## Nanoparticle-Supported Catalysts

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

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Abstract: Iodoarene catalysts immobilized on magnetite (Fe$_3$O$_4$) were developed. The reactivity of catalysts **4a** and **4b** were 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 was recycled up to eight times. This is the first example of a magnetic, nanoparticle-supported iodoarene catalyst.
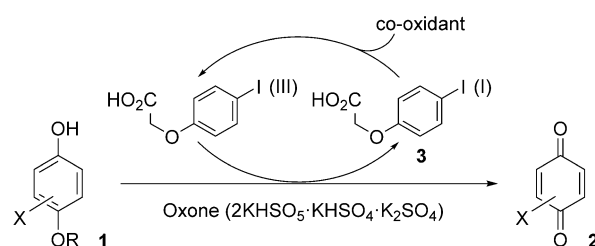
Scheme 1. A catalytic hypervalent iodine oxidation of 4-alkoxyphenols **1** to *p*-quinones **2** using 4-iodophenoxyacetic acid (**3**) with Oxone®.

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 and this produces 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** by using a catalytic amount of 4-iodophenoxyacetic acid (**3**) with Oxone® (2 KHSO$_5$·KHSO$_4$·K$_2$SO$_4$) as a co-oxidant (Scheme 1).[5c,e] For the separation of **3**, this catalytic oxidation system is an easier procedure 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** (Figure 1) for oxidation of 4-alkoxyphenols to *p*-quinones.
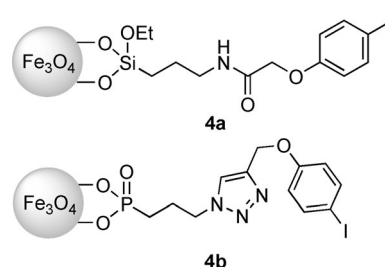

Figure 1. Structures of iodoarene catalyst immobilized on magnetite **4a** and **4b**.

Magnetic nanoparticles have recently shown their efficiency as a core for catalyst support.[6] The catalytic reactivity of these supported catalysts is high 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 simple separation of the catalysts without liquid separation and filtration. We chose magnetite (Fe$_3$O$_4$) 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 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-dimethylaminopyridine (DMAP) in dichloromethane to give **4a**. The organic load-

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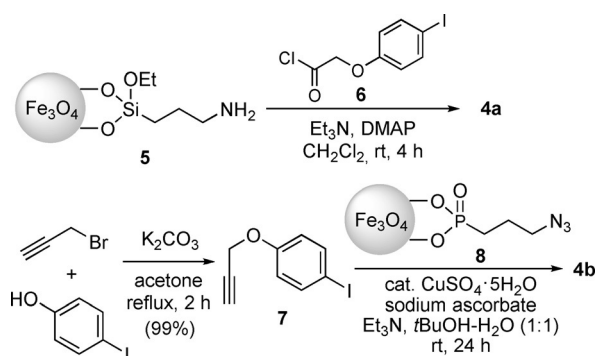
Scheme 2. Synthesis of magnetic nanoparticle-supported iodoarene catalysts **4a** and **4b**.

ing of **4a** was very low (0.087 mmol g^{-1}) as determined by elemental analysis of iodine. Secondly, we synthesized the phosphonic acid-linked catalyst **4b** by Cu-catalyzed cycloaddition of 1-iodo-4-(prop-2-ynyloxy)benzene (**7**)[10] with known magnetite-supported 3-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 CuSO$_4$ via the "click" reaction to afford phosphonic acid-coated catalyst **4b**, whose organic loading (0.33 mmol g^{-1}) was much higher than that of **4a**.

Catalyst **4a** was first evaluated for the oxidation of 4-methoxy-2-pivaloyloxymethylphenol (**1a**) to *p*-quinone **2a** by 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 CF$_3$CH$_2$OH/H$_2$O (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, washing with EtOAc, H$_2$O, acetone, and Et$_2$O, and drying 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

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

Cycle	Solvent	*t* [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 byproduct was isolated.

