COMMUNICATIONS

Palladium(II)-Catalyzed Oxidation of Alcohols with Air as Reoxidant

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Abstract: Oxidation of primary and secondary aliphatic and secondary benzylic alcohols into their corresponding aldehydes and ketones was achieved in good yields with palladium catalysts using air as the reoxidant of palladium. The use of palladacycle **1** resulted in higher yields and a faster reaction than the use of Pd(OAc)₂ as the palladium source.

The classical oxidation of primary and secondary alcohols to aldehydes and ketones can be performed in many ways. Traditionally, stoichiometric oxidants such as chromium salts have been widely used but these reagents suffer from big disadvantages since they are toxic and harmful for the environment.[1] Several catalytic methods have been developed and they are often milder and more selective than stoichiometric oxidations.[2] Metals used for oxidations are copper,[3,4] ruthenium,[3,5] and palladium.[3,6,7] Noyori and coworkers have developed a method with aqueous H_2O_2 in the presence of a tungsten catalyst and a phase-transfer agent.[8] Recently, methods where O_2 or high pressure of air is used as the reoxidant together with palladium(II) catalysts have been reported.[6] Such systems are non-toxic and environmentally friendly. However, for both practical and safety reasons it would be optimal to use oxygen from the atmosphere in place of pure oxygen without applying pressure. Uemura et al. have reported that continuous bubbling was required as well as longer reaction time when benzyl alcohol was oxidized to benzaldehyde with air instead of oxygen.[7]

Cyclopalladated imine complexes have been shown to be successful catalysts for Heck and Suzuki cross couplings.[9] In our studies of these complexes we discovered by coincidence that palladacycle **1** (Figure 1) catalyses the oxidation of secondary benzylic alcohols to their corresponding ketones and aldehydes in ordinary air without any additional reoxidants.

The palladacycle **1** was prepared from palladium acetate and (4*S*)-4-isopropyl-2-phenyl-4,5-dihydro-1,3-oxazole (**2**) (Scheme 1) which, in turn, was obtained from the reaction of benzonitrile with valinol as described by Williams et al.[10]
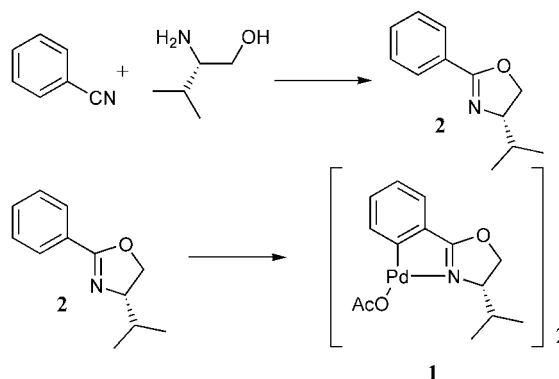
Scheme 1.

To assess the potential of the palladacycle as a catalyst in the oxidation of alcohols with air as the only reoxidant, a comparison of **1** with the palladium(II) catalyst most frequently used today for these reactions, Pd(OAc)₂, was performed. The reaction studied first
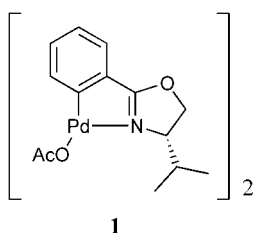
Figure 1. Structure of palladacycle **1**.

Table 1. Oxidation of *rac*-1-phenylethanol catalyzed by palladacycle **1** or Pd(OAc)$_2$.

Catalyst	Method[a]	Yield[b] after 2 h	Yield[b] after 4 h	Yield[b] after 24 h
1	A	0%		33%
Pd(OAc)$_2$	A	24%		89%
1	B	45%	48%	56%
Pd(OAc)$_2$	B	28% (28 – 34)[c]	30%	36% (36 – 42)[c]
1	C	51% (28 – 51)[c]	78% (71 – 78)[c]	100%
Pd(OAc)$_2$	C	53% (39 – 53)[c]	56% (44 – 56)[c]	58% (48 – 58)[c]
1	D	35%	45%	52%
Pd(OAc)$_2$	D	58%	62%	66%

[a] Method A: 1-phenylethanol (1.0 mmol), catalyst (5 mol % Pd), NaHCO$_3$ (2.0 mmol), DMSO (1.0 mL), 80 °C. Method B: 1-phenylethanol (1.0 mmol), catalyst (10 mol % Pd), K$_2$CO$_3$ (0.95 mmol), *o*-xylene (1.6 mL), 130 °C. Method C: 1-phenylethanol (1.0 mmol), catalyst (5 mol % Pd), pyridine (0.2 mmol), toluene (10 mL), 3 Å MS (500 mg), 80 °C. Method D: 1-phenylethanol (0.5 mmol), catalyst (5 mol% Pd), pyridine (0.1 mmol), toluene (2.0 mL), perfluorodecalin (2.0 mL), 3 Å MS (250 mg), 80 °C.
[b] The yield was determined with GC using naphthalene as internal standard.
[c] The value within brackets shows the variation in yield between different runs of the same reaction.

