Catalysis Today xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Catalysis Today

journal homepage: www.elsevier.com/locate/cattod

Regiodivergent oxidation of alkoxyarenes by hypervalent iodine/oxone® system

Hideyasu China*, Kokoro Tanihara, Hirotaka Sasa, Kotaro Kikushima, Toshifumi Dohi*

College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga, 525-8577, Japan

ARTICLE INFO

Keywords:
p-Quinone
Methoxyarene
Organoiodine catalyst
Oxone®

ABSTRACT

We have found that the combination of Oxone® with an organoiodine compound, *i.e.*, 2-iodobenzoic acid (2-IB), selectively yields *p*-quinones from monomethoxyarenes under mild conditions. In this reaction system, an organoiodine compound is immediately oxidized by Oxone® to generate cyclic hypervalent iodine (III) species *in situ*, which serves as the specific mediator for the selective *p*-quinone synthesis, preventing *o*-quinone formation.

1. Introduction

Quinones have attracted attention in the fields of pharmacology [1–6] and materials chemistry [7–11] as a useful synthetic intermediate [12]. In quinone synthesis, developing the appropriate strategy and selective oxidation reaction is important because structural isomers, *p*- and *o*-quinones, are both possible products. Classically, inorganic oxidants, such as potassium nitrosodisulfonate (Fremy's salt), cerium (IV) ammonium nitrate (CAN), pyridinium chlorochromate (PCC), and silver(II) oxide, have been used [13–15]. In terms of developing the green chemistry process, safer and more practical metal-free oxidation methods are strongly desired in recent years. Some organic oxidants, such as phenyliodine(III) bis(trifluoroacetate) (PIFA) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), have now become popular in this regard [14]. Typically, the synthesis of *p*-quinones is achieved by conversion of 1,4-dioxygenated arenes [16] and phenols [17] by using PIFA, a hypervalent iodine oxidant (Scheme 1a). Although phenols are more readily available than 1,4-dioxygenated arenes, *p*-quinone yields are relatively low because of the production of *o*-quinone byproducts (Scheme 1b). Conversely, *p*-quinone synthesis from 1,4-dioxygenated arenes gives relatively high yields, while some additional steps are required to prepare *p*-methoxy phenols and 1,4-dimethoxyarenes. Oxone®, an inexpensive, commercially available, and stable sulfate mixture ($2KHSO_5/KHSO_4/K_2SO_4$), has recently attracted attention as a green inorganic oxidant and various useful reactions using Oxone® have already been developed [18]. *p*-Quinone syntheses from 4-methoxyphenols [19,20] and 1,4-dimethoxyarenes [21,22] using a combination of Oxone® and an organoiodine catalyst have also been reported.

On the other hand, synthesis of *p*-quinones from monomethoxyarenes is difficult to realize due to the selectivity problems during ring oxygenation. Several methods for the conversion of monomethoxyarenes using organometallic catalysts [23–31] have been reported to form a mixture of *p*- and *o*-quinones (Scheme 1c). Deprotection of the methoxy group is required to regenerate the highly reactive phenol moiety for the multi-step synthesis to *p*-quinones from monomethoxyarenes.

Therefore, the new synthetic strategy for selective formation of *p*-quinones from monomethoxyarenes is advantageous in terms of the process chemistry. However, the reported method using $KHSO_5$ in combination with Fe-porphyrin as the catalyst for the oxidation of 1-methoxynaphthalene **1** [31] is known to yield a desired *p*-quinone **2** with a similar yield of an undesired *o*-quinone **3** contaminant (Scheme 2).

In this study, we demonstrate a new, selective *p*-quinone synthesis from monomethoxyarenes using Oxone® in the presence of an organoiodine compound under mild conditions (Scheme 3).

