Communications

Mechanistic Insight into the Palladium-Catalyzed 1,4-Oxidation of 1,3-Dienes to 1,4-Dicarboxy-alk-2-enes**

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The oxidation of simple 1,3-dienes to 1,4-dicarboxy-alk-2-enes was first reported by Bäckvall et al.[1] This type of 1,4-oxidation enables the direct preparation of synthetically useful bifunctional allylic systems (Scheme 1), which undergo a variety of stereoselective reactions to give highly substituted, stereodefined carbocycles.[2] We wished to utilize this
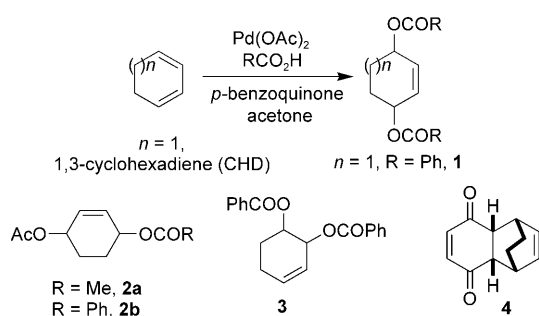
Scheme 1. 1,4-Oxidation of 1,3-dienes to form *cis* 1,4-biscarboxylates. The main impurities and side products are shown for the reaction of CHD with benzoic acid (R=Ph).

methodology to prepare the stable and crystalline *cis* bisbenzoate **1** (n=1, R=Ph) from 1,3-cyclohexadiene (CHD, Scheme 1). During the course of our investigation, we observed several previously unreported kinetic phenomena. These observations gave us a greater understanding of the mechanism of this transformation and led to the discovery of a new, highly active palladium complex for diene oxidation.

The 1,4-oxidation of cyclic dienes is highly diastereoselective; the corresponding *cis* biscarboxylate is formed under acidic conditions, and the *trans* biscarboxylate is formed when the alkali salt of the carboxylate is used to buffer the medium.[1b] Other conditions, such as the presence of LiCl, also change the stereochemical outcome of the reaction.[1c] The reaction is thought to proceed through complexation of the diene to the palladium(II) carboxylate, followed by

addition of the nucleophile to the 1-position of the diene. The resulting palladium(II)–π-allyl complex accepts the second nucleophile at the 4-position to give the product and Pd^0. The Pd^0 species is then reoxidized to the palladium carboxylate by *p*-benzoquinone in the presence of an acid.[3] Complexation of *p*-benzoquinone to the transient palladium(II)–π-allyl complex has also been suggested.[4]

A preliminary study indicated that the catalyst loading of 5 mol % used under the original conditions and in our initial experiments was above the solution-solubility limit of the active catalyst; less than 2.5 mol % Pd(OAc)$_2$ was required for true kinetic behavior to be observed. We therefore used a lower catalyst loading of 1.25 mol % for further rate analyses.[5] As reported previously, the main impurities are the Diels–Alder adduct **4**,[1a] formed between CHD and *p*-benzoquinone, the 1,2-regioisomer **3**, and, in this case, the bisacetate and mixed monoacetate monobenzoate products **2a** and **2b**, respectively.[6]

A plot of the concentration of bisbenzoate **1** (*cis* and *trans*) against reaction time for the oxidation (Figure 1 shows this relationship for the initial conversion up to 15 %) showed a reaction with an increasing rate and a sigmoidal reaction profile. (The use of either Pd(OAc)$_2$ or Pd(OBz)$_2$ (Bz = benzoyl) as the catalyst gave identical results.) This result suggested that an autocatalytic-like process was occurring,
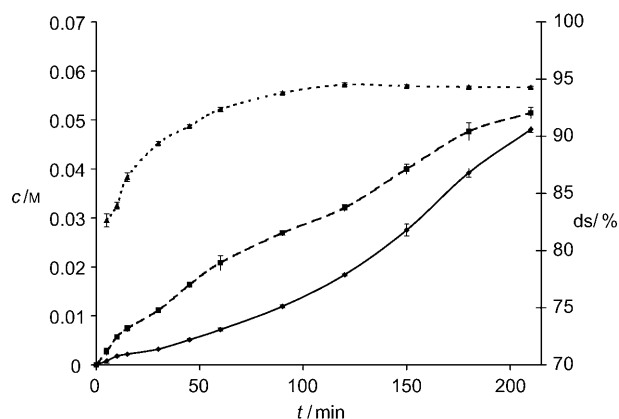
Figure 1. Analysis of the reaction progress of the palladium-catalyzed 1,4-oxidation of 1,3-cyclohexadiene according to Scheme 1.[5] Solid line: concentration of product **1** (*cis* and *trans*) versus reaction time for the first 3.5 h of the reaction (ca. 15 % conversion); dashed line: concentration of the Diels–Alder adduct **4**; dotted line: diastereoselectivity (ds) with respect to the proportion (%) of the *cis* isomer in the *cis*/*trans* product mixture. All data are averaged from three reactions at (21.1 ± 0.1) °C with Pd(OBz)$_2$ (1.25 mol %) as the catalyst. End-of-reaction yields (determined by HPLC of the reaction mixture): **1** (*cis* and *trans*, d.r. 94:6), 55 %; **4**, 22 %.

