



Accepted Article

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To be cited as: *Eur. J. Inorg. Chem.* 10.1002/ejic.201700931

Link to VoR: <http://dx.doi.org/10.1002/ejic.201700931>

Cationic Palladium(II) Complexes for Catalytic Wacker-Type Oxidation of Styrenes to Ketones using O₂ as the Sole Oxidant

Hongxin Chai,^{[a][b]} Qun Cao,^[a] Laura M. Dornan,^[a] N. Louise Hughes,^[a] Clare L. Brown,^[a] Peter Nockemann,^[a] Jiarong Li^[b] and Mark J. Muldoon*^[a]

Abstract: A series of new cationic palladium(II) complexes were prepared and studied for their ability to catalyze the Wacker-type oxidation of styrenes to their corresponding acetophenones using O₂ as the sole oxidant. Catalysts are active at room temperature and the study highlights the importance of solvent choice and the need for ligand development in improving catalyst performance.

The oxidation of alkenes to carbonyls is a valuable transformation in synthetic chemistry. Pd(II) catalytic systems are renowned and have a history of commercial application, such as the Wacker process for the oxidation of ethylene, a leading example of industrial catalysis.¹ A modified method using DMF as the solvent, often referred to as the Wacker-Tsuji oxidation, enables the synthesis of methyl ketones from longer chain olefins.² Molecular oxygen is the ideal oxidant, however, the triplet nature of ground state dioxygen³ causes some challenges. Traditionally, Wacker-type palladium chemistry has relied on co-catalysts such as copper salts in order to address the problem that simple palladium salts are not readily re-oxidised by O₂. Copper co-catalysts are not ideal as they act as more than just an electron transfer mediator (ETM), which can cause unwanted products and limit catalyst optimization.⁴ Consequently, studies have looked at alternative oxidants such as hypervalent iodine,⁵ iron(III) sulfate,⁶ potassium bromate,⁷ or peroxides such as *tert*-butyl hydroperoxide (TBHP)⁸ and aqueous H₂O₂.^{8a,9,10} Benzoquinones are often used as stoichiometric oxidants, but can be used catalytically with O₂ as the terminal oxidant, when they are combined with additional ETMs.¹¹ Ideally, the oxidation of Pd(0) to Pd(II) would be carried out directly by O₂, but this is a significant challenge. There are a number of examples,¹² but many of these systems are only suitable for aliphatic alkenes, as oxidising styrenes in a selective manner is challenging, due to the fact that such substrates can undergo a number of unwanted side-reactions.^{10a} Some examples of aerobic systems suitable for styrenes are shown in Figure 1.^{13,14,15} There is a need for more efficient catalysts for these reactions and developing Pd(II) oxidation catalysts is an area in which we are particularly interested.¹⁶ It is evident from other Pd(II) studies, that ancillary ligands lead to improved catalytic performance,¹⁷ but this has not been well-studied for Wacker-type oxidation of styrenes.

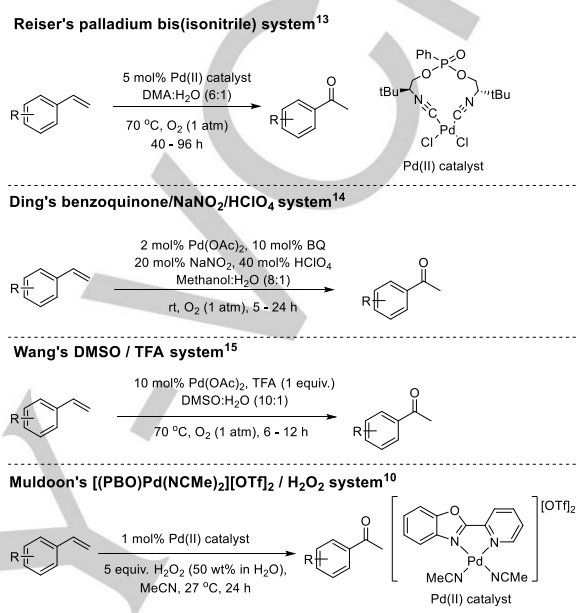


Figure 1. Previous examples of aerobic Pd(II) catalyzed Wacker oxidation of styrenes and our recent PBO based catalyst which uses H₂O₂ as the oxidant.

