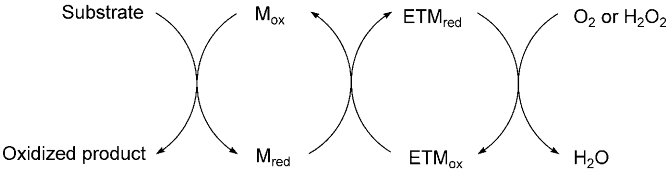
DOI: 10.1002/chem.200900980

# Efficient Reoxidation of Palladium by a Hybrid Catalyst in Aerobic Palladium-Catalyzed Carbocyclization of Enallenes

**Eric V. Johnston, Erik A. Karlsson, Staffan A. Lindberg, Björn Åkermark, and Jan-E. Bäckvall***[a]

Oxidation reactions play an important role in synthetic transformations, and there is a current need for the development of more selective and more efficient catalytic oxidation methods. There is an increasing demand from society to develop bioinspired, environmentally benign oxidation processes.[1] In such processes, it is desirable to use oxidants such as molecular oxygen and hydrogen peroxide, which do not give rise to any waste products and, therefore, fulfill the requirement of "green chemistry".[1a,2] In a catalytic oxidation reaction, the substrate-selective catalyst, which may be a transition metal, oxidizes the substrate to the desired product. The reduced form of the catalyst is subsequently reoxidized by the oxidant, which in a green process should be $O_2$ or $H_2O_2$. Direct reoxidation of the transition-metal catalyst by $O_2$ or $H_2O_2$ have been reported.[3,4,5,6] This approach fails in many cases owing to a high activation barrier that leads to slow electron transfer between the reduced form of the metal and $O_2$ or $H_2O_2$, and this may result in catalyst deactivation through competing pathways. One way to overcome this large jump in oxidation potential is to mimic the biological respiratory chain, which uses several coupled redox catalysts as electron-transfer mediators (ETMs). For example, in a metal-catalyzed oxidation, an ETM may be employed to facilitate electron transfer between the reduced substrate-selective catalyst ($M_{red}$) and the stoichiometric oxidant ($O_2$ or $H_2O_2$, Scheme 1).



Scheme 1. Electron transfer facilitated by an ETM.

There are only a handful of examples of palladium-catalyzed aerobic oxidations involving C–C bond formation compared with the number of examples involving C–O and C–N bond formation, and in most of them high catalytic loading or high oxygen pressure is required.[7] Previously, our research group reported an aerobic Pd-catalyzed oxidative carbocyclization of allene-substituted olefins with the aid of two ETMs (Scheme 2).[8] One way to increase the efficiency of this aerobic carbocyclization would be to covalently link the two ETMs into one catalyst, thus enhancing the rate of the reoxidation of palladium. We have recently designed and prepared hybrid catalysts **1** and **2**, which consist of a Schiff base unit with pendant hydroquinone groups (Scheme 2).[9] Herein, we describe the use of the hybrid catalyst **1** to obtain efficient Pd-catalyzed aerobic carbocyclization of enallenes **3** to bicyclic trienes **4**.

