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LETTER

# Oxidation of 3,5-di-*tert*-butylcatechol and 2-aminophenol by molecular oxygen catalyzed by an organocatalyst†

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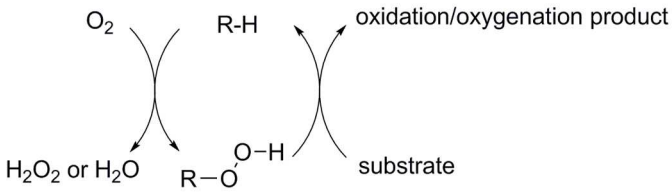
**1,3,2-Oxazaphospholes are able to catalyze the oxidation of 3,5-di-*tert*-butylcatechol with $^3O_2$ to the corresponding *o*-quinone and 2-aminophenol to 2-aminophenoxazine-3-one in methanol. In both cases an overall third order reaction rate equation and a new type of biomimetic organocatalyst for oxidation reactions was found. A one electron transfer of the phenolate, which is formed through deprotonation of substrates by the catalyst, to dioxygen seems to be rate-determining.**

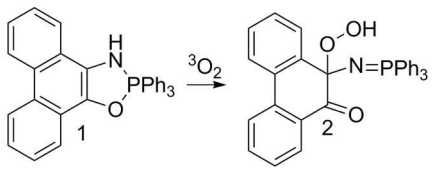
Oxidation reactions are widely applied in organic synthesis and in chemical industry. Triplet dioxygen would be an economically and environmentally[1] successful candidate as primary oxidant, however spin restriction[2] and thermodynamic[3] burden lower its reactivity and so its use in oxidation/oxygenation reactions is rather limited. Unfortunately, not just triplet dioxygen but also hydroperoxides (even $H_2O_2$) are sluggish oxidants[4] and they need activation either with the help of metalloenzymes (metal complexes)[5] or organic compounds. Much work has been carried out for the activation of $^3O_2$ or $H_2O_2$ by metal complexes, mainly of copper,[6] iron,[7] and other metals.[8] Some organic co-factors and their mimics are also able to form hydroperoxides,[9] which oxidize various organic compounds. We were interested to find organic compounds, which react with $^3O_2$ to hydroperoxides, just mimicking organic co-factors, and these can oxidize several organic compounds either in a two or in a four electron oxidation as shown in Scheme 1.

Recently we found that 1,3,2-oxazaphospholes under ambient condition pick up molecular oxygen and form hydroperoxides (Eqn. 1), which can transfer oxygen to triphenylphosphine forming the oxide.[10] The peroxide formed is not stable at room temperature. Iodometric titration of the oxygenated solutions resulted in a peroxide content in the range of 10-30%.[11] This reminds one to



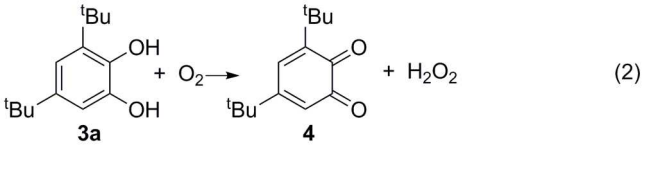

**Scheme 1** General scheme for hydroperoxide formation and oxidation/oxygenation with $O_2$.

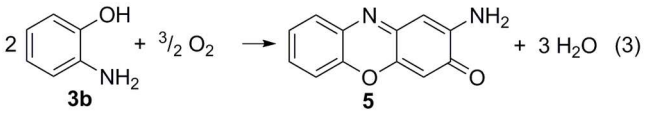
flavin models in which *N,N,N*-3,5,10-trialkylated flavins in its reaction with $^3O_2$ flavin hydroperoxides were observed.[12] Pterins[13] or even deprotonated uric acid[14] form also hydroperoxides with $^3O_2$. Since former studies of the reaction of 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ$^5$-oxazaphosphole (**1**) with triplet dioxygen evidenced that methanol is the best-suited solvent. The reaction time for the oxygenation of the catalyst (**1**) was below 5 min and an unstable hydroperoxide **2** (Eqn. 1) was formed under ambient conditions.[10]




(1)