Indeed, the only reported study which uses a defined molecular complex for these reactions is the example by Reiser and co-workers.¹³ As can be seen in Figure 1, this catalyst is not particularly active; at 70 °C the reactions require 5 mol% loading of the complex and reactions take up to 4 days. In the other aerobic examples shown in Figure 1, the system by Ding and co-workers is more active, but relies on ETMs and a high loading of hazardous perchloric acid.¹⁴ The method by Wang and co-workers exploits DMSO as a coordinating solvent (which can essentially act as a ligand) to enable direct re-oxidation of Pd(0), but catalyst loadings of 10 mol% are required.¹⁵

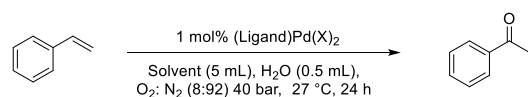
In the case of peroxide mediated Wacker-type oxidation of styrenes, there are more examples of using ancillary ligands. The Sigman group have explored ligand effects for TBHP,^{8c,e,f} and we explored a range of ligands for H₂O₂ based oxidations.^{10a} We found that a cationic complex with the 2-(2-pyridyl)benzoxazole (PBO) ligand delivered good performance for the oxidation of styrenes using aqueous H₂O₂ as the oxidant (Figure 1).¹⁰ As part of those studies we found during control experiments that some acetophenone product was formed when water was added but H₂O₂ was absent. This indicated that the catalyst could possibly be further developed for an aerobic Wacker system.

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In order to optimize the aerobic reaction, we examined a number of conditions and Table 1 highlights that the reaction is dramatically affected by a number of factors. In our previous studies using H₂O₂, we found that PBO was the best ligand for styrenes and that phenanthroline (Phen) type ligands were the best for aliphatic substrates.^{10a} Sheldon and co-workers had utilised Phen based catalysts for aerobic oxidation of aliphatic substrates^{12b,c} so we tested it in these studies, but it can be seen that it was essentially inactive (Entry 2) and did not compare well to PBO. In the H₂O₂ system, we had found that acetonitrile was the optimal solvent for the oxidation of styrenes,¹⁰ but it can be seen that methanol was the best solvent for these aerobic reactions (Entry 8).

Table 1. Optimization studies for aerobic catalysis



| Entry | Ligand | Counterion (X) | Solvent | Conv. ^[a] [%] | Yield ^[a] [%] |
|-------------------|--------|----------------|-------------------|--------------------------|--------------------------|
| 1 | PBO | OTf | MeCN | 29 | 23 |
| 2 | Phen | OTf | MeCN | 12 | 1 |
| 3 | PBO | OTf | Ethyl acetate | 6 | 1 |
| 4 | PBO | OTf | DMA | 5 | 3 |
| 5 | PBO | OTf | DMSO | 6 | 4 |
| 6 | PBO | OTf | <i>t</i> -Butanol | 22 | 17 |
| 7 | PBO | OTf | Ethanol | 60 | 55 |
| 8 | PBO | OTf | Methanol | 77 | 72 |
| 9 | PBO | OAc | Methanol | 15 | 5 |
| 10 | PBO | Cl | Methanol | 7 | <1 |
| 11 ^[b] | PBO | OTf | Methanol | 69 | 66 |
| 12 ^[c] | PBO | OTf | Methanol | 73 | 66 |
| 13 ^[d] | PBO | OTf | Methanol | 55 | 40 |
| 14 ^[e] | PBO | OTf | Methanol | 91 | 84 |

[a] Conversion and yield determined by GC using biphenyl as an internal standard with results an average of two reactions; [b] 4.5 mL methanol, 1 mL H₂O; [c] 5.25 mL methanol, 0.25 mL H₂O. [d] 5.5 mL methanol with no added H₂O; [e] 40 °C

The beneficial effects of alcohols, and in particular methanol, as solvents for Wacker oxidation has been known for some time.¹⁸ As pointed out by leading pharmaceutical companies, methanol is a more desirable solvent than DMA or DMSO;¹⁹ solvents which are commonly used in aerobic Wacker reactions. The choice of counterion is also very important (Entries 8-10) and only cationic complexes (obtained with the triflate counterion in this case) are active under these

conditions. A major aim was to see if the catalyst system could be improved by alteration of the ligand structure, so we prepared and studied an additional 9 cationic catalysts, based around the PBO type ligand structure (Figure 2).

