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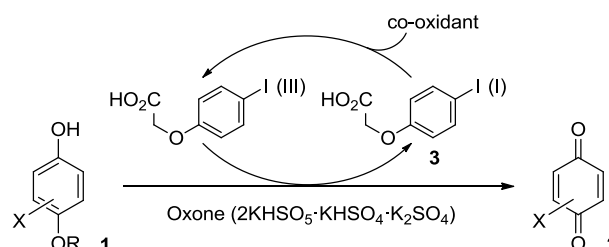
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Recyclable Magnetic Nanoparticle-Supported Iodoarene Catalysts for Oxidation of 4-Alkoxyphenols to Quinones

Hisanori Nambu, Ikumi Shimokawa, Tomoya Fujiwara, and Takayuki Yakura*^[a]

Abstract: Iodoarene catalysts immobilized on magnetite (Fe_3O_4) were developed. The catalysts **4a** and **4b** showed reactivities similar to that of 4-iodophenoxyacetic acid (**3**) for the oxidation of 4-alkoxyphenols in the presence of Oxone[®] as a co-oxidant to give the corresponding *p*-quinones in high yields. In addition, **4b** was readily recovered by the use of an external magnet and could be recycled up to eight times. This is the first example of a magnetic nanoparticle-supported iodoarene catalyst.

Environmentally benign procedures are required for the production of pharmaceuticals, flavors and fragrances, and agrochemicals. Hypervalent iodine compounds have recently received significant attention as efficient, useful, and non-metallic oxidants in organic synthesis owing to their low toxicity, ready availability, and ease of handling.^[1] With respect to the principles of Green Chemistry, hypervalent iodines are not ideal because stoichiometric amounts of iodine reagents are necessary during oxidation to produce equimolar amounts of iodine waste. Recyclable polymer-supported hypervalent iodine reagents have been developed as environmentally friendly oxidants.^[1c,d,2] Soluble and recyclable hypervalent iodine reagents have also been developed.^[2b,3] Moreover, catalytic systems based on in situ generation of hypervalent iodine species have been reported.^[4,5] We have also reported catalytic hypervalent iodine oxidation of 4-alkoxyphenols **1** to *p*-quinones **2** using a catalytic amount of 4-iodophenoxyacetic acid (**3**) with Oxone[®] ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) as a co-oxidant (Scheme 1).^[5c,e] For the separation of **3**, this catalytic oxidation system uses an easier procedure when compared with the usual iodoarene catalyst system because of the solubility of **3** in an alkaline solution. However, to recover **3**, acid–base liquid separation treatments must be conducted several times. Herein, we report the development of easily recoverable and recyclable magnetic nanoparticle-supported iodoarene catalysts **4a** and **4b** (Fig. 1) for oxidation of 4-alkoxyphenols to *p*-quinones.



Scheme 1. A catalytic hypervalent iodine oxidation of 4-alkoxyphenols **1** to *p*-quinones **2** using 4-iodophenoxyacetic acid (**3**) with Oxone[®].

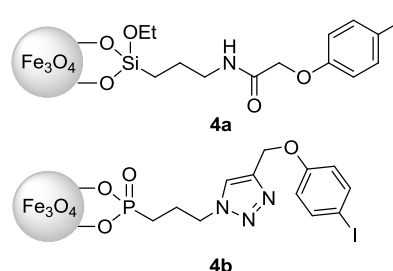


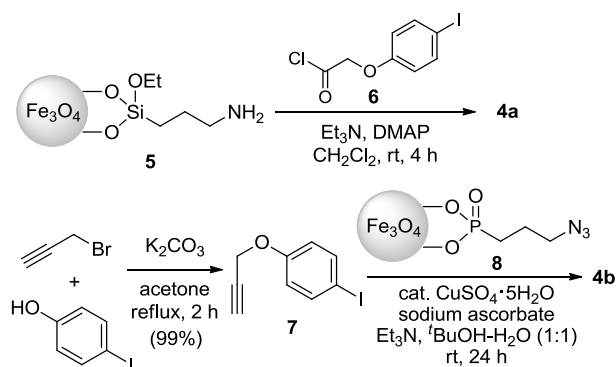
Figure 1. Structures of iodoarene catalyst immobilized on magnetite **4a** and **4b**.

