 7.00 (t,  $^3J_{\text{HH}} = 7.3$  Hz, 1H, *p*-Ph), 1.90 (d,  $^3J_{\text{HP}} = 4.2$  Hz, 2H,  $\text{CH}_2$ ), 1.53 (s, 6H,  $\text{CMe}_2$ ), 1.37 (d,  $^2J_{\text{HP}} = 10.7$  Hz, 9H,  $\text{PMe}_3$ ).  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  170.7 (COOPd), 154.6 ( $\text{C}^2$ ), 152.05 (*i*-Ph), 145.9 ( $\text{CH}^6$ ), 139.0 ( $\text{CH}^4$ ), 128.1 (*m*-Ph), 126.8 (*o*-Ph), 126.7 ( $\text{CH}^3$ ), 126.2 ( $\text{CH}^5$ ), 125.7 (*p*-Ph), 41.84 ( $\text{CMe}_2$ ), 36.19 ( $\text{CH}_2$ ), 32.68 ( $\text{CMe}_2$ ), 15.10 (d,  $^1J_{\text{CP}} = 31.8$  Hz,  $\text{PMe}_3$ ).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  -4.32. IR (nujol mull,  $\text{cm}^{-1}$ ): 1670 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1598 m ( $\nu(\text{C}=\text{C})$  arom), 1352 st ( $\nu(\text{O}-\text{CO})$ ), 958 st ( $\nu(\text{P}-\text{C})$ ). Elemental analysis: calc. for  $\text{C}_{19}\text{H}_{26}\text{NO}_2\text{PPd}$ : C 52.12, H 5.99, N 3.20; found: C 52.16, H 6.18, N 3.29.

**General procedure for the synthesis of 1-Lut, 1-CNPy, 1-DMAP, and 1-PPh<sub>3</sub>.** A solution of pyridine-2-carboxylic acid (0.037 g, 0.3 mmol) in a mixture of  $\text{Et}_2\text{O}$  (5 mL) and  $\text{CH}_2\text{Cl}_2$  (5 mL) was added to a solution of  $[\text{PdCH}_2\text{CMe}_2\text{-o-C}_6\text{H}_4\text{(cod)}]$  (0.104 g, 0.3 mmol) in  $\text{Et}_2\text{O}$  (10 mL) at room temperature. After stirring for 2 h, a green precipitate of **1** was formed. A solution of 0.3 mmol of the corresponding pyridine derivative or  $\text{PPh}_3$  in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added and the resulting mixture was vigorously stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was washed with hexane (2  $\times$  5 mL) and  $\text{Et}_2\text{O}$  (2  $\times$  5 mL) to afford the corresponding pure complex after drying under vacuum.

**1-Lut:** colourless solid, 100% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  8.34 (d,  $^3J_{\text{HH}} = 5.9$  Hz, 1H,  $\text{CH}^6$ ), 8.27 (d,  $^3J_{\text{HH}} = 5.6$  Hz, 1H,  $\text{CH}^6$ ), 8.08 (dd,  $^3J_{\text{HH}} = 7.8$ ,  $J_{\text{HH}} = 1.5$  Hz, 1H,  $\text{CH}^3$ ), 7.90 (td,  $^3J_{\text{HH}} = 7.7$ ,  $J_{\text{HH}} = 1.5$  Hz, 1H,  $\text{CH}^4$ ), 7.41–7.32