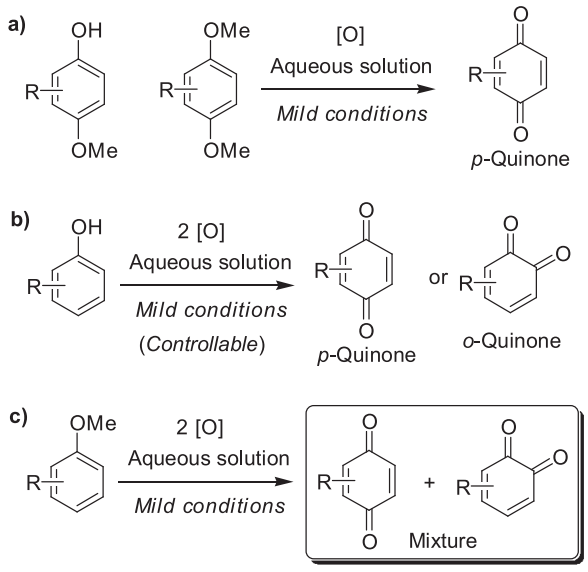
2. Experimental

2.1. General information

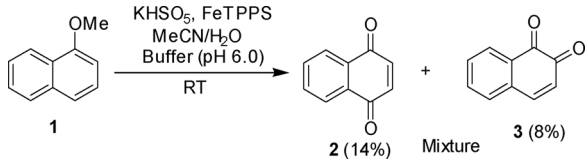
^1H and ^{13}C NMR spectra were recorded on an ECS 400 NMR spectrometer (JEOL Ltd., Tokyo, Japan) at 400 MHz and 100 MHz, respectively, using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hertz and multiplicity reported according to the following convention: singlet (s), doublet (d), double doublet (dd), triplet (t), triple doublet (td), quartet (q), broad singlet (brs), and

* Corresponding authors.
E-mail addresses: hchina7a@fc.ritsumei.ac.jp (H. China), td1203@ph.ritsumei.ac.jp (T. Dohi).

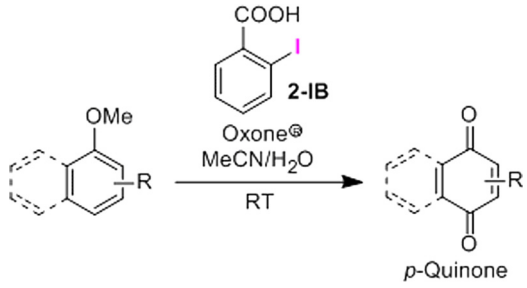
https://doi.org/10.1016/j.cattod.2019.08.060
Received 22 May 2019; Received in revised form 28 August 2019; Accepted 29 August 2019



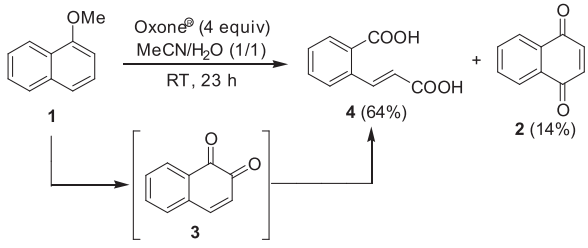
Scheme 1. General method of *p*-quinone synthesis from phenols and anisoles.



Scheme 2. *p*-Quinone synthesis from a monomethoxyarene using a combination of Fe catalyst with persulfate oxidant.



Scheme 3. *p*-Quinone synthesis from methoxyarenes using Oxone® and an organoiodine catalyst.



Scheme 4. Oxidation of 1-methoxynaphthalene 1 using Oxone®.

multiplet (m). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). qNMR analysis was performed with 40 s of reduction delay time, 6 ppm of offset value, and 6 ppm of sweep value in the presence of 1,4-dinitrobenzene as an internal standard in $CDCl_3$. Substrates **7a** [32], **7b** [33], **10a** [34], and **10b** [35,36] were prepared from 1,2-naphthalenediol, 1,3-naphthalenediol, 1,7-naphthalenediol, and 5-amino-1-naphthol, respectively.

2.2. Optimization of reaction conditions for p-quinone synthesis

To a suspension of 1-methoxynaphthalene **1** (0.1 mmol, 15.8 mg), organoiodine catalyst (1.0 equiv., 0.10 of IBX, IBA, or 2-IB), Oxone®, and 1,4-dinitrobenzene (0.05 mmol, 8.4 mg) as an internal standard in MeCN (1.25 mL) was added water (1.25 mL). If necessary, V_2O_5 (10 mol %, 0.01 mmol, 1.8 mg) and/or 10 M H_2O_2 (5.0 equiv., 0.50 mol, 50 μL) were added to the mixture. After the mixture was stirred at room temperature, the organic layer was extracted with $CDCl_3$ (2.5 mL). The yields of **2** were determined by qNMR analysis of the extracts.

2.3. Effect of the water content

1,3-Dimethoxybenzene **5** (0.1 mmol, 13.8 mg), 2-IB (1.0 equiv., 0.1 mmol, 24.8 mg), Oxone® (0.3 mmol, 184 mg), and 1,4-dinitrobenzene (0.05 mmol, 8.4 mg) as an internal standard was suspended by addition of a mixed solvent of MeCN/water (various ratio, total volume: 1.0 mL). After the mixture was stirred at room temperature for 1.5 h, the organic layer was extracted with $CDCl_3$ (1 mL). The yields of **6** were determined by qNMR analysis of the extracts.

