In situ coupled oxidation cycle catalyzed by highly active and reusable Pt-catalysts: dehydrogenative oxidation reactions in the presence of a catalytic amount of *o*-chloranil using molecular oxygen as the terminal oxidant†

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Received 28th July 2010, Accepted 13th September 2010
DOI: 10.1039/c0cc02865g

An *in situ* coupled oxidation cycle that allows catalytic oxidation of a substrate with catalytic amounts of *o*-chloranil and novel reusable polymer-immobilized platinum nanocluster catalysts using molecular oxygen as the terminal oxidant was developed.

Oxidation is a basic and very important process in organic synthesis and many methodologies and reagents for oxidation have been developed so far.[1] Quinones with high oxidation potential, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and chloranils, are versatile and important oxidizers in organic synthesis (Fig. 1).[2] However, stoichiometric use of these quinones often leads to difficulty in removing concomitant by-products, hydroquinones. The high cost of these expensive oxidizers is another problem. Such issues may be overcome by using a catalytic amount of quinone and a stoichiometric amount of co-oxidant.[3] Of all co-oxidants, molecular oxygen is an ideal oxidizer from environmental and economic points of view, because molecular oxygen is abundant in air and water is the sole by-product after oxidation.

However, because molecular oxygen is a triplet, highly selective direct reactions between molecular oxygen and common singlet organic compounds are difficult under mild conditions in spite of the high oxidative potential of molecular oxygen.[4] An alternative approach is transfer of the oxidative potential of molecular oxygen to singlet organic compounds that can easily react with common organic substrates in the presence of a reusable catalyst. Under these conditions, a more abundant and environmentally benign oxidation system could be realized (Scheme 1).[5,6]

Here, we report an *in situ* coupled oxidation cycle that allows catalytic oxidation of a substrate with catalytic amounts of *o*-chloranil and novel reusable, polymer-immobilized platinum nanocluster catalysts using molecular oxygen as the terminal oxidant. To the best of our knowledge, this is the first example of *in situ* regeneration of quinones with high oxidation potential using molecular oxygen under ambient conditions.

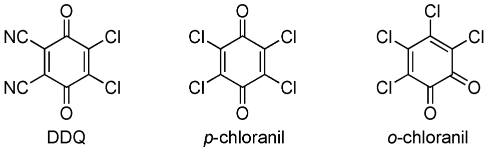
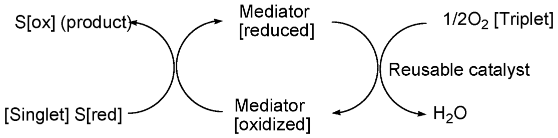


Fig. 1 Quinones with high oxidation potential.



Scheme 1 *In situ* coupled oxidation cycle using molecular oxygen as the terminal oxidant.

Recently, we have developed aerobic oxidation of hydroquinones using polymer-incarcerated gold and platinum nanocluster catalysts.[7] This project commenced with the development of polymer-incarcerated platinum catalysts, which were effective for oxidation of hydroquinones with both electron-donating and electron-withdrawing groups. However, the structure of this polymer contains benzyloxy moieties, which may be oxidized by *o*-chloranil, leading to partial decomposition of the catalyst.[9] We addressed this issue by preparing two types of novel durable platinum cluster catalysts under oxidative conditions using organic–inorganic hybrid copolymer **1**, which contains trimethoxysilyl groups for cross-linking,[8] and polystyrene based polymer **2** without benzyloxy moieties (Scheme 2). Copolymer **1** and sodium borohydride were dissolved in diglyme at room temperature and a diglyme solution of sodium hexachloroplatinate(IV) was added dropwise. After the solution was stirred for several hours at room temperature, a mixture of aqueous sodium hydroxide solution and isopropanol was added, and microcapsules were formed immediately. The solution containing microcapsules was heated at 90 °C for 3 h, and then successive filtration, washing, grinding, and heating at 120 °C without solvent afforded an organic–inorganic hybrid platinum nanocluster catalyst (HB Pt) as a gray powder. On the other hand, oxidation-resistant polymer-incarcerated platinum catalyst (RPI Pt) was prepared from copolymer **2**, which does not have benzyloxy moieties, according to the procedure for the preparation of PI Pt.[7] The metal loadings were analyzed by inductively coupled plasma (ICP) analysis, and the size of the platinum nanoclusters was determined by transmission electron microscopy (TEM) (3–9 nm).[9]