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as opposed to a purely catalytic reaction.[7] We sought to determine the cause of this kinetic phenomenon.

The diastereoselectivity for the formation of the bisbenzoate **1** changed over the course of the reaction (Figure 1). These observations (change in rate and selectivity) suggested a change in the nature of the catalyst early in the reaction (to give rise to competing reaction pathways), rather than simply the liberation of more catalyst into solution (through the breaking up of aggregates).[8] From our observations, it appears that there is more than one catalytic species capable of producing the product. One catalyst (active at $t = 0$) produces the benzoate **1** slowly and with low stereoselectivity. A second catalyst, generated during the reaction, reacts at a faster rate with greater selectivity. We sought to elucidate which reaction products could be associated with this apparent change in catalyst structure.

^{1}H NMR spectroscopic analysis in [D$_6$]acetone indicated that the carboxylates exchanged rapidly on palladium under the reaction conditions (Pd(OAc)$_2$, PhCO$_2$H, *p*-benzoquinone), as evidenced by the formation of AcOH. However, there were no significant interactions observed between Pd(OAc)$_2$ and either the *cis* bisbenzoate **1** or the isolated Diels–Alder adduct **4**. Hydroquinone (HQ) showed a weak interaction with Pd(OAc)$_2$,[9] although substantial complexation was only observed with a significant excess of hydroquinone ($> 20:1$ HQ/Pd). This observation seemed inconsistent with the rate changes that occurred early in the reaction.

If the reaction proceeds through a Pd^{II}–Pd^0 cycle, as originally proposed,[1a] interactions of the reaction products (e.g. benzoate **1**, hydroquinone, Diels–Alder adduct **4** (DA)) with palladium(0) may also be possible. When [Pd$_2$-(dba)$_3$]·CHCl$_3$ and the isolated Diels–Alder adduct **4** were combined in [D$_6$]acetone, only the unbound dibenzylideneacetone (dba) was observable by ^{1}H NMR analysis; a green solid was also noted to have precipitated from the solution.[10] Characterization of this material by NMR spectroscopy in CDCl$_3$ showed significantly shifted enone resonances and the apparent desymmetrization of the Diels–Alder system. This result was consistent with an 18-electron 2:1 Diels–Alder adduct/palladium(0) complex,[11] as confirmed by HRMS. The [Pd(DA)$_2$] complex (**5**) was formed readily on a multigram scale in either acetone or diethyl ether (Scheme 2).[12]