was the oxidation of *rac*-1-phenylethanol to acetophenone (Scheme 2). Four different reaction conditions were explored, see Table 1. Three of them (A, C, and D) were selected since they have been working successfully in these oxidations when palladium acetate was employed as a catalyst and the reoxidant was oxygen gas.[6b,6c,7] The reaction conditions in method B were chosen since they are known to be compatible with cyclometallated imine catalysts in the Suzuki cross coupling in air.
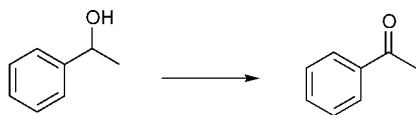
Scheme 2.
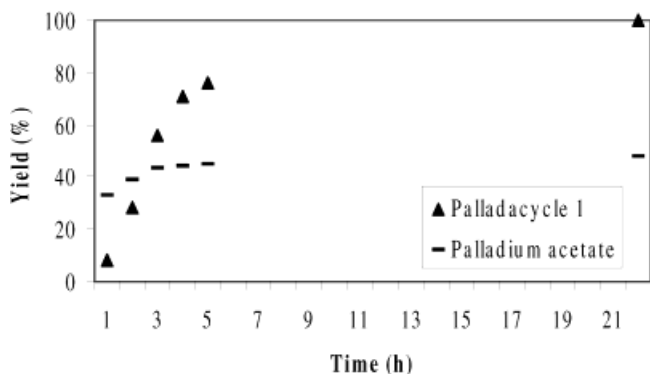
Figure 2. Graph showing the difference in product formation when palladacycle **1** and Pd(OAc)$_2$ were used to catalyze the oxidation of *rac*-1-phenylethanol.

The two different catalysts behaved differently under the different conditions. Palladium acetate was most efficient as a catalyst in DMSO with NaHCO$_3$ as the base; the yield was 89% after 24 hours whereas in *o*-xylene with K$_2$CO$_3$ only 36% yield after 22 hours was obtained. The palladacycle **1** gave a very fast and efficient reaction in toluene with pyridine as a base; after 4 hours the yield was 78% and after 22 hours quantitative conversion was observed. Under these conditions palladium acetate gave 56% yield after 4 hours and 58% after 22 hours. Product formation was somewhat faster in the beginning of the reaction with palladium acetate than with palladacycle **1**, but the former reaction slowed down and almost stopped after a few hours, while the reaction with the palladacycle went to completion (see Figure 2).

All methods besides method D were also tried when air was bubbled continuously during the reaction. In some cases a small improvement regarding the speed of the reaction was observed. Perfluorinated solvents have been reported to be advantageous in oxidations since they exhibit high O$_2$-solubility, chemical inertness, and resistance to oxidation.[6b,11] A perfluorinated solvent, perfluorodecalin, had a positive effect when palladium acetate was used as a catalyst, but a negative effect when palladacycle **1** was used. Since neither the use of perfluorinated solvent nor bubbling of air increased the rate of the reaction dramatically when palladacycle **1** was the catalyst, it seems that the amount of available oxygen is not the rate-limiting factor.

Since palladacycle **1** is a chiral catalyst there is a possibility of a difference in rate between the two enantiomers of a racemic alcohol. Analysis of the enantiomeric composition in the starting 1-phenylethanol was performed after ca 50% conversion by chiral gas chromatography. No significant resolution was observed.

We also studied the selectivity and activity of the catalyst in the oxidation of some other substrates under the best conditions found for palladacycle **1** (method C). Both primary and secondary aliphatic alcohols were selectively oxidized to the corresponding aldehyde or ketone, see Table 2. 1-Octanol was transformed into octanal with 65% conversion after 24 h. 2-Octanol was oxidized to the corresponding ketone with quantative conversion after 24 h.

Table 2. Oxidations of primary aliphatic and secondary aliphatic alcohols with palladacycle **1** as a catalyst, using the reaction conditions in method C.

Substrate	Conversion after 24 h[a]	Product
1-octanol	65%	octanal
2-octanol	quantitative	2-octanon

[a] The conversion was determined by GC-MS.

In summary, we have shown that cyclopalladated imine complexes are promising catalysts for the oxidation of aliphatic and benzylic alcohols to their corresponding aldehydes and ketones. It is possible to achieve higher yields than with palladium acetate as the catalyst. The reaction conditions are important in order to obtain a high yield. Palladium acetate and palladacycle **1** have differing optimal reaction conditions.