Hantzsch's pyridine synthesis, preparation of pyridines *via* oxidation of 1,4-dihydropyridines that are synthesized by

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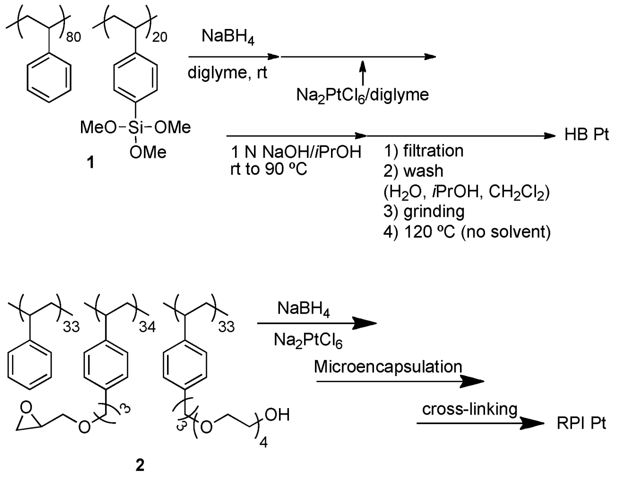
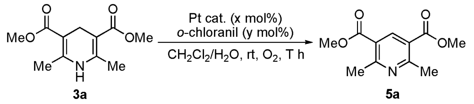
† Electronic supplementary information (ESI) available: Experimental details and TEM images of the catalysts. See DOI: 10.1039/c0cc02865g



Scheme 2 Preparation of an organic–inorganic hybrid platinum nanocluster catalyst (HB Pt) and an oxidation-resistant polymer-incarcerated platinum catalyst (RPI Pt).

Table 1 Aerobic oxidation with catalytic amounts of *o*-chloranil and Pt catalysts



Entry	Pt cat.	*x*/*y*	CH_2Cl_2/H_2O (mL/mmol)	Time/h	Yield[a] (%)
1	HB	0/110	4/0.2	2	> 99
2	HB	2.5/0	4/0.2	2.5	0
3	HB	1.0/10	4/0.2	2.5	> 99
4	HB	0.25/2.5	4/0.2	6	> 99[b]
5	HB	0.25/0.50	2/0.1	24	95
6	RPI	0.25/0.50	2/0.1	5	97[b]
7	RPI	0.25/2.5	2/0.1	21	92[c]
8	RPI	0.10/0.10	2/0.1	24	93

[a] Isolated yield. [b] No leaching of Pt was confirmed by ICP analysis (detection limit: 0.21 ppm; no peak of Pt was observed). [c] Air (1 atm) was used instead of O_2 (1 atm).

