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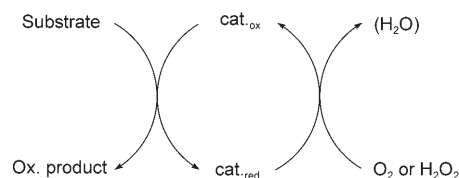
Pd^{II}-Catalyzed Aerobic Allylic Oxidative Carbocyclization of Allene-Substituted Olefins: Immobilization of an Oxygen-Activating Catalyst**

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Oxidation reactions are of fundamental importance in nature, and they are key transformations in organic synthesis.^[1] Traditional oxidation methods include the use of stoichiometric amounts of high-oxidation-state metal reagents. These methods are still used in the production of a large number of organic compounds.^[2] Recently, there has been an increasing demand for environmentally friendly and sustainable chemical processes ("green chemistry").^[3] As a consequence, considerable efforts are being made to replace stoichiometric

methods by catalytic processes, and importantly, it is highly desirable in oxidation reactions that the oxidant is either molecular oxygen or hydrogen peroxide.^[1a,4] These oxidants are environmentally friendly and give no effluents (at most, water). At present there is a lack of efficient oxidative C–C bond-forming reactions with molecular oxygen as the oxidant, as these reactions are associated with the formation of radicals, thus leading to by-products from auto-oxidation. Herein, we report a novel aerobic oxidative carbocyclization reaction through a multistep electron-transfer process. The oxygen-activating catalyst FePc (Pc = phthalocyanine) was immobilized on a resin, and it was demonstrated that the immobilized catalyst can be recycled five times without any detectable loss of activity.

In a catalytic oxidation reaction, the substrate-selective catalyst, which may be a transition metal, oxidizes the substrate to the desired product (Scheme 1). The reduced form of the catalyst is subsequently reoxidized by the oxidant, which in a "green process" should be O₂ or H₂O₂.



Scheme 1. "Green" catalytic oxidation (cat. = substrate-selective catalyst; for example, a transition metal).

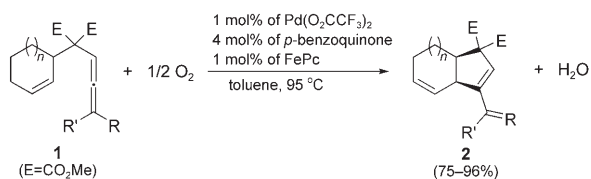
However, one problem to overcome is the often high energy barrier for the reoxidation of the reduced form of the catalyst. This problem can be avoided by mimicking biological oxidation processes, in which large jumps in oxidation potentials are avoided by the use of several coupled redox catalysts as electron-transfer mediators (ETMs).^[1a,5–10] We have designed and developed coupled catalytic systems for the 1,4-oxidation of dienes,^[5] allylic oxidation,^[5a,6] oxidation of alcohols,^[7] dihydroxylation of olefins,^[8] and oxidation of amines.^[9] In the area of aerobic palladium-catalyzed oxidations, there are examples in which palladium is directly reoxidized by O₂ without ETMs. These examples involve the oxidation of alcohols to ketones, alkenes to carbonyl compounds, and intramolecular heterocyclizations of alkenes,^[11,12] whereas oxidation with the formation of C–C bonds are less common.^[11,13–16] In most of these aerobic oxidation reactions with C–C bond formation, catalytic loadings of 5–10 mol % of Pd are required, except in a few cases.^[11a,15] For example, Jacobs and co-workers reported a highly efficient palladium-catalyzed oxidative Heck coupling between anisole and ethyl *trans*-cinnamate under O₂.^[15] The use of 1 mol % of Pd(OAc)₂ gave the product in 98 % yield, but 8 atm (0.8 MPa) of O₂ pressure was required. Our group recently described a palladium-catalyzed allylic oxidation of allene-substituted olefins by *para*-benzoquinone.^[17] Stoichiometric amounts of *para*-benzoquinone as the oxidant leads to a large waste of hydroquinone, and it is desirable to replace the oxidant with, for example, molecular oxygen. The aerobic oxidation of enallenes **1** to carbocyclization products **2** carried out in the