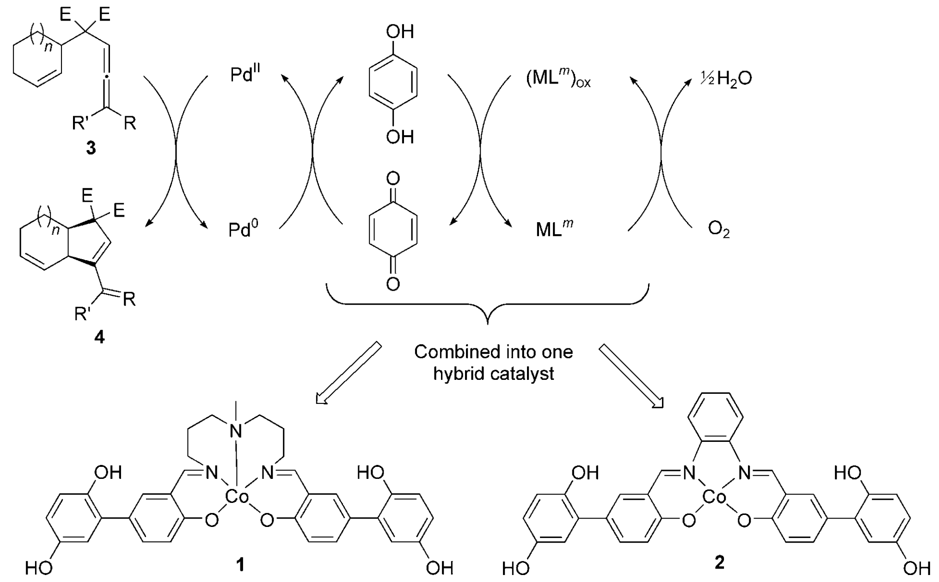
The starting materials **3a–e** were prepared as previously described (see the Supporting Information).[10,11] The hybrid catalysts **1** and **2** were prepared according to a new method developed in our laboratory.[12] Oxidation of **3a** with molecular oxygen at room temperature in the presence of catalytic amounts of $Pd(OAc)_2$ (5 mol%) and hybrid catalyst **1** (5 mol%) in THF under an $O_2$ atmosphere resulted in moderate conversion to **4a** and long reaction times (Table 1, entry 1). The use of other solvents such as dichloromethane, acetonitrile, or toluene gave no significant increase in the rate. However, the rate of the aerobic oxidation of **3a** was improved in the presence of a protic solvent. Thus, oxidation of **3a** with molecular oxygen at room temperature in THF/MeOH in the presence of catalytic amounts of $Pd(OAc)_2$ (5 mol%) and hybrid catalyst **1** (5 mol%) resulted in an increased conversion, yet still with long reaction times (Table 1, entry 2).

Interestingly, carrying out the reaction in pure methanol led to a significant increase in the rate of the aerobic oxidation at room temperature, with full conversion to **4a** after

---

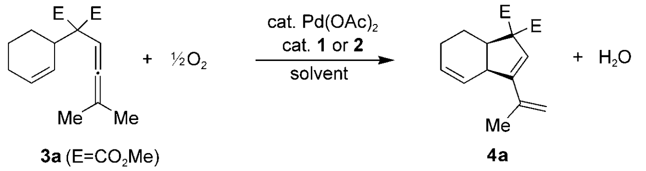
[a] E. V. Johnston, E. A. Karlsson, S. A. Lindberg, B. Åkermark, J.-E. Bäckvall
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
Fax: (+46) 8-154-908
E-mail: jeb@organ.su.se

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900980.



Scheme 2. In biomimetic aerobic oxidation, the use of ETMs enables low-energy electron transfer from the substrate to molecular oxygen. The merging of two ETMs would facilitate the electron transfer ($E=CO_2Me$, $R=R'=Me$ or $R,R'=(CH_2)_5$).

Table 1. $Pd^{II}$-catalyzed aerobic allylic oxidation of substrate **3a**.[a]



| | Catalyst [mol %] | Solvent | $T$ [°C] | Time [h] | Conversion [%][b] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (5)/**1** (5) | THF | 23 | 24 | 47 |
| 2 | $Pd(OAc)_2$ (5)/**1** (5) | THF/MeOH 4:1 | 23 | 24 | 95 |
| 3 | $Pd(OAc)_2$ (5)/**1** (5) | MeOH | 23 | 5 | 100 |
| 4 | $Pd(OAc)_2$ (2.5)/**1** (2.5) | MeOH | 40 | 3 | 100 |
| 5 | $Pd(OAc)_2$ (2.5)/**1** (2.5) | EtOH | 40 | 3 | 100 |
| 6 | $Pd(OAc)_2$ (2.5)/**1** (2.5) | EtOH | 75 | 0.3 | 100 |
| 7 | $Pd(OAc)_2$ (1)/**1** (1) | EtOH | 75 | 2 | 100 (97)[c] |
| 8[d] | $Pd(OAc)_2$ (1)/**1** (1) | EtOH | 75 | 0.8 | 100 (97)[c] |
| 9 | $Pd(OAc)_2$ (2.5)/**2** (2.5) | EtOH | 75 | 4 | 100 |

[a] All reactions were carried out on a 1 mmol scale in 5 mL of solvent under $O_2$ (1 atm) with palladium acetate and hybrid catalyst **1** or **2**. [b] Conversions were determined by using $^1H$ NMR spectroscopy after filtration through a silica plug. [c] Isolated yield. [d] 2 mL of solvent was used.