We used reaction calorimetry to compare the catalytic activity of the new complex **5** to that of Pd(OAc)$_2$ and Pd(OBz)$_2$ catalysts.[13] The reaction heat flow was observed upon consecutive injections of CHD to a preequilibrated solution of the palladium catalyst, benzoic acid, and *p*-benzoquinone in acetone.[14]
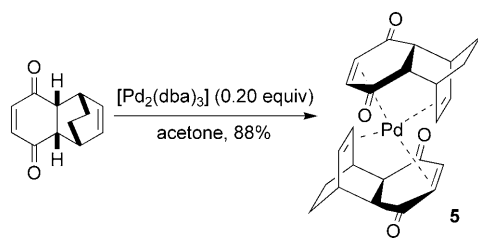
For the first injection of CHD, Pd(OAc)$_2$ and Pd(OBz)$_2$ gave identical rate profiles (Figure 2). In each case, the rate (which is proportional to heat flow) had a profile resembling that of an autocatalytic-like reaction. This result confirmed our earlier findings (Figure 1). For the reaction starting with the [Pd(DA)$_2$] complex (**5**), the maximum rate was observed from the onset of the reaction.
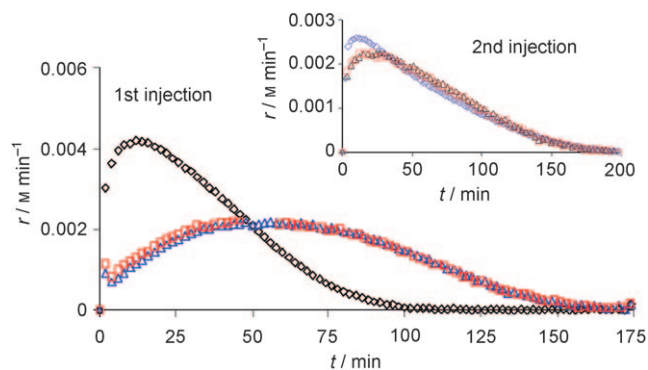
Figure 2. Rate (*r*) of product formation (*cis* and *trans*) versus time with Pd(OAc)$_2$ (□), Pd(OBz)$_2$ (△), and [Pd(DA)$_2$] (**5**; ◇). Reactions were carried out at 40.0°C with 1.25 mol% of the palladium compound.

Subsequent injections of CHD for all catalysts (Pd(OAc)$_2$, Pd(OBz)$_2$, and [Pd(DA)$_2$]) led to positive-order rate profiles without an induction periods, and significantly all displayed similar profiles to the initial injection with the [Pd(DA)$_2$] catalyst **5**. Furthermore, the reaction rates with all three catalysts were now superimposable; that is, each reaction now contained an identical amount of the same catalytically active species.

The formation of benzoate **1** was observed by HPLC methods (under identical conditions to those used for our initial experiments) using our new catalyst. It was found that the reaction with the complex [Pd(DA)$_2$] (**5**) had a linear reaction profile (was truly catalytic) and proceeded at a much higher rate than the reactions with the other catalysts (Figure 3; conversion at 210 min is 60% with **5** versus 15% with Pd(OBz)$_2$ (compare Figure 1)). Furthermore, the use of this catalyst led to a consistent diastereomeric ratio and less of the Diels–Alder side product **4** upon complete reaction. The above data suggests that the [Pd(DA)$_2$] complex directly produces the true active catalyst for the oxidation reaction; presumably, the active catalyst is "[PdDA]" (**6**), which is formed from **5** through the decomplexation of one DA ligand (Scheme 3).

We propose that the bidentate Diels–Alder adduct forces the reaction to proceed through a cationic pathway, thus enhancing the rate of oxidation (Scheme 3). Initial computational analysis[15, 16] of this process indicates that the Diels–Alder adduct encapsulates the palladium atom to a significant extent to produce an environment in which only one carboxylate moiety can be present at the stage of diene activation (complex **8**). The forced cationic nature of this complex may therefore explain the enhanced reactivity of this catalyst. The reaction displays a zero-order dependence on *p*-

Scheme 2. Formation of the [Pd(DA)$_2$] complex (**5**). [Pd$_2$(dba)$_3$] was substituted for [Pd$_2$(dba)$_3$]·CHCl$_3$ for larger-scale syntheses.

Scheme 3. Proposed catalytic cycle for the 1,4-oxidation of 1,3-cyclohexadiene. Also shown is a computational model of complex **8** obtained at the DZVP level[15] by using PC GAMESS/Firefly.[16] BQ = *p*-benzoquinone.

benzoquinone. This finding indicates that *p*-benzoquinone is not involved in the turnover-limiting step of the reaction and is consistent with the bidentate nature of the Diels–Alder adduct, which would prevent additional ligands binding to the palladium center once the diene oxidation has begun. Additional studies are currently underway and will be published in due course.

In summary, we have isolated a new and highly reactive catalyst for the oxidation of dienes. We have shown that the palladium-catalyzed oxidation of 1,3-cyclohexadiene proceeds through a previously unreported pathway, whereby

the main side product, a tricyclic Diels–Alder adduct **4**, acts as a ligand for palladium to generate the true catalytic species in situ. This reaction pathway competes with the previously reported ligation-free mechanism and may therefore operate in cases in which the diene is capable of forming such a Diels–Alder adduct.

