Fast and mild palladium(II)-catalyzed 1,4-oxidation of 1,3-dienes *via* activation of molecular oxygen with a designed cobalt(II) porphyrin†

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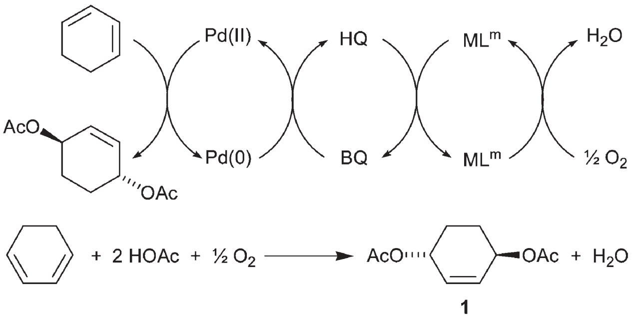
The use of a Co(porphyrin)-amide ligand, 2, in the palladium(II)-catalyzed 1,4-diacetoxylation of conjugated dienes under O_2 results in aerobic oxidation. The catalyst was highly active under O_2, and the 1,4-diacetoxylation reaction could also be performed under air.

Palladium(II)-catalyzed 1,4-oxidation is a useful synthetic method for the oxidation of conjugated dienes.[1] A wide range of nucleophiles can be added across the diene with high regio- and stereoselectivity. A biomimetic aerobic variant of this 1,4-diacetoxylation was developed by the use of a one-pot triple catalytic system, employing a metal macrocyclic complex of a porphyrin, a phthalocyanine or a salene derivative as oxygen activating agents.[2] The overall process results in a net oxidation of the diene by molecular oxygen *via* three consecutive electron transfer steps in a triple catalytic process (Scheme 1).

The efficiency of this process was improved by the use of a bifunctional cobalt[tetrakis(hydroquinone)porphyrin], Co(TQP), which acts as both an oxygen activating agent and electron transfer mediator.[3] Interestingly, with the corresponding hydroquinone-protected Co[*meso*-tetra(2,5-dimethoxyphenyl)porphyrin] Co(TDMPP), the reaction proceeded even in the absence of quinone as an electron transfer mediator, and a mechanism involving a direct electron transfer from palladium to the oxidized metallo macrocycle was proposed.[4] The Co(porphyrin) derivative with a methoxy group only in the 2-position (Co(2-TMMPP)) showed similar activity. A drawback is that in most cases only poor to moderate yields were obtained for these aerobic palladium(II)-catalyzed oxidations and aromatized starting material was found to be the major side-product.

Inspired by recent reports on direct oxygen activation in Pd(II)-catalyzed aerobic oxidation reactions,[5] we decided to further investigate the design of Co(porphyrin) complexes as co-catalysts for efficient palladium-catalyzed aerobic oxidations. We expected that an electron-donating amide ligand attached to the metallo porphyrin would favor coordination to palladium. This would ensure palladium coordination in the near proximity of the oxygen activating metallo porphyrin, probably leading to a more active catalyst and hence improved yields. It is known that amides form strong complexes with Pd(II),[6] and the compatibility of amide ligands with 1,4-oxidation has already been demonstrated in asymmetric 1,4-oxidation reactions.[7] Herein we report the application of the novel complex **2**, in which a cobalt(II) porphyrin functionalized with an amide ligand, is used as an oxygen-activating agent (Fig. 1).

The porphyrin was employed in the aerobic 1,4-diacetoxylation reaction of 1,3-cyclohexadiene with 2.5 mol% $Pd(OAc)_2$ and 2.75 mol% of Co(porphyrin)-amide **2**. The reaction was performed on a 1 mmol scale using a gas buret filled with oxygen to simultaneously measure the oxygen uptake.[8] The rate of the oxygen consumption was initially very fast (6 mL in 20 min; ~50% conversion), but decreased rapidly when a significant amount of palladium black was observed. After full conversion, **1** was isolated in 19% yield (Table 1, entry 1). Addition of LiOAc improved the yield and no precipitation of palladium black was observed (entries 2–5). The reaction is slightly slower with LiOAc and the rate depends on the concentration of LiOAc. Product formation was highest at 0.15 M acetate concentration and **1** was obtained in 46% yield.[9] When this reaction was repeated with a higher catalyst loading (5 mol% $Pd(OAc)_2$) the yield was improved to 68% (entry 6). The relative stereochemistry of the product **1** was also dependent on the acetate concentration. Addition of small



Scheme 1 The triple catalytic system and the overall reaction of the diacetoxylation. ML^m = metal macrocyclic complex.