(m, 3H,  $\text{CH}^5$  and *o*-Ph), 7.06–6.87 (m, 5H, *m,p*-Ph,  $\text{CH}^{3'}$  and  $\text{CH}^{5'}$ ), 2.89 (s, 3H,  $\text{R}' = \text{Me}$ ), 2.32 (s, 3H,  $\text{R}'' = \text{Me}$ ), 2.12 (br, 1H, PdCHH), 2.09 (br, 1H, PdCHH), 1.36 (br s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  169.6 (COOPd), 160.7 ( $\text{C}^2$ ), 156.2 ( $\text{C}^2$ ), 151.8 ( $\text{CH}^6$ ), 151.0 (*i*-Ph), 149.7 ( $\text{C}^4$ ), 147.3 ( $\text{CH}^6$ ), 138.8 ( $\text{CH}^4$ ), 127.9 (*m*-Ph), 127.1 ( $\text{CH}^3$ ), 126.8 ( $\text{CH}^{3'}$ ), 126.4 ( $\text{CH}^5$ ), 126.1 (*o*-Ph), 125.25 (*p*-Ph), 123.3 ( $\text{CH}^{5'}$ ), 41.9 ( $\text{CMe}_2$ ), 39.4 ( $\text{CH}_2$ ), 31.7 ( $\text{CMe}_2$ ), 26.8 ( $\text{R}' = \text{Me}$ ), 21.0 ( $\text{R}'' = \text{Me}$ ). IR (nujol mull,  $\text{cm}^{-1}$ ): 1638 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1596 m ( $\nu(\text{C}=\text{C})$  arom), 1351 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2\text{Pd}$ : C 58.92, H 5.59, N 5.97; found: C 58.83, H 5.66, N 5.90.

**1-CNPy**: colourless solid, 90% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CH}_2\text{Cl}_2$ ):  $\delta$  8.60 (d,  $^3J_{\text{HH}} = 5.7$  Hz, 2H,  $\text{CH}^2$ ), 8.40 (d,  $^3J_{\text{HH}} = 5.6$  Hz, 1H,  $\text{CH}^6$ ), 8.11 (d,  $^3J_{\text{HH}} = 7.6$  Hz, 1H,  $\text{CH}^3$ ), 7.96 (td,  $^3J_{\text{HH}} = 7.6$ ,  $J = 1.6$  Hz, 1H,  $\text{CH}^4$ ), 7.52–7.38 (m, 3H,  $\text{CH}^5$  and  $\text{CH}^{5'}$ ), 7.33 (m, 2H, *o*-Ph), 7.06–6.84 (m, 3H, *m,p*-Ph), 2.14 (s, 2H,  $\text{CH}_2$ ), 1.42 (s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  169.3 (COOPd), 156.6 ( $\text{C}^2$ ), 153.2 ( $\text{CH}^{2'}$ ), 151.2 (*i*-Ph), 147.5 ( $\text{CH}^6$ ), 139.4 ( $\text{CH}^4$ ), 128.0 (*m*-Ph), 127.5 ( $\text{CH}^3$ ), 127.1 ( $\text{CH}^5$ ), 126.7 ( $\text{CH}^{3'}$ ), 126.2 (*o*-Ph), 125.6 (*p*-Ph), 115.8 (CN), 43.6 (PdCH $_2$ ), 42.2 ( $\text{CMe}_2$ ), 31.2 ( $\text{CMe}_2$ ). IR (nujol mull,  $\text{cm}^{-1}$ ): 2213 w ( $\nu(\text{C}\equiv\text{N})$ ); 1655 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1591 m ( $\nu(\text{C}=\text{C})$  arom), 1342 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2\text{Pd}$ : C 56.72, H 4.54, N 9.02; found: C 56.80, H 4.44, N 9.64.