2.4. General procedure for the synthesis of p-quinones in the presence of Oxone® and 2-IB

To a suspension of anisole derivative (1.0 mmol), 2-IB (1.0 mmol, 248 mg), and Oxone® (3.0 mmol, 1.844 g) in MeCN (4 mL) was added water (6 mL). The mixture was stirred at room temperature until complete consumption of the starting material (confirmed by TLC analysis). Then, the insoluble material was removed by filtration with CH_2Cl_2 and then the organic layer was extracted with CH_2Cl_2 (50 mL) at twice. The extract was washed with a saturated $NaHCO_3$ aqueous solution (100 mL) and then filtered through filter paper for dehydration. After the solvent was removed by evaporation, the desired product was purified by flash silica gel chromatography with appropriate solvent.

2: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.98 (2H, s), 7.76 (2H, m), 8.08 (2H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 126.4, 131.9, 133.9, 138.7, 185.0 ppm. [37]

3: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.45 (1H, d, J = 10.1 Hz), 7.38 (1H, d, J = 7.8 Hz), 7.46 (1H, d, J = 10.1 Hz), 7.52 (1H, td, J = 7.8, 0.9 Hz), 7.67 (1H, td, J = 7.8, 1.4 Hz), 8.12 (1H, dd, J = 7.8, 1.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 127.9, 129.9, 130.2, 130.9, 131.6, 134.8, 135.9, 145.4, 178.9, 180.9 ppm. [38]

6: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.85 (3H, s), 5.96 (1H, s), 6.73 (2H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 56.3, 107.7, 134.5, 137.3, 158.6, 181.8, 187.5 ppm. [37]

8: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.92 (3H, s), 6.19 (1H, s), 7.69-7.79(2H, m), 8.08 (1H, dd, J = 7.3, 1.8 Hz), 8.13 (1H, dd, J = 7.3, 1.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 56.4, 109.9, 126.2, 126.7, 131.0, 132.0, 133.4, 134.4, 160.4, 180.1, 184.8 ppm. [39]

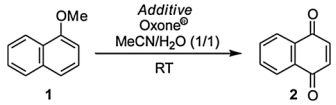
9: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 4.03 (3H, s), 5.99 (1H, s), 7.59 (1H, td, J = 7.8, 1.4 Hz), 7.70 (1H, td, J = 7.8, 1.4 Hz), 7.87 (1H, dd, J = 7.8, 0.9 Hz), 8.13 (1H, dd, J = 7.8, 0.9 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 56.8, 103.1, 124.8, 129.1, 130.4, 131.6, 132.0, 135.0, 168.7, 179.4 ppm. [40]

11a: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.95 (3H, s), 6.92 (1H, s), 6.93 (1H, s), 7.21 (1H, dd, J = 8.7, 2.8 Hz), 7.48 (1H, d, J = 2.8 Hz), 8.01 (1H, d, J = 8.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 55.9, 109.6, 120.5, 125.4, 128.9, 133.9, 138.2, 139.0, 164.1, 184.1, 185.1 ppm. [41]

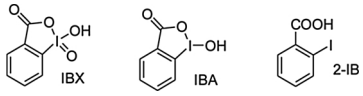
11b: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.30 (3H, s), 6.91 (1H, d, J = 10.1 Hz), 6.95 (1H, d, J = 10.6 Hz), 7.72(1H, t, J = 8.0 Hz), 7.81 (1H, dd, J = 7.8, 1.4 Hz), 9.07 (1H, dd, J = 8.2, 0.9 Hz), 11.85 (1H, brs) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 25.7, 115.9, 121.9, 126.0, 132.1, 135.7, 137.9, 139.9, 141.3, 169.9, 184.4, 189.0 ppm. [42]

14a: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.07 (3H, d, J = 1.4 Hz), 3.82 (3H, s), 5.93 (1H, s), 6.56 (1H, q, J = 1.4 Hz) ppm. ^{13}C NMR (100 MHz,

Table 1
Optimization of the reaction conditions for *p*-quinone synthesis by oxidation of methoxynaphthalene 1 using Oxone® and an organoiodine compound.



