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

Hisanori Nambu, Ikumi Shimokawa, Tomoya Fujiwara, and Takayuki Yakura

Abstract: Iodoarene catalysts immobilized on magnetite (Fe₃O₄) 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.

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. With respect to the principles of green chemistry, hypervalent iodoarenes are not ideal because stoichiometric amounts of iodoarene reagents are necessary during oxidation and this produces equimolar amounts of iodine waste. Recyclable, polymer-supported hypervalent iodoarene reagents have been developed as environmentally friendly oxidants. Soluble and recyclable hypervalent iodoarene reagents have also been developed. Moreover, catalytic systems based on in situ generation of hypervalent iodoarene species have been reported. 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 (2KHSO₅·KHSO₄·K₂SO₄) as a co-oxidant (Scheme 1). 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.

Magnetic nanoparticles have recently shown their efficiency as a core for catalyst support. 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 (Fe₃O₄) nanoparticles for use as magnetic supports because of their simple synthesis, low cost, and relatively large magnetic susceptibility. Either silane or phosphate anchors are often selected to combine the magnetic nanoparticle and catalyst sites. 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 was obtained by coupling magnetite with 3-amino propyl triethoxysilane, 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-
ing of 4a was very low (0.087 mmolg⁻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)[9c] prepared by a three-step sequence from the commercially available diethyl 3-bromopropylphosphonate. Alkynyl-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 mmolg⁻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[12, 13] 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 by an external magnet, and washed with EtOAc, H₂O, acetone, and Et₂O, 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 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 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, the reusability of phosphonic acid-coated catalyst 4b was better 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 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 Et₂O solutions, by 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-butyldiphenylisilyloxy (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

![Scheme 2. Synthesis of magnetic nanoparticle-supported iodoarene catalysts 4a and 4b.](image)

![Table 1. Recyclability of 4a for the oxidation of 1a.](image)

![Table 2. Recyclability of 4b for the oxidation of 1a in CF₃CH₂OH/buffer[12, 13].](image)

![Table 3. Recyclability of 4b for the oxidation of 1a in CF₃CH₂OH/buffer[12, 13].](image)
Table 3. Oxidation of 4-alkoxyphenols 1 using catalyst 4b.[1,2]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>t [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>OMe 1a</td>
<td>4</td>
<td>80 (98)</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>OR 1b</td>
<td>0.5</td>
<td>81 (96)</td>
</tr>
<tr>
<td>3</td>
<td>R = H</td>
<td>2b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R = Me</td>
<td>2b</td>
<td>2</td>
<td>95 (93)</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>2b</td>
<td>3</td>
<td>93 (99)</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>N3 2c</td>
<td>2.5</td>
<td>73 (98)</td>
</tr>
<tr>
<td>7</td>
<td>OTBDPS</td>
<td>OTBDPS 4</td>
<td>4</td>
<td>79 (85)</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>1g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>2f</td>
<td>3</td>
<td>75 (99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2h</td>
<td>3</td>
<td>76 (97)</td>
</tr>
</tbody>
</table>

[a] Reactions were conducted in CF<sub>3</sub>CH<sub>2</sub>OH/0.1 M phosphate buffer solution (1:2) at room temperature. [b] Yields in parentheses are that of recovered catalyst 4b. [c] CF<sub>3</sub>CH<sub>2</sub>OH/0.1 M phosphate buffer solution (3:1) was used as a solvent.

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<sup>®</sup> (246 mg, 0.40 mmol) in CF<sub>3</sub>CH<sub>2</sub>OH/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<sub>2</sub>O, three times with acetone, twice with Et<sub>2</sub>O, and dried in vacuo. Then, the recovered catalyst 4b was reused in the next reaction cycle. The organic layer was washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide p-quinone 2.

Keywords: alkoxyphenols · hypervalent iodine · magnetic nanoparticles · oxidation · quinones


[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⁻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. 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] 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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