As a continuation of our work on studies of models of organic cofactors in oxidation reactions we studied the reactions of some phenolic compounds, namely 3,5-di-*tert*-butylcatechol (**3a**) and *o*-aminophenol (**3b**), which are isoelectronic, with triplet dioxygen catalyzed by 2,3-dihydro-2,2,2-triphenylphenantro [9,10-*d*]1,3,2-λ$^5$-oxazaphosphole (**1**). Much work has been done until now on the oxidation of 3,5-di-*tert*-butylcatechol[15] just to gain insight into the possible mechanism of intra and extradiol cleavage of catechol dioxygenases. A fair number of model oxidations of *o*-aminophenol[16] have also been carried out as model reaction for 2-aminophenoxazine-3-one synthase. The former enzyme contains two copper ions in their active site,[17] while 2-aminophenoxazine-3-one synthase is a multicopper enzyme catalyzed reaction.[18] So it was obvious that we tried 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ$^5$-oxazaphosphole (**1**) as a bioinspired catalyst for catechol oxidation and a model reaction for the flavin co-factor in the case of 2-aminophenoxazine-3-one synthase. In their stoichiometric reactions beside of the corresponding *o*-quinone (**4**) $H_2O_2$ and in the case of *o*-aminophenol beside of 2-aminophenoxazine-3-one (**5**) $H_2O$ is formed (Eqn. 2 and 3). That was evidenced by $O_2$-uptake experiments (Fig. 1) and iodometric titration of the solution.[11]




Kinetic studies of both reactions resulted in an overall third order rate equation (Eqn. 4) for **3a** and and **3b** with $k_{obs}$ values

reaction rate = $k_{obs}$ [catalyst] [$O_2$] [**3**] (4)

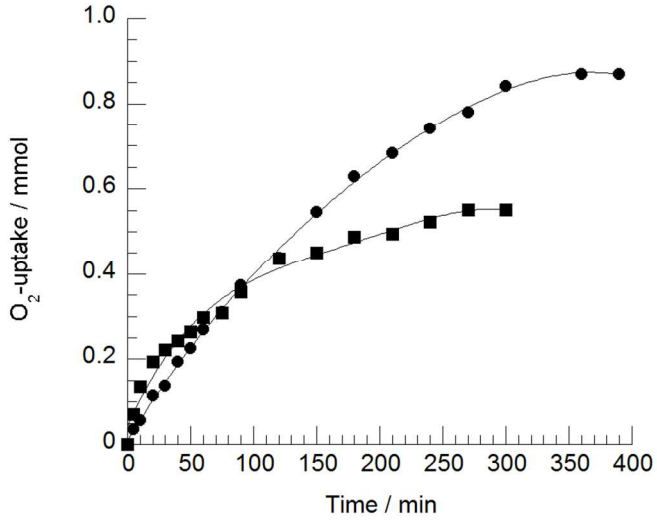



**Figure 1** Dioxygen-uptake of the oxidation of **3a** (●) and **3b** (■) catalyzed by **1**. [**3a**] = 8.9 × 10$^{-2}$ M, [catalyst] = 8.9 × 10$^{-3}$ M, V = 10 mL, T = 60 °C; [**3b**] = 8.9 × 10$^{-2}$ M, [catalyst] = 8.9 × 10$^{-3}$ M, V = 10 mL, T = 60 °C.

of 0.76±0.11 and 0.62±0.03 M$^{-2}$s$^{-1}$ respectively. The rates of the reaction were followed by UV-Vis spectroscopy at 400 (**3a**) (Fig. 2) and 434 (**3b**) (Fig. S1†) nm. A typical time plot of the oxidation of **3a** and **3b** can be seen in Fig. 1. The dependence on the dioxygen concentration (Fig. S2-S3†), on catalyst concentration (Fig. S4-S5†), the log **3b** *vs* time of **3b** oxidation (Fig. S6†) and on the initial concentrations on **3a** (Fig. S7†) and **3b** (Fig. S8†) plotted against the reaction rate gave straight lines, clearly evidenced that both reactions follow an overall third order rate equation. The activation parameters for **3a** oxidation are $\Delta E^{\ddagger}$ = 34.03±03 kJmol$^{-1}$, $\Delta H^{\ddagger}$ =