condensation of 1,3-dicarbonyl compounds, aldehydes and ammonia, is a traditional but highly efficient method for production of symmetric pyridines, in which a stoichiometric amount of DDQ is usually used in the oxidation step from dihydropyridine to pyridine.[10,11] To probe the viability of the designed *in situ* coupled oxidation cycle, the oxidation of Hantzsch's dihydropyridine to pyridine using catalytic amounts of *o*-chloranil and Pt catalysts under an oxygen atmosphere was investigated (Table 1). A stoichiometric amount of *o*-chloranil rapidly oxidized dihydropyridine **3a** to pyridine **5a** (entry 1). On the other hand, HB Pt was not effective for direct aerobic oxidation of dihydropyridine (entry 2). When catalytic amounts of both *o*-chloranil and HB Pt were used under atmospheric oxygen, the reaction proceeded smoothly to give the desired product quantitatively (entries 3–5). We also found that RPI Pt was effective for this reaction (entries 6 and 7). It is noted that the amounts of *o*-chloranil/HB Pt and *o*-chloranil/RPI Pt could be reduced to 0.25 mol%/0.5 mol% and 0.1 mol%/0.1 mol% respectively, to obtain excellent yields (quantitative conversions) after further optimization (entries 5 and 8). Moreover, no leaching of platinum to the reaction mixture was observed after filtration of Pt catalysts (entries 4 and 6), and atmospheric air can be used as an oxidant to afford the product in good yield while longer reaction time was required (entry 7). We also tested other quinones both with electron withdrawing groups (EWG) and with electron donating groups (EDG). Quinones with EWG showed higher reactivity than those with EDG, and *o*-chloranil was found to be the best.[9]

Recovery and reuse of the HB Pt catalyst was examined using 0.25 mol% of HB Pt and 2.5 mol% of *o*-chloranil. Remarkably, a high yield of the desired product was obtained until the seventh use, although the remaining starting material was detected in the eighth and ninth uses (Table 2). TEM analysis of HB Pt after the ninth use showed that the sizes of the platinum nanoclusters increased from a range of 3–9 nm to 5–15 nm.[9] Deactivation of the HB Pt catalyst could be attributed to aggregation of platinum nanoclusters.

The substrate scope for this reaction system was then investigated. Dihydropyridine substituted by both aromatic and alkyl groups at the 4-position was successfully oxidized to the corresponding pyridines in good to excellent yields (Table 3, entries 1–10). Substrates bearing both electron-rich and electron-poor aromatic substituents were oxidized (entries 5–9). Both HB Pt and RPI Pt worked well for this oxidation, although slight difference of activities depending on substrates was observed. Nonsymmetric dihydropyridines, whose preparation method was reported by Manning and Davies,[12] were also good substrates for this oxidation system as well as symmetric dihydropyridines (entries 11–13).

The oxidation system was applicable to other reactions. Indoline could also be oxidized efficiently to indole in high yield (Scheme 3).[13] A *p*-methoxybenzyl (PMB) protected alcohol could be deprotected with catalytic amount of RPI Pt and *o*-chloranil to afford the desired alcohol in good yield (Scheme 4). It is noteworthy that when a stoichiometric amount of *o*-chloranil was used for oxidation of a tetrahydroquinoline derivative,[14] a mixture of ketone and ketal derived from tetrachlorocatechol was obtained as a major product; however, the use of a catalytic amount of *o*-chloranil provided the desired ketone in high yield as the sole product (Scheme 5).

In conclusion, we have developed an *in situ* coupled oxidation cycle that was applied to dihydropyridine, indoline, PMB, and tetrahydroquinoline oxidation. Novel platinum nanocluster catalysts were developed for this system. It is noted that the oxidations proceeded smoothly in the

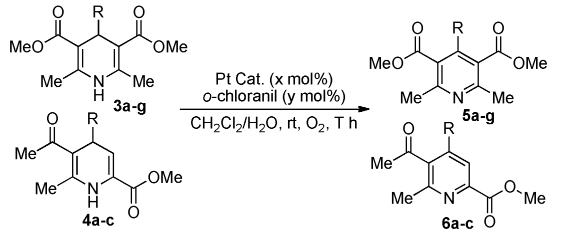
Table 2 Recovery and reuse of HB Pt

$$\mathbf{3a}\ \xrightarrow[\text{CH}_2\text{Cl}_2/\text{H}_2\text{O (4/0.2 mmol/mL), rt, O}_2\text{, 6 h}]{\text{HB Pt (0.25 mol\%), o-chloranil (2.5 mol\%)}}\ \mathbf{5a}$$

Run	1	2	3	4	5	6	7	8	9
Yield (%)	99	> 99	99	94	98	> 99	97	90	85

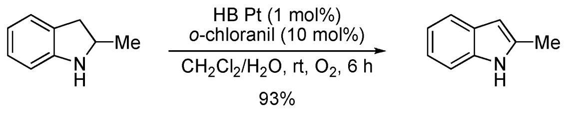
[a] Recovered HB Pt was washed after each use in a mixture of 1 N NaOH and isopropanol (1 : 1).