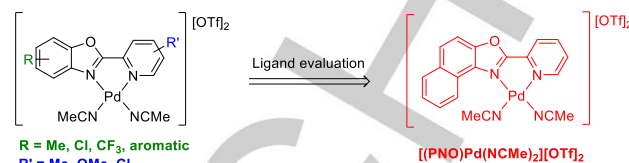


Figure 2. The PNO ligand emerged from catalyst screening studies, using 0.25 mol% catalyst for the oxidation of styrene.

The structures of the complexes and catalyst screening data are shown in the Supporting Information, but the best catalyst employed was the 2-(pyridin-2-yl)naphtho[1,2-*d*]oxazole (PNO) ligand. The PNO ligand can be easily prepared in high yield from inexpensive commercially available starting materials.²⁰ The cationic complex is then generated by complexing the ligand with Pd(OAc)₂, followed by the addition of triflic acid and precipitation of the triflate complex using diethyl ether (Figure 3). Further details of the methods for preparing all of the catalysts are in the Supporting Information.

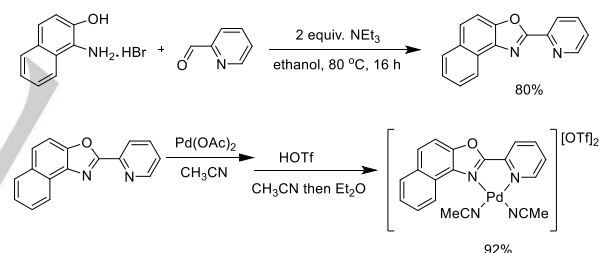


Figure 3. Route for the synthesis of [(PNO)Pd(NCMe)₂][OTf]₂

We were able to obtain a crystal structure of the new [(PNO)Pd(NCMe)₂][OTf]₂ catalyst and this is shown in Figure 4. The palladium exhibits a distorted square planar coordination, with the coordinating acetonitriles slightly out of plane, with angles (N1-Pd1-N3) = 173.7(1)° and (N4-Pd1-N2) = 167.6(1)°. The Pd-N bonds lengths are ranging from 1.989(3) - 2.022(3) Å. In the packing of the crystal structure, there are weak π-π stacking interactions between the aromatic parts of the ligands with a centroid - centroid distance of 3.560 Å.

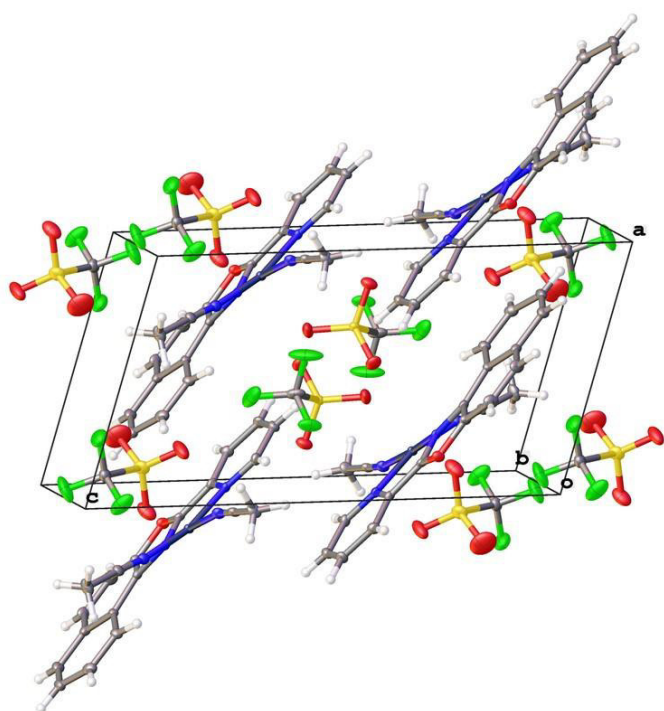


Figure 4. X-Ray crystal structure of the [(PNO)Pd(NCMe)₂][OTf]₂ catalyst

In our screening conditions, we used a low catalyst loading (0.25 mol%) to assess the influence of ligand structure on

