Anionic *N*,*O*-ligated Pd(II) complexes: highly active catalysts for alcohol oxidation[†]

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There is a need to develop effective catalytic methods for alcohol oxidation. Pd(II) complexes have shown great promise as catalysts, however a comparatively small number of ligands have been reported so far. Herein we report the use of commercially available anionic N,O-ligands to produce highly active catalysts.

The oxidation of an alcohol to a carbonyl compound is a fundamentally important reaction, yet it is actually avoided by the pharmaceutical industry.¹ This is because most of the popular methods that are employed on a small laboratory scale are not suitable on a larger scale due to the toxic nature of the reagents and by-products. Therefore there is a need to develop efficient aerobic oxidation catalysts as these would allow oxidation reactions to be carried out in a more sustainable manner. Palladium(II) is well known for its ability to catalyze oxidation reactions, although until recently most homogeneous catalysts required the use of co-catalysts to utilise O_2 as the terminal oxidant.² In the last decade, ligated Pd(II) complexes that can undergo direct O2 coupled turnover without co-catalysts have emerged as a promising class of catalysts for selective oxidation reactions.³ A number of elegant studies have delivered a good understanding of both parts of the catalytic cycle.4,5 Despite the interest in catalytic alcohol oxidation using Pd(II) complexes, the catalysts that have been reported to date are not widely utilised on a larger industrial scale. For this to transpire, catalysts with improved stability and activity need to be developed. Compared to other areas of homogeneous catalysis (e.g. hydrogenation and hydroformylation), a relatively small number of structurally diverse ligands have been reported so far.³ We feel that a greater number of ligands need to be studied if we are to improve catalytic performance and understand the factors that make a good ligand for these reactions. Exploring the use of simple, inexpensive and commercially available ligands seemed a sensible place to begin searching for new ligands. Herein we report the first use of anionic N,O-chelating ligands for Pd(II) catalysed oxidation of alcohols. Although such N,O-ligands are well known for their chelating ability, there are relatively few reports of their use as ligands in catalysis with Pd and Pt.⁶ We decided to focus on the use of bidentate ligands because previous work on phenanthroline type ligands⁵ demonstrated

that bidentate ligands enable catalysts to operate effectively with only one equivalent of ligand. This is an important design criterion, as catalyst performance can be more readily controlled and improved if only one equivalent of ligand is required.

In this preliminary study we have focused on using 2- and 1-octanol as the substrates, because unactivated aliphatic alcohols are less reactive to catalytic oxidation (this applies to heterogeneous/solid catalysts also).⁷ As a result, there is a greater need to discover catalysts that can oxidise such substrates with good rates and selectivity. Table 1 gives the initial turnover frequencies (TOF) for the oxidation of 2-octanol by catalysts consisting of (ligand)Pd(OAc)₂. The screening reactions were carried out using neat substrate as the solvent.[†] Along with the structurally varied N,O-ligands, neocuproine (1) was also studied for comparison. Previously Sheldon and co-workers demonstrated that (1)Pd(OAc)₂ was an excellent catalyst for the oxidation of unactivated alcohols and is probably the most active catalyst that has been reported to date.^{5f} An additional source of acetate is also beneficial to the reaction and in this instance tetrabutylammonium acetate ([NBu₄][OAc]) was utilised. [NBu₄][OAc] was employed due





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to its solubility in organic solvents, moreover it improved the solubility of many of the anionic Pd(II) complexes which in some cases were poorly soluble in even polar organic solvents.[†] Acetate acts as a labile anionic ligand and also a base for alcohol deprotonation.^{4e,5g} Like others we found that a certain minimum concentration of acetate was required for an optimum rate.^{5e} 8% O₂ in N₂ gas mixtures were employed, as the use of *Limiting Oxygen Concentrations* (LOC) in the gas phase would be required in an industrial setting due to safety reasons. Consequently we feel it is valuable to try and develop systems that can operate effectively under such conditions. We confirmed that the conditions employed were not mass transfer limited in O₂.[†]

By examining the initial TOFs shown in Table 1 we are able to observe some of the structural features that are important for efficient catalysis. In most cases, electron withdrawing substituents improve catalyst performance, which is consistent with previous studies on a range of bipyridine ligands.^{5d} In comparing pyridine to quinoline derivatives we can see that the extended aromatic structure improves the TOF, which may be due to the greater π accepting ability of the quinoline ligands.⁸ An interesting feature that was observed, was the difference in TOF between the dicarboxylic pyridine derivatives (13-16), where 2,6-pyridinedicarboxylic acid (16) is significantly more active than the other derivatives. Although it is possible, for this ligand to bind to Pd in a tridentate fashion,^{6g} previous studies have shown that tridentate ligands are inactive for such Pd(II) catalysed alcohol oxidation.^{5c,5h} Therefore the high TOF would indicate that a stable tridentate complex is not formed under the reaction conditions, although hemilabile binding is of course a possibility. When we observed this effect, we had not yet studied all of the ligands in Table 1, and we decided to investigate some quinoline ligands with similar structural features. It was found that 18 and 19 resulted in excellent TOFs, with 19 delivering an impressive initial TOF of 1500 h^{-1} . It is worth considering that at the start of these studies, 16, 18 and 19 are not structures that probably would have been predicted as being excellent ligands. In fact, in the case of 8-hydroxyquinoline-2-sulfonic acid (19) there appears to be few examples of this ligand being used in catalysis.⁹ At present we cannot confirm the exact reasons behind the positive influence of having this second acidic group near the metal. It could be simply electronic or steric effects (e.g. preventing dimer formation or catalyst aggregation). It is also conceivable that having such a group so close to the active site accelerates the reaction, perhaps via hydrogen bonding interactions or proton transfers. The correct explanation will require further more detailed investigations.