Experimental Section

General Remarks

Pd(OAc)$_2$ was dissolved in boiling benzene and the suspension was filtered and concentrated. Toluene was distilled from Na/benzophenone. Molecular sieves (3 Å MS) from Laporte were activated under high temperature and reduced pressure. Perfluorodecalin was purchased from Aldrich and used without further purification. Pyridine and other bases were purchased and used without further purification. 1-Phenylethanol was purified by chromatography before use. 1-Octanol and 2-octanol were commercially available and used without further purification. Acetic acid was refluxed over KMnO$_4$ and then distilled. *o*-Xylene was distilled over Na/benzophenone before use.

Palladacycle (1)

Pd(OAc)$_2$ (0.616 g, 2.74 mmol) was added to a solution of (4*S*)-4-isopropyl-2-phenyl-4,5-dihydro-1,3-oxazole (**2**) (0.519 g, 2.74 mmol) and acetic acid (2.9 mL) in a dry, 10-mL flask. The reaction mixture was heated to 95 °C under a nitrogen atmosphere for 45 min and then allowed to reach room temperature. After stirring for 70 min at rt the thick brown slurry was filtered. The precipitate was washed with large amounts of cold acetic acid and water. The solution was concentrated and the residue was dissolved in CHCl$_3$ and then filtered through celite. The solution was concentrated and dried under vacuum to give **1** as a yellow solid; yield: 0.993 g (96%); [α]$_D^{20}$: +260 (*c* 0.46, CH$_2$Cl$_2$); mp 180-183 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.17 (1 H, app d, *J* = 7.5 Hz), 7.13–7.04 (1 H, m), 7.02–7.06 (2 H, m), 4.06 (1 H, dd, *J* = 8.6 and 5.8 Hz), 3.37 (1 H, dd, *J* = 9.9 and 8.6 Hz), 3.10–3.04 (1 H, ddd, *J* = 9.9, 5.8 and 4.1 Hz), 2.11 (3 H, s), 2.07–1.98 (1 H, m), 0.77 (6 H, dd, *J* = 7.0 and 3.0 Hz); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 180.96, 173.29, 147.80, 131.25, 131.07, 130.07, 125.27, 123.55, 70.69, 66.29, 29.61, 24.10, 18.52, 15.27. After recrystallisation from hexane/CHCl$_3$ yellow-orange crystals were formed from which crystallographic data were collected.[12]

General Procedure for Alcohol Oxidation using Method A

Alcohol (1.0 mmol), naphthalene (internal standard, 64.1 mg, 0.50 mmol), NaHCO$_3$ (168 mg, 2.0 mmol), Pd(OAc)$_2$ or palladacycle **1** (5 mol % Pd) and DMSO (1.0 mL) were added to a dry 5-mL flask, equipped with a drying tube. The reaction was stirred at 80 °C for the indicated time (see Table 1).

A sample was taken, diluted with diethyl ether and filtered before injecting into the GC-MS. The yield was calculated from a calibration curve.

General Procedure for Alcohol Oxidation using Method B

Alcohol (1.0 mmol), naphthalene (internal standard, 64.1 mg, 0.50 mmol), K$_2$CO$_3$ (131 mg, 0.95 mmol), Pd(OAc)$_2$ or palladacycle **1** (10 mol % Pd) and *o*-xylene (1.6 mL) were added to a dry 5-mL flask, equipped with a drying tube. The reaction mixture was stirred at 130 °C for the indicated time (see Table 1). A sample was taken, diluted with diethyl ether and filtered before injecting into the GC-MS. The yield was calculated from a calibration curve.

General Procedure for Alcohol Oxidation using Method C

Pyridine (16 μL, 0.20 mmol) and 3 Å MS (500 mg) were added to a mixture of Pd(OAc)$_2$ or palladacycle **1** (5 mol % Pd), naphthalene (internal standard, 64.1 mg, 0.50 mmol) and toluene (4 mL) in a dry, 25-mL flask equipped with a drying tube. The yellow slurry was heated to 80 °C for 10 min and a solution of alcohol (1.0 mmol) and toluene (4 mL) was added dropwise with a syringe, after which additional toluene (2 mL) was added to rinse the syringe. The reaction mixture was stirred at 80 °C for the indicated time (see Table 1). A sample was taken, diluted with diethyl ether and filtered before injecting into the GC-MS. The yield was calculated from a calibration curve or the conversion was determined.

General Procedure for Alcohol Oxidation using Method D

Pyridine (8.1 μL, 0.10 mmol) was added to a mixture of Pd(OAc)$_2$ or palladacycle **1** (5 mol % Pd), naphthalene (internal standard, 32.1 mg, 0.25 mmol) and toluene (1.5 mL) in a dry 10-mL flask under vigorous stirring. After a few minutes, perfluorodecalin (2 mL) and 3Å MS (250 mg) were added, followed by a solution of the alcohol (0.50 mmol) and toluene (0.5 mL). The mixture was stirred at 80 °C for the indicated time (see Table 1). A sample was taken, diluted with diethyl ether and filtered before injecting into the GC-MS. The yield was calculated from a calibration curve.

Acknowledgements

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