**1-DMAP**: colourless solid, 93% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  8.17 (d,  $^3J_{\text{HH}} = 7.5$  Hz, 2H,  $\text{CH}^2$ ), 8.09 (d,  $^3J_{\text{HH}} = 5.7$  Hz, 1H,  $\text{CH}^6$ ), 8.03 (d,  $^3J_{\text{HH}} = 7.2$  Hz, 1H,  $\text{CH}^3$ ), 7.84 (td,  $^3J_{\text{HH}} = 7.6$ ,  $J = 1.6$  Hz, 1H,  $\text{CH}^4$ ), 7.53 (d,  $^3J_{\text{HH}} = 7.4$  Hz, 2H, *o*-Ph), 7.25 (t,  $^3J_{\text{HH}} = 7.3$  Hz, 1H,  $\text{CH}^5$ ), 7.06 (t,  $^3J_{\text{HH}} = 7.7$  Hz, 2H, *m*-Ph), 6.93 (t,  $J = 7.3$  Hz, 1H, *p*-Ph), 6.47 (d,  $^3J_{\text{HH}} = 7.4$  Hz, 2H,  $\text{CH}^{3'}$ ), 3.05 (s, 6H,  $\text{NMe}_2$ ), 2.03 (s, 2H,  $\text{CH}_2$ ), 1.35 (s, 6H,  $\text{CMe}_2$ ).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  169.6 (COOPd), 156.31 ( $\text{C}^2$ ), 154.8 ( $\text{C}^4$ ), 151.7 (*i*-Ph), 151.1 ( $\text{CH}^{2'}$ ), 147.4 ( $\text{CH}^6$ ), 138.4 ( $\text{CH}^4$ ), 127.9 (*m*-Ph), 126.9 ( $\text{CH}^3$ ), 126.3 (*o*-Ph), 126.2 ( $\text{CH}^5$ ), 125.3 (*p*-Ph), 107.6 ( $\text{CH}^{3'}$ ), 42.15 ( $\text{CMe}_2$ ), 41.7 (PdCH $_2$ ), 39.5 ( $\text{NMe}_2$ ), 31.26 ( $\text{CMe}_2$ ). IR (nujol mull,  $\text{cm}^{-1}$ ): 1655 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1600 m ( $\nu(\text{C}=\text{C})$  arom), 1344 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2\text{Pd}$ : C 57.09, H 5.62, N 8.68; found: C 56.99, H 5.58, N 8.91.

**1-PPh $_3$** : yellow solid, 94% yield, 1 : 0.7 mixture of *cis/trans* isomers.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  8.33–6.64 (m, 48 H, CH arom), 2.18 (br s, 2H, PdCH $_2$  major isomer), 1.92 (br s, 2H, PdCH $_2$  minor isomer), 1.36 (br s, 6H,  $\text{CMe}_2$ , major isomer), 1.15 (br s, 6H,  $\text{CMe}_2$ , minor isomer).  $^{31}\text{P}$  { $^1\text{H}$ } NMR (121 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  39.0 (major isomer), 32.7 (minor isomer). IR (nujol mull,  $\text{cm}^{-1}$ ): 1657 st ( $\nu(\text{C}=\text{O}, \text{C}=\text{N})$ ), 1597 m ( $\nu(\text{C}=\text{C})$  arom), 1341 st ( $\nu(\text{O}-\text{CO})$ ). Elemental analysis: calc. for  $\text{C}_{34}\text{H}_{32}\text{NO}_2\text{PPd}$ : C 65.44, H 5.17, N 2.24; found: C 65.35, H 5.27, N 2.37.

### General procedure for the catalytic aerobic alcohol reaction

A glass vial (1.5 mL) equipped with a stir bar was charged with the corresponding catalyst (0.0045 mmol), alcohol (0.45 mmol) and solvent (0.5 mL). The vial was placed in a multi-sample screening reactor which was flushed with pure  $\text{O}_2$ . The reactor was charged with  $\text{O}_2$  at the specified pressure and placed in an

oil bath preheated at the working temperature on a magnetic stirrer/heating dish. At the prescribed time the reactor was placed in an ice bath and carefully depressurized. The mixture was filtered through a celite pad and the resulting mixture was analysed by GC, using biphenyl as an internal standard.

### Decomposition of 1-Py

Solutions of **1-Py** (3.44 mg, 7.8  $\mu\text{mol}$ ) containing mesitylene (1.88 mg, 15.6  $\mu\text{mol}$ ) as an internal standard in  $\text{CD}_3\text{OD}$  (0.6 mL) or  $\text{CD}_2\text{Cl}_2$  (0.6 mL) were transferred to NMR tubes capped with J. Young valves and placed in a preheated oil bath at 50  $^\circ\text{C}$  or 100  $^\circ\text{C}$ . The course of the decompositions was monitored by  $^1\text{H}$  NMR.

### Decomposition of 1-Py in the presence of $\text{O}_2$

A solution of **1-Py** (5.2 mg, 11.8  $\mu\text{mol}$ ) in 2.5 mL of  $\text{CD}_3\text{OD}$  transferred containing mesitylene as an internal standard was transferred to a glass Fischer-Porter® reactor. The reactor was vented with  $\text{O}_2$ , pressurized at 4 bar of oxygen and heated at 50  $^\circ\text{C}$  for 50 min in a thermostated oil bath with magnetic stirring. The  $^1\text{H}$  NMR spectrum showed that the amount of **1-Py** remaining was 52% of the original amount.