a longer time of 4.5 h for completion. The catalytic reactivity of **4a** in the third use was poor and gave 68% yield of **2a** with a significant amount of unknown byproduct after 8.0 h. These results indicate that **4a** decomposes under these conditions and that pure **4a** could not be recovered.
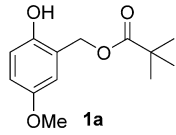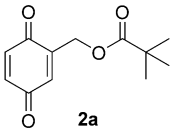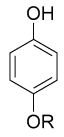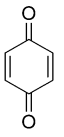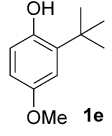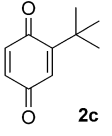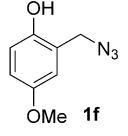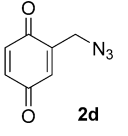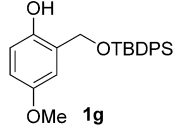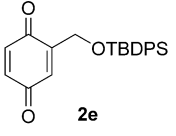
Next, we investigated the use of 0.1 M phosphate buffer instead of H$_2$O to avoid the strong acidic conditions caused by the presence of Oxone®. The oxidation of **1a** with **4a** in CF$_3$CH$_2$OH/0.1 M phosphate buffer (1:2) also proceeded smoothly at room temperature to afford **2a** in 91% yield after 2 h and recovery of **4a** in 98% yield.[11] The reusability of **4a** in CF$_3$CH$_2$OH/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, the reusability of phosphonic acid coated catalyst **4b** was better in the oxidation of **1a** (Table 2).

Table 2. Recyclability of **4b** for the oxidation of **1a** in CF$_3$CH$_2$OH/buffer[a] (1:2).

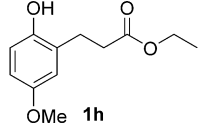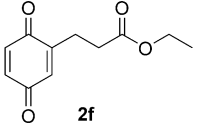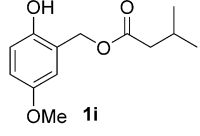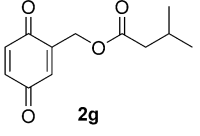| Cycle	*t* [h]	Yield [%]	Recovery of 4b [%]
1	4	80	98
2	4	81	97
3	5.5	80	98
4	7.5	82	96
5	8	82	96
6	11	81	99
7	15	78	96
8	24	71[b]	96

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

The catalyst **4b** was also rapidly collected by an external magnet, and washed with EtOAc, H$_2$O, acetone, and Et$_2$O. No signs of iodoarene catalyst were detected in the crude reaction mixture, obtained by concentration of the EtOAc solution, and the residues (< 1 mg), obtained by concentration of acetone and Et$_2$O solutions, by ^{1}H NMR spectroscopy. The recovered catalyst **4b** was recycled up to eight times, although the reaction times gradually increased.[12, 13] In all cases, **4b** was recovered in over 96% yield. These results suggest that the phosphonic acid-coated catalyst **4b** is more stable than the silica-coated catalyst **4a** under acidic conditions.[14, 15]

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**, which has a bulky *tert*-butyl group at the C2 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

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

Entry	Substrate	Product	t [h]	Yield [%]
1	**1a**	**2a**	4	80 (98)[b]
2	**1b**: R=H	**2b**	0.5	81 (96)[b]
3	**1c**: R=Me	**2b**	2	95 (93)[b]
4	**1d**: R=Et	**2b**	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 $CF_3CH_2OH/0.1$ M phosphate buffer solution (1:2) at room temperature. [b] Yields in parentheses are that of recovered catalyst **4b**. [c] $CF_3CH_2OH/0.1$ M phosphate buffer solution (3:1) was used as a solvent.

$CF_3CH_2OH/0.1$ M phosphate buffer owing to its solubility (entry 7). The use of ethyl ester **1h**[16] led to a good product yield (75%, entry 8). This oxidation was 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** was recovered by an external magnet in 86–99% yield.

In summary, magnetic nanoparticle-supported catalysts **4a** and **4b** were easily synthesized as magnetic iodoarene nanocatalysts and were evaluated for the oxidation of 4-alkoxyphenols **1** to *p*-quinones **2**. Catalyst **4b** was 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 by 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 $CF_3CH_2OH/0.1$ 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 by using an external magnet, and the supernatant was carefully decanted. The catalyst **4b** was washed three times with EtOAc, three times with H_2O, three times with acetone, twice with Et_2O, and dried in vacuo. Then, the recovered catalyst **4b** was reused in the next reaction cycle. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide *p*-quinone **2**.

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[11] Oxidation of **1a** with 4-iodophenoxyacetic acid (**3**) in $CF_3CH_2OH/0.1$ 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^{-1}) 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 with sat. $Na_2S_2O_3$ 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] Tucker-Schwartz and Garrell also suggested that the phosphonic acid-coated particles remain stable under the highly acidic oxidizing conditions. See ref. [8c].

[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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