5 h. An increase of the temperature to 40 °C allowed the catalytic loading to be lowered to 2.5 mol %, which gave full conversion within 3 h (Table 1, entry 4). The use of ethanol gave the same result (Table 1, entry 5). By increasing the temperature of the reaction in ethanol to 75 °C, full conversion of **3a** to **4a** was obtained after 0.3 h. A decrease in the catalytic loading to 1 mol % of $Pd(OAc)_2$, and 1 mol % of hybrid **1** gave **4a** with full conversion and in 97 % isolated yield after 2 h. When the amount of solvent was reduced from 5 mL to 3 mL, the reaction was completed in 0.8 h (Table 1, entry 8). We also carried out the corresponding oxidation with catalyst **2** in place of **1**. Oxidation of **3a** by using 2.5 mol % of **2** and 2.5 mol % of $Pd(OAc)_2$ reached full conversion to **4a** after 4 h (Table 1, entry 9). This is significantly slower than the corresponding reaction with hybrid **1**, which reached full conversion after only 0.3 h. The slower reaction is most likely due to the fact that catalyst **2** is quite insoluble in ethanol.

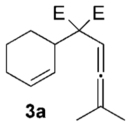
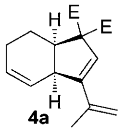
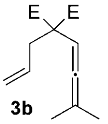
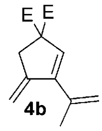
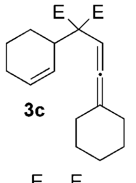
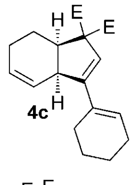
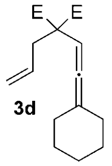
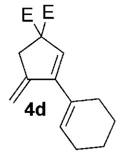
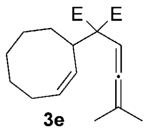
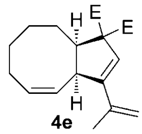
To estimate the efficiency of hybrid catalyst **1**, we ran the corresponding reaction to that of Table 1, entry 6, but with separate Co(salmdpt) (2.5 mol %, salmdpt$H_2$ = bis[3-(salicylideneimino)propyl]methylamine) and benzoquinone (5 mol %). The separate-component reaction reached completion after 1.5 h, whereas in Table 1, entry 6 in which hybrid catalyst **1** was used, the corresponding reaction took only 0.3 h. This illustrates that hybrid catalyst **1** accelerated the reaction of substrate **3a** by a factor of five, and also gave a more selective reaction.

To study the scope of the reaction, a variety of substrates were tested under the reaction conditions described above for the aerobic oxidation of **3a** with 1 mol % each of $Pd(OAc)_2$ and **1**. All of the substrates **3a–e** afforded **4a–e** in high yields (Table 2, entries 1–5). The effect of ring size was studied (Table 2, entries 1 and 5), and as previously reported, six- and eight-membered-ring derivatives led to *cis*-fused ring systems.[9] The reaction proceeded readily with substrates that contained either terminal or internal alkenes.

To investigate whether there was any direct reoxidation of palladium by $O_2$ in ethanol, we carried out the reaction of **3a** without the hybrid catalyst **1** at 75 °C. The reaction was very unselective and gave $<5$ % of the desired oxidation product, and substantial amounts of byproducts were formed. Two nonoxidative side reactions predominate: the $Pd^0$-catalyzed cycloisomerization[13] and the thermal Alder-ene reaction of **3a**.[14] Clearly, the catalytic reoxidation system is necessary for this reaction to proceed in a selective manner.

Although palladium-catalyzed oxidation reactions with direct reoxidation of $Pd^0$ by molecular oxygen are efficient in some cases, this approach fails in many other cases as a result of unfavored electron transfer between $Pd^0$ and $O_2$. Thus, to obtain high selectivity and high efficiency in Pd-catalyzed aerobic oxidations, the use of cocatalysts (ETMs) are often required. The use of the hybrid catalyst **1** gives approximately a five-fold decrease in reaction time compared with the use of separate benzoquinone and Co(salmdpt) catalysts in ethanol. In the absence of hybrid catalyst **1** or any

Table 2. Palladium(II)-catalyzed aerobic allylic oxidation of 1.[a]

| | Substrate | Product | $T$ [h] | Yield[b] [%] |
|---|---|---|---|---|
| 1 |  3a |  4a | 0.8 | 97 |
| 2 |  3b |  4b | 11 | 94 |
| 3 |  3c |  4c | 2–3 | 96 |
| 4 |  3d |  4d | 2–3 | 94 |
| 5 |  3e |  4e | 2–3 | 96 |