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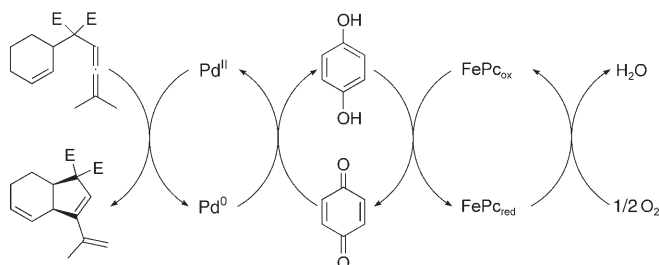
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present work is shown in Scheme 2. The reaction involves highly efficient carbon–carbon bond formation with low catalytic loading under aerobic conditions.



Scheme 2. Oxidative cyclization of allene-substituted olefins.

The new process developed is an aerobic oxidation through a multistep electron-transfer process involving three redox systems: $\text{Pd}^{\text{II}}/\text{Pd}^0$ –*para*-benzoquinone/hydroquinone– $\text{ML}^{\text{m}}_{\text{ox}}/\text{ML}^{\text{m}}_{\text{red}}$, where ML^{m} is FePc, an oxygen-activating macrocyclic metal complex (Scheme 3). The only stoichiometric waste product is water.



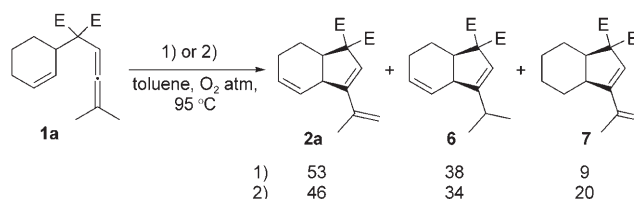
Scheme 3. Triple-coupled catalytic system for aerobic allylic oxidation.

The requisite starting materials **1a–g** were prepared as described previously (see Supporting Information).^[17–19] Initial attempts to oxidize **1a** with molecular oxygen at room temperature in the presence of catalytic amounts of $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ (5 mol %), *para*-benzoquinone (20 mol %), and FePc (5 mol %) in THF in an O_2 atmosphere were unsuccessful, thereby resulting in poor yields and long reaction times. A few solvents (THF, dichloromethane, acetonitrile, and toluene) were investigated, but no significant solvent effect was observed for the reaction. An increased reaction temperature led to efficient aerobic oxidation, and **2a** was obtained in 99% yield after 3 h when the reaction was performed in toluene at 95 °C in an O_2 atmosphere. A decrease in the catalytic loading to 1 mol % of $\text{Pd}(\text{O}_2\text{CCF}_3)_2$, 4 mol % of *para*-benzoquinone, and 1 mol % of FePc together with a slow addition of **1a** gave **2a** in 96% yield after 8 h.

Contrary to previous quinone-mediated palladium-catalyzed aerobic oxidations for C–O bond formation^[5,6] which required protic solvents, the present aerobic oxidation works efficiently in toluene. The mechanism of this reaction was discussed and investigated in an earlier report on the anaerobic reaction.^[17]

As mentioned above, there are other systems in which Pd^0 is reoxidized to Pd^{II} directly by O_2 .^[11–15] The background reactions of the triple catalytic system were investigated to show that this system is necessary for an efficient aerobic

oxidation. We therefore carried out the reaction 1) without *para*-benzoquinone and 2) without $\text{Fe}^{\text{II}}\text{Pc}$. The reaction was nonselective in both experiments, and the desired oxidation product was obtained only in moderate yield together with substantial amounts of by-products (Scheme 4). One of the



Scheme 4. Aerobic allylic oxidation of allene-substituted olefin **1a**.