activity for the oxidation of styrene (see Supporting Information for details). However, Figure 5 shows the reaction profiles for the oxidation of 3-methyl styrene over 8 hours using 3 mol% illustrating the superior performance of the PNO catalyst over the PBO catalyst.

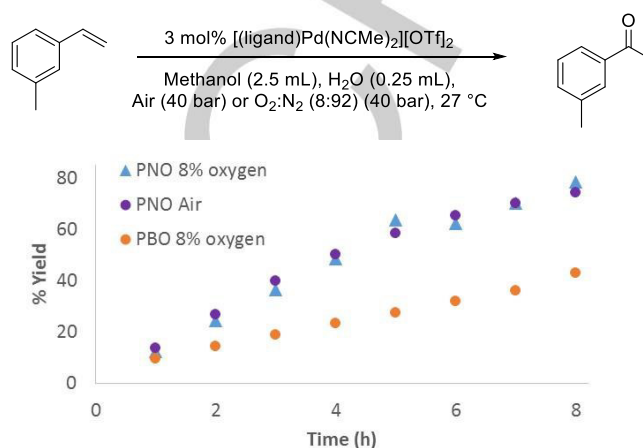
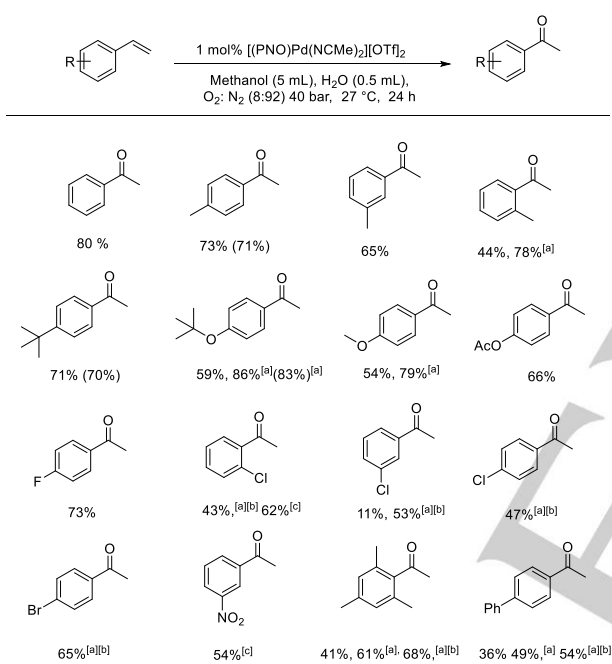


Figure 5. Comparison of PNO and PBO ligands for the oxidation of 3-methyl styrene

For Pd(II) catalyzed oxidations, where O₂ is there to re-oxidize the Pd(0) intermediate, if O₂ is present in excess then reactions tend to be zero-order in [O₂].²¹ If the catalyst concentration is too high then the system can become mass transfer limited in O₂, leading to an increased rate of catalyst decomposition. As can be seen in Figure 5, the PNO catalyst was not influenced by O₂ concentration under these conditions. Table 2 shows the yields for a number of substrates using the PNO catalyst. It is worth highlighting that the majority of reactions in our studies (and all in Table 2) have utilized 8% O₂. Carrying out aerobic reactions has obvious safety implications and one way to address this is to employ limiting oxygen concentrations (LOC). An LOC for methanol of 8.6% O₂ has been measured at 25 °C and 1 atm pressure.²² The temperature and pressure alters the LOC and unfortunately there is a lack of data for conditions that may be employed for catalytic reactions. Recently, in an effort to address this lack of data, Stahl and co-workers measured the LOC of nine common organic solvents at different pressures and temperatures.²³ In the case of methanol, they found the LOC at 100 °C to be 7.6% at 1 bara pressure and 6.9% at 20 bara pressure. Therefore, it is likely that even using our 8% O₂ cylinder (which is under the LOC for many organic solvents), we are outside the LOC under some of the conditions that we have used. On a small scale such as this, it is possible to manage the dangers of using pure oxygen and oxygen rich gas mixtures, and we are well-equipped to do so in our laboratory. Nevertheless, a key point is that we have demonstrated that the catalyst can operate effectively under