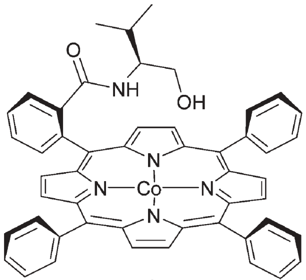


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Fig. 1 Cobalt(II) porphyrin **2**.

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† Electronic supplementary information (ESI) available: synthesis and characterization of complex **2** and detailed experimental data. See http://www.rsc.org/suppdata/cc/b4/b417758d/

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Table 1 Aerobic 1,4-diacetoxylation of 1,3-cyclohexadiene[a]

Entry	Ligand	Oxidant	LiOAc (M)	Yield (%)[b]	*Trans–cis*[c]
1	**2**	O_2	—	19	35 : 65
2	**2**	O_2	0.05	21	49 : 51
3	**2**	O_2	0.15	46	47 : 53
4	**2**	O_2	0.3	37	43 : 57
5	**2**	O_2	0.6	31	35 : 65
6[d]	**2**	O_2	0.15	68	45 : 55
7[e]	**2**	O_2	0.15	32	83 : 17
8	**2**	Air	—	28	29 : 71
9	**2**	Air	0.15	54	40 : 60
10[f]	Co(TPP)	O_2	—	0	—

[a] All reactions were performed on a 1.0 mmol scale. Reaction conditions: the diene was added to a solution of $Pd(OAc)_2$ (2.5 mol%), **2** (2.75 mol%) and LiOAc (if required) in 2 mL HOAc. The reaction mixture was stirred at rt under an oxygen atmosphere for 16 h. [b] Isolated yields of 1,4-diacetoxy-2-cyclohexene. [c] Determined by ^1H NMR. [d] With 5 mol% $Pd(OAc)_2$ and 5.5 mol% **2**. [e] In 2 mL CH_2Cl_2–HOAc 5 : 1. [f] With 2.5 mol% Co(TPP).

amounts of LiOAc (0.05 M) decreased the *cis*-selectivity from 65 to 51%. Addition of more LiOAc led to a recovery of the *cis*-selectivity and at LiOAc concentrations of 0.6 M or higher, **1** was obtained with 65% *cis*-selectivity. The stereoselectivity could be altered by the use of co-solvents and a reaction in CH_2Cl_2–HOAc = 5 : 1 resulted in 83% *trans*-selectivity (entry 7). However, with all solvent mixtures, lower yields were obtained than with neat acetic acid.

From the fast conversion of the diene with complex **2** in the absence of LiOAc, it seems that the oxygen complex of **2** is a very powerful oxidant. However, with a 19% yield of **1**, the reaction resulted mainly in the formation of benzene, a product formed by decomposition of the intermediate (π-allyl)palladium complex. The improved yields in the presence of LiOAc suggest a stabilizing effect of acetate on either the Pd(II) intermediate or the Co(porphyrin). It is believed that the electron transfer takes place directly from the palladium to the oxidized cobalt metal center (Fig. 2). Since the rate of the reaction decreases at higher concentrations of LiOAc, it seems likely that acetate coordinates to the cobalt metal center in the porphyrin and thus competes with coordination of oxygen. Less cobalt-bonded oxygen would then result in a slower reaction. UV–vis spectroscopy titrations in acetic acid revealed the binding of acetate to the (Co)porphyrin **2** complex with corresponding binding constants of $K_1 = 2.2 \times 10^3\ M^{-1}$ and $K_2 = 1.0 \times 10^4\ M^{-1}$. These results confirm that coordination of acetate to cobalt indeed takes place. Noteworthy is that the addition of acetate has a stabilizing effect on the cobalt(II) porphyrin, as demonstrated by the improved yields in the presence of acetate.[9] The previously reported aerobic reactions using Co(TDMPP) and Co(2-TMMPP) were run in the absence of LiOAc and under oxygen. Concluding from our results with complex **2** as presented here, we believe that decomposition of the active complexes in those reactions can be one of the explanations for the lower yields. The absence of an extra amide ligand attached to the porphyrin for the coordination to Pd(II) can also have an effect on the yield.