### Attempted observation of reaction intermediates

A solution of **1-Py** (5 mg, 11.5  $\mu\text{mol}$ ) in a 1 : 1 mixture of isopropanol and toluene was placed in a Fischer-Porter®. The reactor was vented with  $\text{O}_2$ , pressurized at 4 bar of oxygen and heated at 50  $^\circ\text{C}$  in a thermostated oil bath for 60 min with magnetic stirring. After 1 h the volatile compounds were removed under reduced pressure. The solid remaining was dissolved in  $\text{C}_6\text{D}_5\text{Cl}$  and analysed by  $^1\text{H}$  NMR. The spectrum showed a mixture containing the surviving **1-Py** and undisclosed species containing pyridine and picolinate ligands.

### Identification of Pd(II) bispicolinate (G) after catalytic reaction

A Fisher-Porter glass reactor (100 mL) was charged with **1-Py** (18 mg, 41  $\mu\text{mol}$ ), 1-phenylethanol (0.5 mL, 4.1 mmol) and toluene (5 mL). The reactor was vented with  $\text{O}_2$  at atmospheric pressure and then pressurized at 4 bar and placed in a preheated oil bath at 100  $^\circ\text{C}$ . After 12 h stirring, a precipitate was formed. The reaction mixture was centrifuged and the solid was washed with  $\text{Et}_2\text{O}$  ( $2 \times 3$  mL) and dried under reduce pressure. ESI-MS (acetonitrile solution):  $\text{M}^+\text{Na}^+$ ,  $m/z$  372.95 calcd for  $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_4\text{Pd}$ ; found 372.9. The identity of the complex was confirmed by comparison of its IR spectrum with that of an authentic sample prepared according a literature method.<sup>37b</sup>

### X-ray structure analysis for 1-Py

A suitable crystal coated with dry perfluoropolyether was mounted on a glass fibre and fixed in a cold nitrogen stream. Intensity data were collected on a Bruker-Nonius X8Kappa Apex II CCD diffractometer equipped with a graphite monochromator to obtain a  $\lambda(\text{Mo K}\alpha) = 0.71073$  radiation. The data were

reduced by SAINT<sup>47</sup> and corrected for absorption effects by the multi-scan method (SADABS).<sup>48</sup> The structure was solved by direct methods (SIR-2002)<sup>49</sup> and refined against all  $F^2$  data by full-matrix least-squares techniques (SHELXTL-6.12)<sup>50</sup> minimizing  $w[F_0^2 - F_c^2]^2$ . All non-hydrogen atoms were included in calculated positions and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions and allowed to ride on their respective attached carbon atoms with the isotropic temperature factors ( $U_{\text{iso}}$  values) fixed at 1.2 times (1.5 times for the methyl groups) those  $U_{\text{eq}}$  values of the corresponding atoms. **1-Py**:  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2\text{Pd}$ ,  $M = 440.81$ , monoclinic,  $a = 11.3433(13)$  Å,  $b = 14.1759(16)$  Å,  $c = 13.0253(15)$  Å,  $\alpha = 90.00^\circ$ ,  $\beta = 111.398(3)^\circ$ ,  $\gamma = 90.00^\circ$ ,  $V = 1950.1(4)$  Å<sup>3</sup>,  $T = 173(2)$  K, space group,  $P2_1/n$ ,  $Z = 4$ ,  $\mu(\text{MoK}\alpha) = 0.968$  mm<sup>-1</sup>, 18 782 reflections measured, 3394 independent reflections ( $R_{\text{int}} = 0.0570$ ). The final  $R_1$  values were 0.0339 ( $I > 2\sigma(I)$ ). The final  $wR(F^2)$  values were 0.0891 (all data). The goodness of fit on  $F^2$  was 1.010. CCDC reference number 892325 contains the supplementary crystallographic data for this paper.

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