Magnetic nanoparticles have recently shown their efficiency as a core for catalyst support.^[6] These supported catalysts show high catalytic reactivity owing to a large surface area to volume ratio. Moreover, they can be easily separated from the reaction by application of an external magnetic field, allowing for simple separation of the catalysts without liquid separation and filtration. We chose magnetite (Fe_3O_4) nanoparticles for use as magnetic supports because of their simple synthesis, low cost, and relatively large magnetic susceptibility. Either silane^[7] or phosphonate^[8] anchors are often selected to combine the magnetic nanoparticle and catalyst sites.^[9] We prepared both silicon and phosphate anchored catalysts to investigate their catalytic activities. First, a silica-coated iodoarene catalyst, **4a**, was prepared, as shown in Scheme 2. The known silica-coated magnetite **5**^[7e] was obtained by coupling of magnetite with 3-aminopropyltriethoxysilane, which acts as the linker to catalyst. Acylation of **5** with acid chloride **6** derived from 4-iodophenoxyacetic acid (**3**) was used to combine the magnetic nanoparticles and catalyst. Amidation of **5** with **6** was conducted in the presence of triethylamine and 4-(*N,N*-dimethylamino)pyridine (DMAP) in dichloromethane to give **4a**. The organic loading of **4a** was very low (0.087 mmol/g) as determined by elemental analysis of iodine. Second, we synthesized the phosphonic acid-linked catalyst **4b** by Cu-catalyzed cycloaddition of 1-iodo-4-(prop-2-ynoxy)benzene (**7**)^[10] with known magnetite-supported 3-

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azidopropylphosphonate (**8**),^[9b,c] prepared by a three-step sequence from the commercially available diethyl 3-bromopropylphosphonate. Alkyne-functionalized iodoarene **7** was prepared by propargylation of 4-iodophenol. Coupling of **7** and **8** was accomplished by treatment with CuSO₄ via the “click” reaction to afford phosphonic acid-coated catalyst **4b**, whose organic loading (0.33 mmol/g) was much higher than that of **4a**.

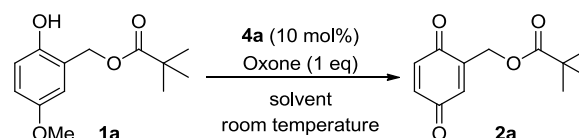


Scheme 2. Synthesis of magnetic nanoparticle-supported iodoarene catalysts **4a** and **4b**.

Catalyst **4a** was first evaluated for the oxidation of 4-methoxy-2-pivaloyloxymethylphenol (**1a**) to *p*-quinone **2a** using our reported procedure^[5c,e] for **3** (Table 1). When **1a** was treated with 10 mol% of catalyst **4a** in the presence of Oxone[®] (1 eq) in CF₃CH₂OH–H₂O (1:2) at room temperature, the reaction was completed within 1.5 h to give the corresponding *p*-quinones **2a** in 84% yield. The magnetic catalyst **4a** was rapidly collected in 93% yield by application of an external magnet, washed with EtOAc, H₂O, acetone and Et₂O, and dried to recover and reuse. The recovered **4a** was used again to oxidize **1a** under the same conditions to give **2a** in 82% yield with recovery of **4a** in 96% yield, although the reaction required a longer time (4.5 h) for completion. The third use of **4a** showed poor catalytic reactivity and gave 68% yield of **2a** with a significant amount of unknown by-product after 8.0 h. These results indicate that **4a** decomposes under these conditions and that pure **4a** could not be recovered by our hands. Next, we investigated the use of 0.1 M phosphate buffer instead of H₂O to avoid the strong acidic conditions caused by the presence of Oxone[®]. The oxidation of **1a** with **4a** in CF₃CH₂OH–0.1 M phosphate buffer (1:2) also proceeded smoothly at room temperature to afford **2a** in 91% yield after 2 h and recovery of **4a** in 98% yield.^[11] The reusability of **4a** in CF₃CH₂OH–0.1 M phosphate buffer was examined again. The reactivity of **4a** gradually lowered, resulting in an increase in the reaction time. The fourth use of **4a** needed 24 h to complete the reaction. In contrast, phosphonic acid-coated catalyst **4b** showed better reusability in the oxidation of **1a** (Table 2). The catalyst **4b** was also rapidly collected by an external magnet, and washed with EtOAc, H₂O, acetone and Et₂O. No signs of iodoarene catalyst could be detected in the crude reaction mixture, obtained by concentration of the EtOAc solution, and the residues (<1 mg), obtained by concentration of acetone and Et₂O solutions, by ¹H NMR spectroscopy. The

recovered catalyst **4b** could be efficiently recycled up to eight times, although the reaction times gradually increased.^[12,13] In all cases, **4b** was recovered in over 96% yields. These results suggest that the phosphonic acid-coated catalyst **4b** is more stable than the silica-coated catalyst **4a** under acidic conditions.^[14,15]

Table 1. Recyclability of **4a** for the oxidation of **1a**.



