DOI 10.5012/bkcs.2011.32.8.3179

Pd/C Catalyzed Oxidation of Secondary Benzylic Alcohols using Chlorobenzene under an Inert Condition†

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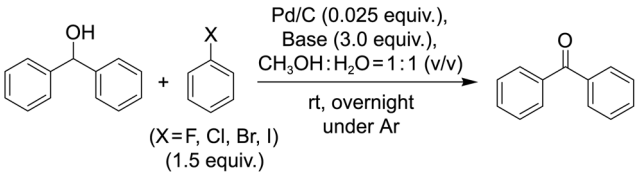
Received March 2, 2011, Accepted June 4, 2011

Key Words : Catalyst, Oxidations, Alcohol, Palladium, Chlorobenzene

Oxidation of alcohol is one of the most important transformation reactions in organic chemistry and numerous methods have been reported.[1] In particular, reactions using a heterogeneous catalyst are remarkable because of the reusability and easy separation of the catalyst.[2] The oxygen-containing oxidants such as air, O_2, H_2O_2, NaOCl, DMSO, and metal oxide are commonly used for oxidation, while reactions using non-oxygen-containing oxidants are relatively less studied. Oxygen-containing systems are not applicable to the oxidation of a substrate that is sensitive to oxygen. In an oxidation reaction, oxygen reacts with hydrogen on a palladium surface after one reaction cycle.[3] This regenerates a fresh palladium surface and boosts an oxidation reaction on it. In the absence of an oxygen source, the catalyst does not effectively catalyze the oxidation reaction and requires another activator. Several research groups investigated this oxidation reaction using a hydrogen transfer reagent such as olefin, nitrobenzene, or halobenzene for activation by regeneration of the fresh metal catalyst surface.[4] For example, the effective oxidation of benzylic alcohols was reported by using a Pd catalyst with chlorobenzene.[5] However, most reactions proceeded at high temperature over long reaction times and usually used homogeneous catalysts. Previously, our group investigated an oxidation reaction with Pd/C, sodium borohydride and potassium carbonate in the presence of oxygen.[6] This method was efficient for the oxidation of various benzylic and allylic alcohols at room temperature. In this method, sodium borohydride was used to boost the oxidation.

We considered the oxidation reaction of various alcohols using halobenzene and heterogeneous Pd/C in an inert condition. We used halobenzene because it is commercially available, inexpensive and can be handled easily. In addition, halobenzene plays a very significant role in this reaction. We used halobenzene as an activator instead of oxygen. Each reaction was performed under an inert condition to confirm that halobenzene could be used as an activator in the absence of oxygen. The freeze-pump-thaw and purging method was used to remove oxygen in reaction solution. Initially, we checked for the effect of halobenzene and base using benzhydrol as the starting alcohol in the given reaction condition in Scheme 1.

Entry 4 in Table 1 reveals that the use of Pd/C (0.025 equiv.), chlorobenzene (1.5 equiv.) and potassium hydroxide (3.0 equiv.) at room temperature afforded the best yield for oxidation. Bromobenzene and iodobenzene could not sufficiently activate the reaction compared to chlorobenzene. This may be explained by a hard-soft acid-base concept. The softer Br and I atoms can strongly interact with the soft palladium metal to afford the stable palladium-halide complex on the palladium surface, and it obstructs the catalytic cycle. Alternatively, the oxidative addition of fluorobenzene to the palladium is difficult due to a very strong C-F bond. Since the halobenzene was used in the reaction, biphenyl as a homocoupling product was obtained in all reaction mixture. It proved that the palladium surface was reactivated by reductive elimination in the catalytic reaction cycle. We also expected the formation of benzene as a byproduct, but we could not separate it because of its volatility. Without halobenzene, the benzophenone was only obtained in lower yields (entries 1 and 2). The base interacted with the hydrogen of the starting alcohol and helped the coordination



Scheme 1

Table 1. The effect of halobenzene and base in oxidation reaction

Entry	X	Base	Isolated Yield (%)
1	–	KOH	28
2	–	K_2CO_3	7
3	F	KOH	25[a]
4	Cl	KOH	45
5	Br	KOH	6
6	I	KOH	3

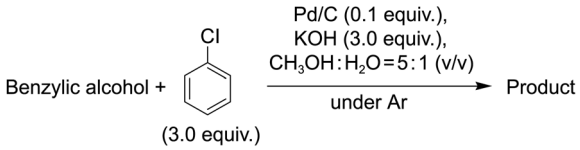
[a]Biphenyl was not obtained in the reaction mixture.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