1) $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ (5 mol %) and FePc (5 mol %); 2) $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ (5 mol %) and *para*-benzoquinone (20 mol %).

by-products **6** was formed through a palladium(0)-catalyzed cycloisomerization reaction of the enallene^[18] and another **7** was formed through a thermal ene reaction.^[20] When both *para*-benzoquinone and $\text{Fe}^{\text{II}}\text{Pc}$ were omitted, the yield of **2a** was very low.^[21] Clearly, the triple catalytic system is necessary for this reaction to proceed in a selective manner.

To study the scope of the reaction, a variety of substrates were tested under the reaction conditions described above for the aerobic oxidation of **1a**. Cyclohexene substrates **1a–d** reacted to furnish **2a–d** in high yields (Table 1, entries 1–4). Note that **2c** was obtained as a mixture of *E/Z* isomers in a ratio of 1:2, in contrast to the anaerobic version, in which the *E/Z* isomer ratio was 4:1.^[17] This result is probably due to the higher temperature of the aerobic reaction, thus leading to the more thermodynamically stable product.

The effect of the ring size was studied (Table 1, entries 5 and 6). The five-membered ring derivative **1e** gave a mixture of isomers **2e** and **2e'** (3:1) in the aerobic oxidation. The formation of **2e'** can be explained by a Pd^{II} -catalyzed isomerization of **2e**.^[22] In contrast to the six- and five-membered ring derivatives, which led to *cis*-fused ring systems, the seven-membered ring derivative afforded a *trans*-fused product **2f**. The two acyclic substrates **1g** and **1h** reacted to give the expected products **2g** and **2h**, respectively, in high yields (Table 1, entries 7 and 8).

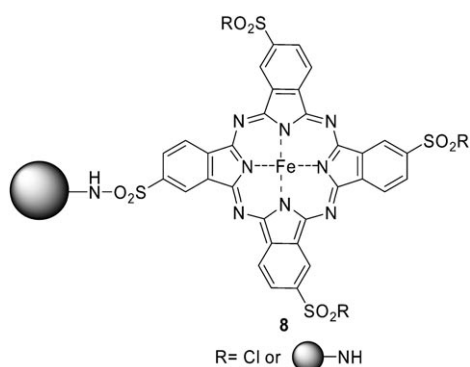
To increase the synthetic utility of the reaction, FePc was attached to a polystyrene resin (Figure 1).^[23] In this way, the macrocyclic complex **8** can be recovered and reused. When employing **8** in the oxidation of **2**, a slightly slower reoxidation occurred than with free FePc, and under these conditions we observed the formation of small amounts of cycloisomerization product **6** (10%) and the ene reaction product **7** (8%). An increase in the amount used of **8** led to a decrease in the amounts of by-products **6** and **7**, and use of 20 and 40 mol % of **8a** gave **2a** in 89 and 93% yield, respectively.

Different quinones were tested to elucidate the effect on the overall rate and selectivity. Electron-deficient quinones gave a less selective reaction than *para*-benzoquinone with lower yields of **2a** and higher amounts of **6** and **7** (see Supporting Information). In contrast, the use of the electron-rich quinone 2-methoxybenzoquinone gave an efficient and

Table 1: Palladium(II)-catalyzed aerobic allylic oxidation of **1**.^[a]

Entry	Substrate	Product	Yield [%]
1			96
2			86 ^[b] 96 ^[c]
3			81 2c/2c' 1:1
4			83 2d/2d' 1:1
5			75 ^[b] 2e/2e' 3:1
6			90
7			90 ^[c]
8			93 ^[c]

[a] Unless otherwise noted, the reactions were carried out on a 1-mmol scale with Pd(O₂CCF₃)₂ (1 mol %), *p*-benzoquinone (4 mol %), and FePc (1 mol %) in toluene (2 mL) at 95 °C for 8 h under O₂ (1 atm.) with slow addition of **1**. [b] Reaction time of 14 h for full conversion. [c] 0.2-mmol scale, with Pd(O₂CCF₃)₂ (5 mol %), *p*-benzoquinone (20 mol %), and FePc (5 mol %) in toluene (2 mL) at 95 °C for 3 h.