Entry	Conditions[b]	Time (h)	Yield (%)
1[a]	Oxone (4)	23	14[e]
2	IBX (1), Oxone (10)	0.5	3[d]
3	IBA (1), Oxone (10)	3	46[d]
4	2-IB (1), Oxone (10)	0.5	40[d]
5	2-IB (1), Oxone (3)	3.0	44[d] (39) [e]
6	2-IB (1), Oxone (3)[c]	3.0	44[d] (43) [e]
7	2-IB (1), Oxone (3), H_2O_2 (5)	3.0	45[d]
8	2-IB (1), Oxone (3), H_2O_2 (5), V_2O_5 (0.1)	1.0	39[d]
9	2-IB (1), Oxone (10), H_2O_2 (5), V_2O_5 (0.1)	0.5	60[d,f]



[a] See ref. [53].
[b] The numerals in parentheses are the equivalent of a reagent.
[c] A solution consisting of MeCN/H_2O (2/3) was used for the reaction.
[d] NMR yields.
[e] Isolated yield.
[f] Isolated yield of byproduct **4** was below 3%.

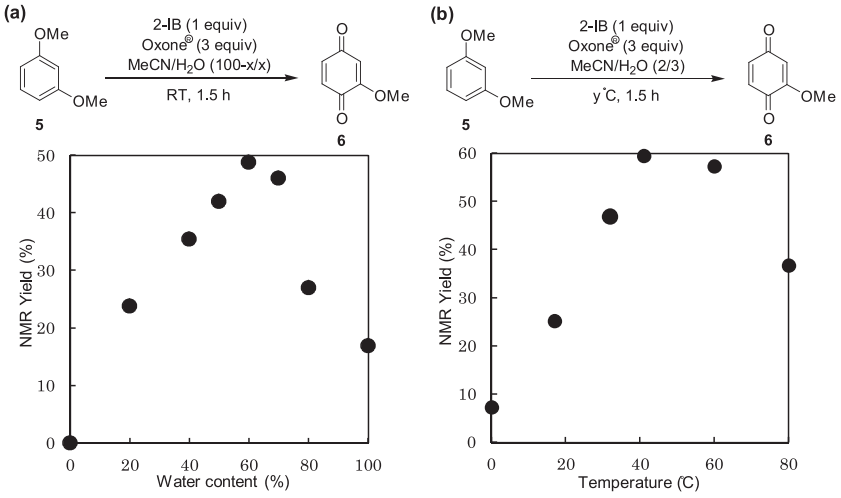


Fig. 1. Effect of (a) water content and (b) temperature for *p*-quinone synthesis from 1,3-dimethoxybenzne **5.**

$CDCl_3$) : δ 15.8, 56.3, 107.6, 131.3, 146.9, 158.7, 182.2, 187.7 ppm. [43]

14b: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.96 (3H, s), 4.03 (3H, s), 6.60 (1H, d, J =10.5 Hz), 6.69 (1H, d, J =10.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 8.7, 60.9, 129.0, 134.7, 136.3, 155.7, 183.3, 188.3 ppm. [44]

14c: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.07 (3H, d, J =1.8 Hz), 3.83 (3H, s), 5.93 (1H, d, J =2.3 Hz), 6.54 (1H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 15.5, 56.3, 107.3, 133.8, 143.6, 158.8, 182.4, 187.5 ppm. [45]

14d: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.83 (6H, s), 5.86 (2H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 56.5, 107.4, 157.3, 176.7, 186.9 ppm. [46]

14e: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.04 (3H, d, J =1.4 Hz), 4.00 (3H, s), 4.02 (3H, s), 6.44 (1H, q, J =1.7 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 15.5, 61.2, 61.3, 131.2, 144.0, 144.8, 145.0, 184.2, 184.4 ppm. [47]

14f: ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.99-2.05 (9H, m), 6.55-6.57 (1H, q, J =1.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) : δ 12.1, 12.4, 15.9, 133.1, 140.7, 140.9, 145.3, 187.4, 187.9 ppm. [48]