Table 2. The optimization of oxidation of benzhydrol by chlorobenzene

Entry	Chlorobenzene (equiv.)	Pd/C (equiv.)	MeOH:H_2O (v/v)	Temp. (°C)	Time (h)	Isolated yield[a] (%)
1	1.5	0.025	5:1	rt	24	45
2	3.0	0.025	5:1	rt	24	52
3	5.0	0.025	5:1	rt	24	53
4	10	0.025	5:1	rt	24	60
5	3.0	0.025	2:1	rt	24	47
6	3.0	0.025	1:1	rt	24	45
7	3.0	0.025	H_2O	rt	24	1
8	3.0	0.025	MeOH	rt	24	42
9	3.0	0.05	5:1	rt	24	71
10	3.0	0.1	5:1	rt	24	80
11	3.0	0.1	5:1	60	1	91

[a]A stating alcohol (benzhydrol) and base (KOH 3.0 equiv.) were used. The biphenyl was obtained in a reaction mixture.



Scheme 2

of alcohol on the catalyst. The reactivity of potassium hydroxide was better than that of the potassium carbonate.

Next, we investigated the effect of the amount of chlorobenzene, the solvent system, the catalyst loading, and temperature on the same reaction as shown in Table 2. The reaction with 10 equiv. of chlorobenzene showed the best result and the use of 3.0 equiv. of chlorobenzene also gave a comparable yield. In order to check the influence of the solvent, several ratios of aqueous methanol were tested (entries 2 and 5-8). Entry 10 showed that 10 mol% catalyst is necessary to obtain product in the best yield at room temperature. A higher reaction temperature increased the yield of product in a shorter reaction time (entry 11).

After the reaction was optimized, this protocol was validated by applying to various secondary benzylic alcohols in aqueous methanol solution under an inert condition (Scheme 2, Table 3). A good yield of oxidized products was obtained except for the cases of substrates containing alpha protons toward the carbonyl group of product (entries 8-10). If the starting alcohol had protons, small amounts of aldol condensation product were obtained as a byproduct leading to a decreased yield of product. Some groups have already reported aldol condensation,[7] oligomerization[8] of carbonyl compound or decomposition of alcohol during this kind of oxidation reaction. In the case of 4-nitrobenzhydrol, 4-aminobenzohenone was obtained as a byproduct resulting from the reduction of a nitro group (entry 4). Our presumed reaction mechanism is as follows. The carbon-chlorine bond of chlorobenzene is cleaved by an oxidative addition with palladium along with the coordination of starting alcohol on the palladium surface. The hydrochloride is captured by base and the following β-hydride elimination of alkoxide affords the corresponding carbonyl product. At this time, biphenyl or benzene is produced by reductive elimination and a fresh palladium (0) surface is regenerated. To confirm this presumed mechanism, 1-chloronaphthalene was used instead of chlorobenzene in the oxidation of benzhydrol (Scheme 3). Among the reaction products, binaphthyl and naphthalene were obtained. This proves that either biphenyl or benzene is produced by reductive elimination and that a fresh palladium (0) surface is regenerated.

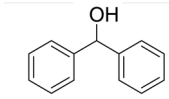
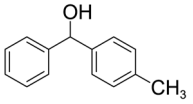
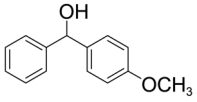
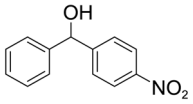
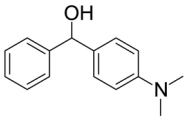
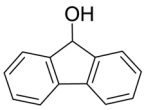
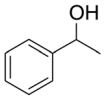
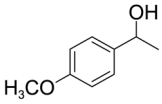
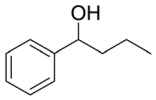
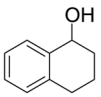
In conclusion, we demonstrated a protocol for the oxidation of benzylic alcohol using Pd/C, potassium hydroxide and chlorobenzene in an oxygen-free aqueous methanol solution under an inert condition. The use of chlorobenzene, which is inexpensive and commercially available, in the absence of oxygen, was the alternative choice to activate the oxidation reaction.