Cycle	Solvent	Time (h)	Yield (%)	Recovery of 4a (%)
1	CF ₃ CH ₂ OH/H ₂ O (1:2)	1.5	84	93
2	CF ₃ CH ₂ OH/H ₂ O (1:2)	4.5	82	96
3	CF ₃ CH ₂ OH/H ₂ O (1:2)	8	68 ^[b]	97
1	CF ₃ CH ₂ OH/buffer ^[a] (1:2)	2	91	98
2	CF ₃ CH ₂ OH/buffer ^[a] (1:2)	4	91	100
3	CF ₃ CH ₂ OH/buffer ^[a] (1:2)	8	91	100
4	CF ₃ CH ₂ OH/buffer ^[a] (1:2)	24	80	100

[a] Buffer: 0.1 M phosphate buffer solution. [b] Unknown by-product was isolated.

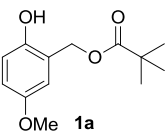
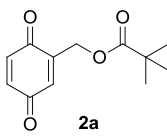
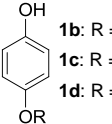
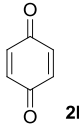
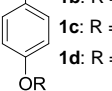
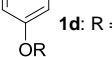
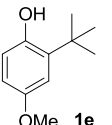
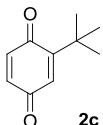
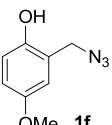
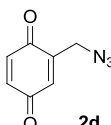
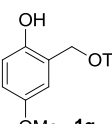
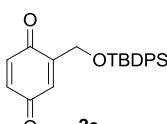
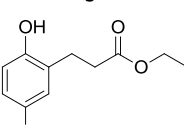
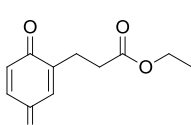
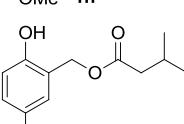
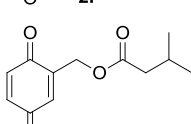
Table 2. Recyclability of **4b** for the oxidation of **1a** in CF₃CH₂OH/buffer^[a] (1:2).

Cycle	Time (h)	Yield (%)	Recovery of 4b (%)
1	4	80	98
2	4	81	97
3	5.5	80	98
4	7.5	82	96
5	8	82	96
6	11	81	99
7	15	78	96
8	24	71 ^[b]	96

[a] Buffer: 0.1 M phosphate buffer solution. [b] Starting material **1a** was recovered in 3% yield.

We next investigated the ability of our synthesized catalysts to oxidize other 4-alkoxyphenols. At this point we chose to pursue **4b** because of its better recyclability and higher loading of iodoarene. Table 3 shows the results of using **4b** under the same conditions as those in Table 2 to oxidize 4-alkoxyphenols bearing several substituents. Simple hydroquinone (**1b**), 4-methoxyphenol (**1c**), and 4-ethoxyphenol (**1d**) were oxidized to *p*-benzoquinone (**2b**) in excellent yields (entries 2–4). The reaction of the phenol **1e**, possessing a bulky *tert*-butyl group at the 2-position, proceeded smoothly to give the corresponding quinone **2c** in 73% yield (entry 5). Azido and *tert*-butyldiphenylsilyloxy (TBDPSO) groups were tolerated under the oxidation conditions (entries 6 and 7), although the reaction of **1g** required changing the solvent to a 3:1 mixture of CF₃CH₂OH–0.1 M phosphate buffer owing to its solubility (entry 7). The use of an ethyl ester **1h**^[16] led to good product yield (75%, entry 8). This oxidation could be applied to the synthesis of blattellaquinone (**2g**),^[17] the sex pheromone of the German cockroach, *Blattella germanica*, isolated in 2005 (entry 9). Oxidation of **1i** under the standard conditions afforded **2g** in 76% yield. In all cases, the magnetic catalyst **4b** could be recovered by an external magnet in 86–99% yields.