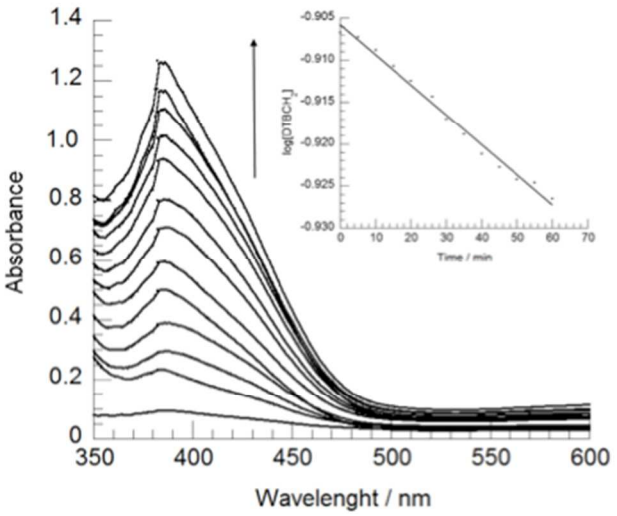
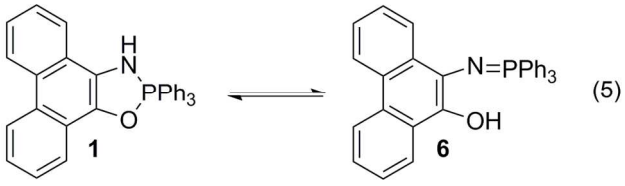



**Figure 2** Time dependence of the oxidation of **3a**. [$DTBCH_2$] = 12.5 × 10$^{-2}$ M, [1,3,2-oxazaphosphole] = 12.5×10$^{-4}$ M, [$O_2$] = 9.5 × 10$^{-3}$ M, T = 298 K, 10 mL MeOH.

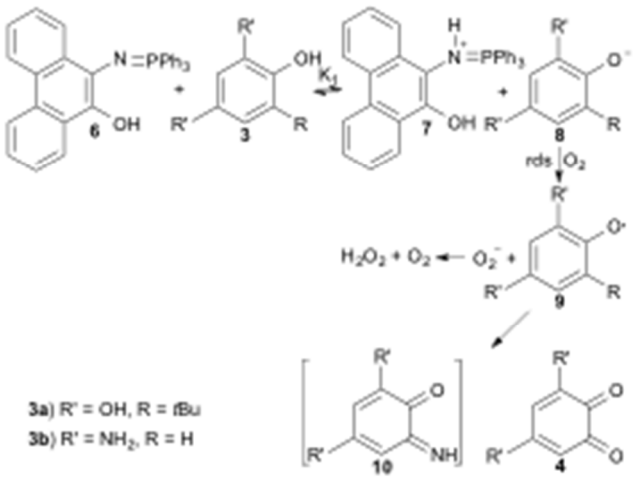
31.47±0.30 kJmol$^{-1}$ and $\Delta S^{\ddagger}$ = -142.04±0.55 Jmol$^{-1}$K$^{-1}$, and for 3**b** oxidation $\Delta E^{\ddagger}$ = 38.08±0.41 kJmol$^{-1}$, $\Delta H^{\ddagger}$ = 35.62±0.40 kJmol$^{-1}$ and $\Delta S^{\ddagger}$ = -129.58±0.66 Jmol$^{-1}$K$^{-1}$ (Fig. S9-S10†).

The KIE (Kinetic Isotope Effect) data of 1. 048 (**3a**) and 1.46 for **3b** oxidation (SFig. S11-S12†) are very small and also suggest that protons are not involved in the rate-determining steps. We know from earlier studies that there is an equilibrium between the ring form 1,3,2-oxazaphosphole (**1**) and the iminophosphorane tautomer (**6**) (Eqn. 5). The equilibrium in solution shifted to the iminophosphorane tautomer (**6**). Studies have shown that iminophosphorane tautomer (**6**) can be deprotonated by itself[19,20] or it is able to deprotonate the substrates **3a** and especially **3b** to the anion **8** and to the protonated iminophosphorane **7.**



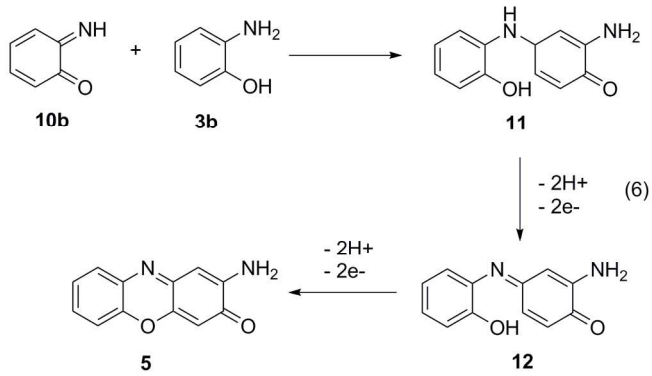

This proceeds probably via a charge transfer complex beetween **6** and **3** (Scheme 2). This reaction is a fast pre-equlibrium ($K_1$), which is largely shifted to the site of the starting components. This

phenolate anion (**8**) reacts then in the rate-determining step to the **9** organic radical and superoxide anion. Phenolate anions are energy-rich molecules[21] and can give up one electron to the ground state dioxygen to form the phenoxyl radical **9** and superoxide anion.