Figure 3. Analysis of the progress of the 1,4-oxidation of 1,3-cyclo-hexadiene under the catalysis of [Pd(DA)$_2$] (**5**; 1.25 mol%) at (21.1 ± 0.1) °C.[5] Solid line: concentration of product **1** (*cis* and *trans*) versus reaction time for the first 3.5 h of the reaction (ca. 60% conversion); dashed line: concentration of the Diels–Alder adduct **4**; dotted line: diastereoselectivity with respect to the proportion (%) of the *cis* isomer in the *cis/trans* product mixture. The average results are shown for three reactions. As a result of the precipitation of quinhy-drone near the end of the reaction, the sampling errors increased slightly as the reaction progressed. End-of-reaction yields (determined by HPLC of the reaction mixture): **1** (*cis* and *trans*, d.r. 92:8), 80%; **4**, 15%.

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[5] We increased the concentration of the reaction mixture while maintaining the concentration of benzoic acid. The following reaction conditions were used: CHD (1 equiv, 0.32 M), benzoic acid (4 equiv, 1.27 M), catalyst (1.25–5 mol%), *p*-benzoquinone (2.2 equiv, 0.69 M), acetone (30 mL per gram of CHD), room temperature. Cyclohexene and benzene are also produced during the oxidation.

[6] Pd(OBz)$_2$ (Bz = benzoyl) became our preferred catalyst, as it limits the number of side products formed (no mixed-carboxylate products are produced).

[7] a) D. G. Blackmond, *Angew. Chem.* **2009**, *121*, 392; *Angew. Chem. Int. Ed.* **2009**, *48*, 386; b) G. Bazsa, M. T. Beck, *Acta Chim. Acad. Sci. Hung.* **1972**, *73*, 425.

[8] The deaggregation of trimeric palladium carboxylate into a monomer was ruled out as the cause of the sigmoidal profile through comparison with the use of Pd(tfa)$_2$ (tfa = trifluoroacetate) as the catalyst, in which case a near-identical sigmoidal profile to that found with Pd(OBz)$_2$ was observed. Pd(tfa)$_2$ is known to be monomeric in solution: T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, G. Wilkinson, *J. Chem. Soc.* **1965**, 3632.

[9] Hydroquinone is the by-product of palladium(0) reoxidation and precipitates during the reaction as quinhydrone.

[10] We had shown in other studies focused on optimization of the palladium source that [Pd$_2$(dba)$_3$]·CHCl$_3$ was as effective as Pd(OAc)$_2$.

[11] a) M. A. Grundl, J. J. Kennedy-Smith, D. Trauner, *Organometallics* **2005**, *24*, 2831; b) S. Porth, J. W. Bats, D. Trauner, G. Giester, J. Mulzer, *Angew. Chem.* **1999**, *111*, 2159; *Angew. Chem. Int. Ed.* **1999**, *38*, 2015.

[12] The solubility of each palladium source was measured in acetone at 20°C: Pd(OAc)$_2$, (28.6 ± 0.3) mg mL^{-1}; Pd(OBz)$_2$, (5.5 ± 0.2) mg mL^{-1}; [Pd(DA)$_2$], (< 0.5 ± 0.1) mg mL^{-1}.

[13] a) A. C. Ferretti, J. S. Mathew, D. G. Blackmond, *Ind. Eng. Chem. Res.* **2007**, *46*, 8584; b) J. S. Mathew, M. Klussmann, H. Iwamura, F. Valera, A. Futran, E. Alan, E. A. C. Emanuelsson, D. G. Blackmond, *J. Org. Chem.* **2006**, *71*, 4711.

[14] To ensure a sufficient heat flow, the oxidation reactions were carried out at 40°C (see the Supporting Information).

[15] DZVP (DFT Orbital): N. Godbout, D. R. Salahub, J. Andzelm, E. Wimmer, *Can. J. Chem.* **1992**, *70*, 560. Basis sets were obtained from the Extensible Computational Chemistry Environment Basis Set Database, Version 02/02/06, as developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory, which is part of the Pacific Northwest Laboratory, P.O. Box 999, Richland, Washington 99352, USA, and funded by the US Department of Energy. The Pacific Northwest Laboratory is operated by the Battelle Memorial Institute for the US Department of Energy under contract DE-AC06-76RLO 1830.

[16] Alex A. Granovsky, PC GAMESS/Firefly version 7.1.C, www http://classic.chem.msu.su/gran/gamess/index.html.