Table 3. Oxidation of 4-alkoxyphenols **1** using catalyst **4b**.^[a]

Entry	Substrate	Product	Time (h)	Yield (%)
1	 1a	 2a	4	80 (98) ^[b]
2	 1b : R = H	 2b	0.5	81 (96) ^[b]
3	 1c : R = Me		2	95 (93) ^[b]
4	 1d : R = Et		3	93 (99) ^[b]
5	 1e	 2c	2.5	73 (98) ^[b]
6	 1f	 2d	2.5	68 (92) ^[b]
7 ^[c]	 1g	 2e	4	79 (86) ^[b]
8	 1h	 2f	3	75 (98) ^[b]
9	 1i	 2g	4	76 (92) ^[b]

[a] Reactions were conducted in CF₃CH₂OH/0.1 M phosphate buffer solution (1:2) at room temperature. [b] Yields in parentheses were recovery of catalyst **4b**. [c] CF₃CH₂OH/0.1 M phosphate buffer solution (3:1) was used as a solvent.

In summary, magnetic nanoparticle-supported catalysts **4a** and **4b** were easily synthesized as the first magnetic iodoarene nanocatalysts and were evaluated for the oxidation of 4-alkoxyphenols **1** to *p*-quinones **2**. Catalyst **4b** could be recycled up to eight times by simple magnetic separation. The oxidation of various 4-alkoxyphenols **1a–i** with **4b** proceeded smoothly at room temperature to give the corresponding *p*-quinones **2a–g** in good to high yields.

Experimental Section

Typical procedure for the oxidation of *p*-alkoxyphenols **1** using magnetic nanoparticle-supported iodoarene catalyst **4b**

Magnetic nanoparticle-supported iodoarene catalyst **4b** (121 mg, 0.04 mmol, 10 mol%) was added to a solution of *p*-alkoxyphenol **1** (0.40 mmol) and Oxone[®] (246 mg, 0.40 mmol) in CF₃CH₂OH–0.1 M phosphate

buffer (2.0 mL, 1:2). After completion of the reaction (checked by TLC), the catalyst **4b** was collected at the bottom of the flask using an external magnet, and the supernatant carefully decanted. The catalyst **4b** was washed three times with EtOAc, three times with H₂O, three times with acetone, two times with Et₂O, and dried in vacuo. Then, the recovered catalyst **4b** was reused in the next reaction cycle. The organic layer was washed with H₂O and brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide *p*-quinone **2**.

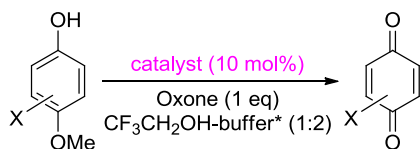
Keywords: hypervalent compounds • magnetic properties • nanoparticles • oxidation • quinones

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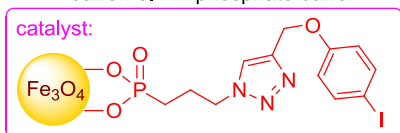
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- [11] Oxidation of **1a** with 4-iodophenoxyacetic acid (**3**) in CF₃CH₂OH–0.1 M phosphate buffer (1:2) at room temperature proceeded to completion within 1.5 h, giving **2a** in 88% yield.
- [12] The catalyst loading **4b** after eight cycles was very low (0.043 mmol/g) as determined by elemental analysis of nitrogen and IR spectroscopy. See the Supporting Information for details.
- [13] The reactivity of the recovered catalyst **4b** with a reductive treatment using sat. Na₂S₂O₃ solution was almost the same as that of **4b** without a reductive treatment. Therefore, a reductive treatment after the reaction is not necessary. See the Supporting Information for details.
- [14] Garrell and Tucker-Schwartz also suggested that the phosphonic acid-coated particles remain stable under the highly acidic oxidizing conditions. See ref. [9c].
- [15] The IR spectrum of the recovered catalyst **4b** after treatment with Oxone® in the absence of substrate **1a** for 4 h was almost the same as that of the original catalyst **4b**. This result indicated that the structure of the catalyst **4b** was almost unchanged by using Oxone®. See the Supporting Information for details.
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*buffer: 0.1 M phosphate buffer



easy reusable (up to 8 cycles)
easy recovery by an external magnet

Iodoarene catalysts immobilized on magnetite (Fe_3O_4) showed reactivities similar to that of 4-iodophenoxyacetic acid for the oxidation of 4-alkoxyphenols in the presence of Oxone[®] as a co-oxidant to give the corresponding *p*-quinones in high yields. These catalysts were readily recovered by the use of an external magnet and could be recycled up to eight times.