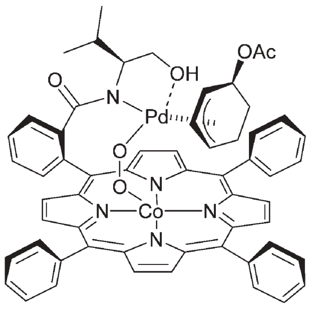

Fig. 2

The high activity of the Co(porphyrin)-amide complex under oxygen encouraged us to run the 1,4-oxidation reaction under air. Surprisingly, in the absence of LiOAc, **1** was obtained in higher yield (28%) than in the reaction performed under oxygen (entry 8). The change in color of the solution during the reaction (from dark red to dark green) and precipitation of palladium black shows that also under these conditions the complex is not completely stable. The addition of LiOAc (0.15 M) had a beneficial effect on the reaction, and **1** could be isolated in 54% (entry 9). The reaction under air is thus higher yielding than the reaction under molecular oxygen and with the same catalyst load, and we showed for the first time that the 1,4-oxidation reaction can effectively be run under air.

The rates of the reactions with Co(porphyrin) **2** with different concentrations of LiOAc are shown in Fig. 3. A comparison of the rates with **2** with the rate of the corresponding reaction employing 2.5 mol% Co(TPP) and 10 mol% hydroquinone showed that the reaction catalyzed by ligand **2** in the presence of acetate concentrations up to 0.6 M was considerably faster than the Co(TPP)–quinone system. The intramolecular electron transfer from palladium to the oxidized metal-macrocycle is therefore more efficient than in the intermolecular electron transfer *via* *p*-benzoquinone. Moreover, a control experiment with Co(TPP) but without *p*-benzoquinone gave no product, which shows that coordination of the porphyrin to palladium is essential for the oxidation reaction (entry 10).

We also studied the effect of the chiral center in complex **2** on the asymmetric induction in the 1,4-oxidation reaction. Unfortunately, under the present reaction conditions there was essentially no asymmetric induction.

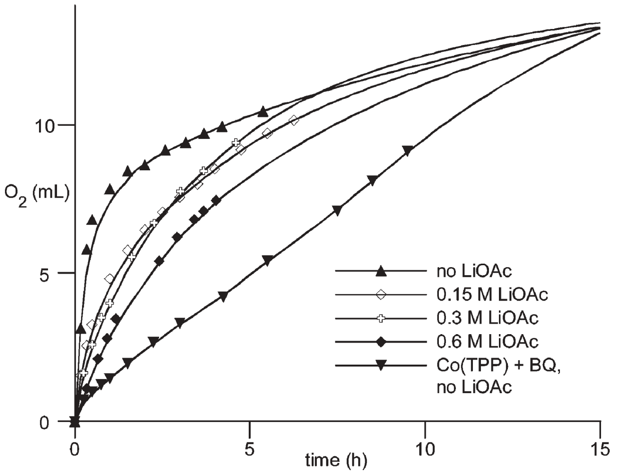

Fig. 3 Plot of the oxygen uptake against time in the aerobic 1,4-oxidation of 1 mmol of 1,3-cyclohexadiene.

In conclusion, we have shown that aerobic 1,4-diacetoxylation reactions can be run under an oxygen atmosphere as well as under air using complex **2**. The diacetate was obtained in yields up to 68% at ambient temperature.

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8 The oxygen consumption gives an indication of the progress of the reaction: 12 mL O_2 corresponds to the conversion of 1 mmol of diene.

9 After completion of the reaction the (Co)porphyrin-amide **2** could be recovered.