Experimental Section

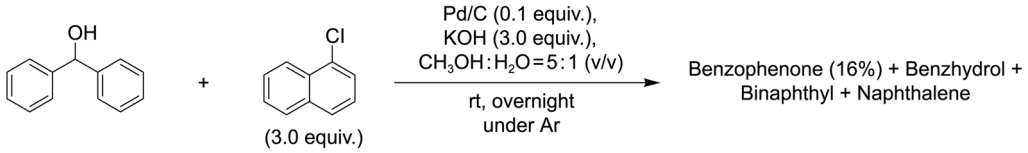
General. All reagents were purchased and used without purification from Aldrich and TCI. The freeze-pump-thaw and purging method[9] was used for the removal of oxygen from the reaction solvent. All reactions requiring inert conditions were conducted in argon. Analytical TLC was conducted on E. Merck 60 F254 aluminum-backed silica gel plates (0.2 mm). Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were obtained using a Varian FT-NMR spectrometer (300 MHz) in $CDCl_3$ solvent and all products were counterchecked with data in the literature. The chemical shifts were reported in δ ppm relative to TMS.

Procedure. The starting alcohol (1 mmol), KOH (3.0 mmol) and catalyst (10 mol% Pd) were added to a Schlenk flask. In another Schlenk flask, the oxygen in the solvent (MeOH : H_2O = 5:1, v/v, 6.0 mL) was removed by the freeze-pump-thaw and purging method. The aqueous solvent was transferred to the reaction flask of the starting alcohol by cannulation. Afterwards, chlorobenzene (3.0 mmol) was added using a syringe, and the reaction was kept under argon. Upon completion of the reaction based on TLC monitoring, the Pd/C was filtered off on celite and the solvent was removed by rotary evaporation. A brine solution

Table 3. The oxidation of various secondary benzylic alcohols

Entry	Substrate	Temp	Time (h)	Isolated Yield (%)[a]
1		rt	Overnight	80
		60 °C	1	91[b]
2		rt	Overnight	83
		60 °C	2	80
3		rt	Overnight	86
		60 °C	1	87
4		rt	Overnight	Trace
		60 °C	2	Trace[c]
5		rt	Overnight	87
		60 °C	0.5	97
6		rt	Overnight	87
		60 °C	3	95
7[d]		rt	Overnight	92
		60 °C	2	72
8[d]		rt	Overnight	40
		60 °C	5	38
9[d]		rt	Overnight	65
		60 °C	6	68
10[d]		rt	Overnight	8
		60 °C	2	Trace

[a]Biphenyl was obtained in reaction mixture.
[b]Without chlorobenzene, benzophenone was obtained in 14% yield.
[c]Among the products, 4-aminobenzophenone was obtained in a 26% yield.
[d]Aldol condensation product was observed in the reaction mixture.



Scheme 3

was added to the residue and the product was extracted using methylene chloride. The organic layer was collected, dried with anhydrous magnesium sulfate, and concentrated by rotary evaporation. The mixture was purified via column chromatography using various hexane/EtOAc eluent systems. All products were known and characterized by comparing their ^{1}H NMR spectra with those that have been published in the literature.

Benzophenone (1).[10] ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 4H), 7.58 (t, J = 8.1 Hz, 2H), 7.47 (t, J = 8.1 Hz, 4H).

4-Methylbenzophenone (2).[10] ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 6.9 Hz, 2H), 7.73 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H).

4-Methoxybenzophenone (3).[10] ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 6.9 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 6.9 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H).

4-Aminobenzophenone (4).[11] Byproduct, ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 7.5 Hz, 4H), 7.52 (t, J = 7.2 Hz, 2H), 7.45 (t, J = 7.1 Hz, 1H), 6.67 (d, J = 7.5 Hz, 2H), 4.13 (br s, 2H).

***N*, *N*-dimethylbenzophenone (5).**[12] ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 6.9 Hz, 1H), 7.44 (t, J = 8.1 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 3.07 (s, 6H).

9-Fluorenone (6).[13] ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H).

Acetophenone (7).[10] ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 6.9 Hz, 2H), 7.57-7.55 (m, 1H), 7.49-7.43 (m, 2H), 2.60 (s, 3H).

4-Methoxyacetophenone (8).[14] ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 2.55 (s, 3H).

Butyrophenone (9).[15] ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 9.0 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H), 1.82-1.70 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H).

α-Tetralone (10).[16] ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 2.95 (t, J = 5.7 Hz, 2H), 2.64 (t, J = 6.0 Hz, 2H), 2.17-2.07 (m, 2H).

Acknowledgments. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0028217). M. L. appreciated the financial support from the Korean Ministry of Education through the second stage of the BK21 project for the Hanyang University graduate program, and also acknowledged the Seoul Metropolitan Government for Seoul Science Fellowship.

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