After screening the ligands using 2-octanol, we compared ligands 1 and 19 for the oxidation of 1-octanol. Once again we compared the initial TOFs for reactions carried out in neat 1-octanol.[†] It was found that both ligands exhibited a similar nonlinear dependence, with increasing TOFs obtained with decreasing catalyst concentration.¹⁰ For example, for **19** a rate of 5450 h^{-1} was obtained with 2.5 $\times 10^{-7}$ mol of catalyst and 4500 h⁻¹ when 3.4 \times 10⁻⁷ mol of catalyst was employed. However, when comparing rates for 1 and 19 at the same concentrations, it was found that 19 delivered TOFs that are higher by a factor of ca. 1.3. In terms of product selectivity, both ligands were found to be very similar, demonstrating 90-95% selectivity to the aldehyde product. Longer reaction times for both 1 and 19 led to increased levels of over oxidation. As time progressed, 1-octanoic acid became the major product and small quantities of the ester (octyl octanoate) also formed. We believe such Pd(II) complexes could be employed to oxidise larger quantities of alcohol selectively to the aldehvde if a continuous flow system was utilised.

As mentioned, **1** is the most active ligand that has been reported to date, ^{5e,f} but under our screening reaction conditions, a number of the *N*,*O*-ligands delivered higher TOFs. Studies by Sheldon and co-workers found that this catalyst was most active in a DMSO : water (50 : 50 vol%) solvent mixture. ^{5e,f} For that reason we compared **19** to **1** using such conditions,[†] and employing catalyst loadings that would allow us to obtain higher conversion in a reasonable time (Fig. 1).

Fig. 1 shows that when 0.5 mol% catalyst loading was used, **19** could deliver 100% conversion in just 1 h, while **1** plateaued at 67%. Therefore, it appears that under these conditions **19** still has an advantage. The result we obtained with **1** is consistent with what was recently reported by Sheldon and co-workers.^{5h} In that report they described how (**1**)Pd(OAc)₂



Fig. 1 Oxidation of 2-octanol using 0.5 mol% (ligand)Pd(OAc)₂ in DMSO : water (50 : 50 vol%). *General conditions*: 100 °C, 50 bar $O_2 : N_2$ (8 : 92), 5 ml of solvent (DMSO : water solvent (1 : 1)), Na[OAc] (1 × 10⁻⁴ mol) and 2-octanol (0.002 mol).

formed nanoparticles in aqueous solvent mixtures such as DMSO : water at this catalyst loading.^{5h} Under these conditions, it may well be that $(19)Pd(OAc)_2$ does not form nanoparticles as readily compared to $(1)Pd(OAc)_2$.¹¹

Of course it is not generally necessary to achieve full conversion in under 1 hour. We have still to fully determine the optimal conditions for (19)Pd(OAc)₂, but it is worth mentioning that 100% conversion of 2-octanol could also be achieved with lower catalyst loadings (*e.g.* 0.1–0.2 mol%). Obviously extended reaction times were required but they were still very viable (*i.e.* several hours). Preliminary studies also indicate that the catalyst can operate efficiently in a range of organic solvents (*e.g.* toluene and ethyl acetate), and can deliver useful rates at lower temperatures (*e.g.* 60 °C).

In summary, we have shown that a number of N,O-ligands are excellent ligands for Pd(II) catalysed oxidation of challenging aliphatic alcohols. (19)Pd(OAc)₂ compares very favourably to other catalysts that have been reported to date,³ including (1)Pd(OAc)₂ which is seen as one of the yardsticks in the field. An additional advantage of 19 is that it should be more oxidatively stable than 1; as under some reaction conditions, the methyl groups of 1 are oxidised, resulting in an inactive catalyst.^{5g} Future work will examine N,O-ligated complexes in more detail, examining a wider range of substrates for alcohol oxidation, as well as other types of oxidative reactions. Endeavours will be made to better understand the reasons behind some of the observed ligand effects, with the ultimate aim of *designing* improved catalysts for selective oxidations.

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- 11 Visually comparing the solutions after the reactions, there appears to be significant catalyst aggregation in the case of 1, while aggregation is not evident with 19. However, we feel that in order to properly examine and compare the aggregation between the two catalysts, we should carry out a more detailed study in the future. In Sheldon's study,^{5h} TEM was used to examine the nanoparticles, and this involves allowing the solvent to evaporate, before analysis of the particles. We felt that this raises the possibility of nanoparticles forming as the solvent evaporates. Therefore, we intend to investigate this area further using techniques, such as Environmental SEM and XAFS that will allow *in situ* analysis of palladium aggregation.