Table 3 Substrate scope for aerobic oxidation of dihydropyridines

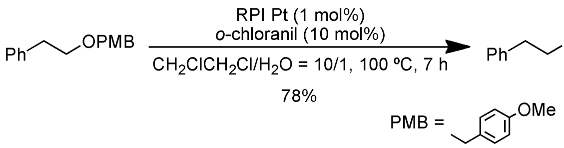


Entry	Substrate	R	Pt cat.	x/y	Solvent^b	Time/ h	Yield^a (%)
1	**3b**	Et	HB	0.5/5	4/0.2	64	82
2	**3c**	Ph	HB	0.5/5	4/0.2	36	> 99
3	**3c**	Ph	HB	0.5/5	4/0.2	36	> 99
4	**3c**	Ph	RPI	1/10	8/0.4	20	> 99
5	**3d**	4-ClC$_6$H$_4$	HB	0.5/10	16/0.8	24	> 99
6	**3e**	4-MeOC$_6$H$_4$	HB	1/10	16/0.8	21	97
7	**3e**	4-MeOC$_6$H$_4$	RPI	1/10	8/0.4	20	> 99
8	**3f**	4-CF$_3$C$_6$H$_4$	HB	1/10	16/0.8	33	90
9	**3f**	4-CF$_3$C$_6$H$_4$	RPI	1/10	8/0.4	20	> 99
10	**3g**	–CH=CH–Ph	HB	1/10	16/0.8	36	> 99
11	**4a**	Ph	HB	1/10	8/0.4	6	91
12	**4b**	4-MeOC$_6$H$_4$	HB	1/10	8/0.4	6	84
13	**4c**	4-CF$_3$C$_6$H$_4$	HB	1/10	8/0.4	6	87

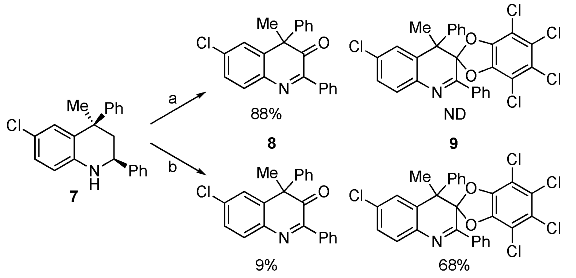
^{a} Isolated yield. ^{b} CH_2Cl_2/H_2O (mL/mmol).



Scheme 3 Aerobic oxidation of an indoline derivative.



Scheme 4 Deprotection of PMB group using catalytic amount of RPI Pt and *o*-chloranil.



Scheme 5 Comparison between a catalytic amount and a stoichiometric amount of *o*-chloranil in the oxidation of tetrahydroquinoline derivative. *Conditions* a: HB Pt (2 mol%), *o*-chloranil (20 mol%), CH_2Cl_2/H_2O, rt, O_2, 96 h. b: *o*-chloranil (3 equiv.), CH_2Cl_2/H_2O, rt, O_2, 24 h. ND = not detected.

presence of a catalytic amount of *o*-chloranil under very mild conditions. Further investigations to apply this aerobic oxidation system to other reactions are now in progress.

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, and NEDO. H. M. thanks the JSPS fellowship for Japanese Junior Scientist. Special thanks to Mr. Kuramitsu (The University of Tokyo) for electronic microscopy analysis.

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