[a] The reactions were carried out on a 1 mmol scale with $Pd(OAc)_2$ (1 mol%), hybrid catalyst **1** (1 mol%) in EtOH (2 mL) at 75 °C under $O_2$ (1 atm). [b] Isolated yield of pure product.

other ETMs, the aerobic carbocyclization is several orders of magnitude slower and other competitive side reactions take over. The use of hybrid catalyst **1** is an important complement to the systems that are already used for reoxidation of $Pd^0$ by $O_2$. The efficiency of intramolecular electron transfer allows for low catalytic loading and mild reaction conditions. This will significantly extend the use of aerobic metal-catalyzed oxidations.

## Acknowledgements

We thank the Swedish Research Council and the K & A Wallenberg Foundation for financial support. We also thank Dr. Katrin Roland for initial studies of the carbocyclization of **3a** in methanol.

**Keywords:** carbocyclization · electron transfer · hybrid catalysts · oxidation · palladium

[1] a) J. Piera, J. E. Bäckvall, *Angew. Chem.* **2008**, *120*, 3558–3576; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506–3523; b) F. G. Gelalcha, G. Anilkumar, M. K. Tse, A. Brückner, M. Beller, *Chem. Eur. J.* **2008**, *14*, 7687; c) P. C. A. Bruijnincx, I. L. C. Buurmans, S. Gosiewska, M. A. H. Moelands, M. Lutz, A. L. Spek, G. van Koten, R. J. M. Klein Gebbink, *Chem. Eur. J.* **2008**, *14*, 1228.

[2] R. A. Sheldon, I. W. C. E. Arends, G. J. ten Brink, A. Dijksman, *Acc. Chem. Res.* **2002**, *35*, 774.

[3] For a review on direct reoxidation of Pd by molecular oxygen, see: S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400.

[4] For examples of direct reoxidation of Pd by $O_2$, see: a) R. M. Trend, Y. K. Ramtohul, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 17778; b) B. A. Steinhoff, S. R. Fix, S. S. Stahl, *J. Am. Chem. Soc.* **2002**, *124*, 766; c) M. Dams, D. E. De Vos, S. Selen, P. A. Jacobs, *Angew. Chem.* **2003**, *115*, 3636; *Angew. Chem. Int. Ed.* **2003**, *42*, 3512; d) D. R. Jensen, M. J. Schultz, J. A. Mueller, M. S. Sigman, *Angew. Chem.* **2003**, *115*, 3940; *Angew. Chem. Int. Ed.* **2003**, *42*, 3810.

[5] a) K. Sato, M. Aoki, M. Ogawa, T. Hashimoto, R. Noyori, *J. Org. Chem.* **1996**, *61*, 8310; b) K. Sato, M. Aoki, J. Takagi, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 12386.

[6] G. J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Science* **2000**, *287*, 1636.

[7] See, for example: a) M. Rönn, P. G. Andersson, J. E. Bäckvall, *Tetrahedron Lett.* **1997**, *38*, 3603; b) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578; c) K. T. Yip, J.-H. Li, O.-Y. Lee, D. Yang, *Org. Lett.* **2005**, *7*, 5717; d) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528; e) C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, *J. Am. Chem. Soc.* **2006**, *128*, 6829.

[8] J. Piera, K. Närhi, J. E. Bäckvall, *Angew. Chem.* **2006**, *118*, 7068; *Angew. Chem. Int. Ed.* **2006**, *45*, 6914.

[9] B. W. Purse, L. H. Tran, J. Piera, B. Åkermark, J. E. Bäckvall, *Chem. Eur. J.* **2008**, *14*, 7500.

[10] J. Franzén, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2003**, *125*, 6056.

[11] The acyclic starting materials **3b** and **3d** were obtained in the same way as the cyclic starting materials **3a**, **3c**, and **3e** from the corresponding acyclic allylic bromide.

[12] E. V. Johnston, E. A. Karlsson, L.-H. Tran, B. Åkermark, J. E. Bäckvall, Eur. J. Org. Chem., DOI: 10.1002/ejoc.200900312; for a previously published procedure for the synthesis of **1** and **2** see Ref. [9].

[13] K. Närhi, J. Franzén, J. E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 6937–6943.

[14] K. Närhi, J. Franzén, J. E. Bäckvall, *J. Org. Chem.* **2006**, *71*, 2914–2917.

Received: April 14, 2009