dilute O₂ conditions. It is also worth pointing out that although the experiments are conducted at 40 bar gas pressure, the catalyst does not need high pressures to operate. We carried out tests which showed that the catalyst could operate at much lower pressures and not affect the initial rate. Nevertheless, the substrate tests in Table 2 were run over 24 hours in small reactors; under such conditions the reaction would become limited in O₂ as the reaction progressed. Therefore, lower pressures could be used if an open system was employed (with an O₂ ballast vessel), or if a larger reactor with a larger head space was used. Although the use of a continuous flow system would be the most suitable approach to safely use of O₂ on a larger scale.²⁴

Table 2. Oxidation of styrenes by [(PNO)Pd(NCMe)₂][OTf]₂



Yields were determined by GC using biphenyl as an internal standard and results are an average of two experiments. Examples of isolated yields are in parenthesis. [a] 2 mol% catalyst; [b] 60 °C; [c] 5 mol% catalyst, 60 °C.

We would like to understand ligand effects and substrate scope better, however, there is a need to first fully understand of the mechanism. As can be seen in Table 1, we found a dramatic improvement in changing the solvent from acetonitrile to alcohols. Uemura and co-workers reported a system which coupled alcohol oxidation with Wacker oxidation of alkenes.²⁵ They proposed that alkenes were oxidised to ketones by a palladium hydroperoxide intermediate (Pd-OOH). This species was generated from aerobic oxidation of Pd(0) following the Pd(II) catalyzed oxidation of an alcohol. However in this coupled system, methanol was not an effective alcohol which is consistent with the difficulty of oxidising methanol using Pd(II) complexes.²⁶ We believe that in our system, it is most likely that oxypalladation by the alcohol dominates and the reaction proceeds *via* the corresponding dialkyl ketal, before

being hydrolysed to the ketone.^{18, 27, 28, 29} Although the mechanism of Pd(II) catalyzed synthesis of acetals and ketals has been studied, the full mechanism has yet to be elucidated.^{27, 28, 29} We are therefore commencing studies which will help us better understand this catalyst system.

In conclusion, the Wacker oxidation of styrenes to ketones is a difficult reaction and utilizing O₂ for direct catalyst turnover is a real challenge. To date there have not been studies exploring a range of ligands. We have shown that a number of factors are important and greatly effect aerobic catalyst performance. Such studies are important if we are to design the next generation of catalysts with performance suitable for industrial application. Future work will involve kinetic and mechanistic studies in order to gain a better understanding of the key steps, assisting us to design better catalysts in the future.

Acknowledgements For financial support, we thank the China Scholarship Council (No. 201506030041) (H. Chai), the Department for Employment and Learning, Northern Ireland (L. M. Dornan) and the EPSRC (N.L. Hughes). For HR ESI-MS analysis of ligands and palladium complexes we thank Conor McGrann.

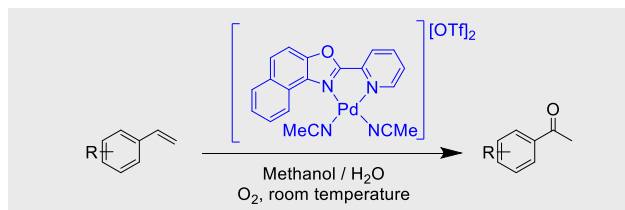
Keywords: oxidation • palladium • ketone • styrene • ketal

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Entry for the Table of Contents

COMMUNICATION



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