**Figure 1.** Complex **8**: FePc linked to a resin.

more selective reaction with no formation of **6**. With this quinone, it was possible to obtain a 100 % selectivity for **2a** in essentially quantitative yield with a slow addition of the starting material **1a** for 12 h.^[24] The mechanism for palladium reoxidation by the quinone appears to be different to that operating in acetic acid.^[25] The previous mechanism involved a Pd⁰–quinone complex that requires acid to rearrange to Pd^{II} and hydroquinone. In the present mechanism, a Pd–H species may react with the *para*-benzoquinone to give hydroquinone.

After the reaction of **1a** with **8**, the latter was recovered and used again (Table 2). We performed the reaction with either *para*-benzoquinone or 2-methoxy-*para*-benzoquinone. The FePc–resin catalyst **8** was recovered, and it was demonstrated that the reaction can be run five times with the same resin catalyst **8** without any detectable loss of activity.

Table 2: Aerobic allylic oxidation of **1a** using different quinones after recycling **8**.^[a,b]

Run	<i>p</i> -benzoquinone Yield ^[c] [%]			2-methoxy- <i>p</i> -benzoquinone Yield ^[c] [%]		
	2a	6	7	2a	6	7
1	89	5	6	94	0	6
2	83	3	11	92	0	8
3	86	9	5	96	0	4
4	88	6	5	92	0	8
5	90	5	5	95	0	5

[a] The reactions were carried out on a 0.2-mmol scale with Pd(O₂CCF₃)₂ (5 mol %), quinone (20 mol %), and **8** (20 mol %) in toluene (2 mL) at 95 °C overnight with gentle stirring. [b] Conversion was 100 % in all cases. [c] Determined by ¹H NMR spectroscopic analysis.

Although palladium-catalyzed oxidation reactions with direct reoxidation of Pd⁰ by molecular oxygen are highly efficient in many cases, this approach fails in other cases as a result of unfavored electron transfer between Pd⁰ and O₂. Thus, the use of cocatalysts (ETMs) for many Pd-catalyzed aerobic oxidation reactions are required to obtain high selectivity and high efficiency of the reaction. The oxidation reported herein is a good example of such a coupled catalytic system in which a palladium-catalyzed aerobic allylic oxidation that leads to C–C bond formation was developed. We believe that the use of coupled catalytic systems (such as that in Scheme 3) will be an important complement to the simple systems with direct reoxidation of Pd⁰ by O₂ and significantly extend the use of aerobic palladium-catalyzed reactions to cases in which the latter approach fails. The immobilization of the oxygen-activating catalyst onto a resin provides a practical catalyst that can be reused many times without any detectable loss of activity and should further increase the utility of the present aerobic allylic oxidation.

Experimental Section

General procedure for the aerobic allylic oxidation of compounds **1a–h**: Oxidation of **1a** to **2a**: Pd(CF₃CO₂)₂ (3.3 mg, 0.01 mmol), *para*-benzoquinone (4.3 mg, 0.04 mmol), and iron phthalocyanine (5.7 mg, 0.01 mmol) were mixed and stirred in toluene (2 mL). Compound **1a**

(278 mg, 1 mmol) was added to the resulting slurry (slow addition during 6 h) with stirring at 95 °C in an oxygen atmosphere. The reaction mixture was cooled down to room temperature after a further 2 h, and 2 M NaOH (10 mL) was added. The resulting mixture was extracted with Et₂O (3 × 5 mL), the combined organic phases were dried (Na₂SO₄), and the solvent was removed under vacuum to yield 265 mg (96%) of pure product **2a**. Purification of **2**, when needed, was carried out by using Biotage SP1 flash chromatography with eluent system pentane/ethyl acetate (10:1).

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