**Scheme 2** Proposed mechanism of the oxidation of **3a** and **3b** with dioxygen catalyzed by **1**.

The color of the reaction mixture is red, which may be due to the relative persistent phenoxyl radical **9** or also to 3,5-di-*tert*-butylbenzoquinone (**4a**). It was interesting to observe that radical **9** does not react with triplet dioxygen in a radical radical reaction. However, it reacts with superoxide anion (added $KO_2$) and not with molecular oxygen. If we start with the substrate 3,5-di-*tert*-butylcatechol (**3a**) the corresponding quinone **4** is formed together with hydrogen peroxide. The last one could be determined quantitatively by iodometry or $O_2$-compsumtion measurement (Fig.1) and was found to be in the range of 85 – 90%. In the case of *o*-aminophenol (**3b**) imino-*o*-quinone (**4b**) and hydrogen peroxide is formed, which comes from **9b** and $HO_2$ disproportion.[22] The product of *o*-aminophenol oxidation the formed imino-*o*-quinone **10b** is not stable. It reacts with the starting aminophenol (**3b**) to the compound **11** in a 1,4-addition reaction. A similar compound to **11** was characterized by UV-vis spectroscopy recently when the 5-methyl derivative of *o*-aminophenol was used.[23] This is then further oxidized to compound **12** and then to the endproduct **5** by $O_2$ or the $H_2O_2$ formed (Eqn. 6). The yields of both products (**4** and **5**) are good and the reactions can have preparative significance.




The use of 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ$^5$-oxazaphosphole (**1**) as an organic catalyst in the oxidation of 3,5-di-*tert*-butylcatechol (**3a**) and *o*-aminophenol (**3b**) to the corresponding *o*-quinone (**4**) and 2-aminophenoxazine-3-one (**5**) by triplet dioxygen are preparative useful and kinetic measurements resulted in an overall third order rate equation. The single electron transfer from the deprotonated substrates **3a** and **3b** to the dioxygen forming *O*-centered radicals (**9**) and superoxide anion. These dismutase to **4** and **10** in fast reactions and also $H_2O_2$ is formed. **10b** reacts then further with *o*-aminophenol and subsequent oxidation leads to 2-aminophenoxazine-3-one (**5**) (Eqn. 6).

The compound 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ$^5$-oxazaphosphole (**1**) is a new organic oxidation catalyst, which mimics biologically important organic cofactors. In these reactions the formation of the hydroperoxide (**2**) does not play a role, the catalyst, as a strong base, deprotonate the substrates (**3a, 3b**) forming energy-rich phenolates, which give an electron to molecular oxygen in the rate-determining steps. These reactions represent a new type of dioxygen activation by phenolates, which lead to well defined endproducts in good yields.

## Experimental

2-Aminophenol (24 mg, 0.223 mmol) or 3,5-di-*tert*-butylcatechol (49 mg, 0.223 mmol) and 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ$^5$-oxazaphosphole (**1**) (104 mg, 0.223 mmol) were dissolved in 10 mL methanol in a Schlenk tube and stirred under dioxygen at 60°C for 5 h. The solvent was distilled off the residue treated with ether and recrystallized from benzene or isooctane. Yields: 2-aminophenoxazine-3-on: 87 and 51%, 3,5-di-*tert*-butylbenzoquinone: 85 and 53% (UV-Vis and preparative, identification see ESI, Fig. S13-S18). Kinetics: into Schlenk vessel the substrates 3,5-di-*tert*-butylcatechol or *o*-aminophenol were weighed in under an argon atmosphere, where already 10 or 20 mL methanol as solvent was present. Thereafter, the catalyst, 1,3,2-oxazaphosphole, was added and the argon replaced by dioxygen. The temperature was adjusted with a water bath, the solution stirred with magnetic bar and samples were taken at regular intervals through a septum. In the samples the formed amount of 3,5-di-*tert*-butylquinone and 2-aminophenoxazine-3-one were measured at 400 (log ε = 3.21)[24] and 434 (log ε = 3.743)[25] nm. The initial rates of the reactions were determined.

## Notes and references

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