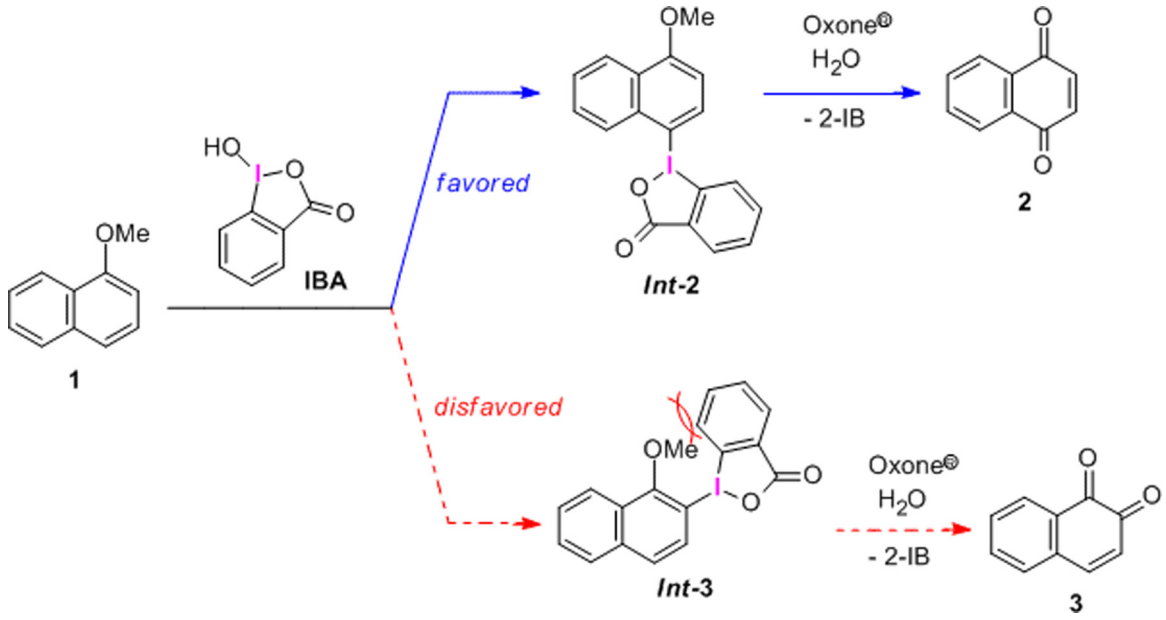
2.5. *p*-Quinone synthesis using catalytic amounts of 2-IB

The modified procedure instead using catalytic amounts of 2-IB (0.05 mmol (5 mol%), 12.4 mg or 0.20 mmol (20 mol%), 49.6 mg) for the reactions of substrates **13c** and **13d** (1 mmol) gave corresponding *p*-quinones **14c** and **14d** in the indicated yields shown in Scheme 8.

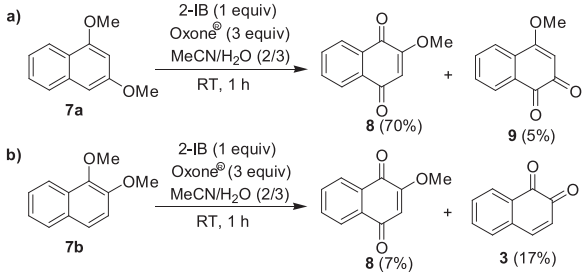
3. Result and discussion

3.1. Optimization of reaction conditions

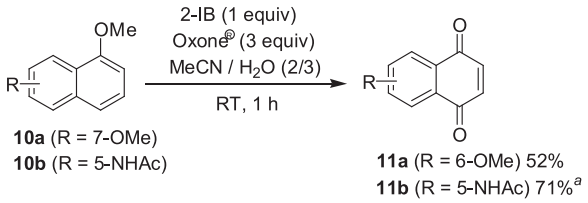
Oxone® can oxidize monomethoxyarene without any additive to give a low yield of *p*-quinone. Indeed, when utilizing Oxone® for the oxidation of 1-methoxynaphthalene **1** without any additive, 2-carboxycinnamic acid **4** was generated as the main product *via* the



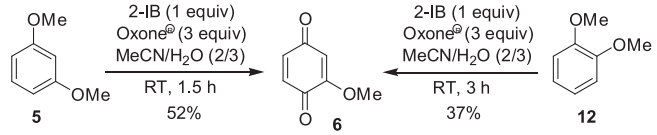
Scheme 5. Plausible reaction mechanism for the *p*-selective oxygenation.



Scheme 6. 1,2 versus 1,3-dimethoxynaphthalenes.



Scheme 7. Functional groups in the naphthalene ring.
a)Yield BRSM (63% conversion)



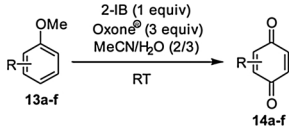
Scheme 8. The reactions of dimethoxybenzene isomers.

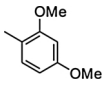
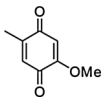
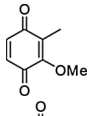
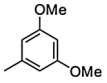
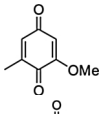
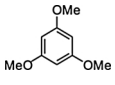
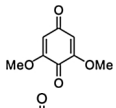
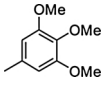
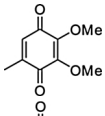
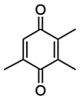
intermediate *o*-quinone **3** (Scheme 4) [49].

On the other hand, some hypervalent iodine oxidants generated by treatment with Oxone® are known to preferentially produce *p*-quinones from phenols over *o*-quinone formations [19–22]. Thus, we expected that the combination of Oxone® and a hypervalent iodine oxidant as a mediator would provide an efficient synthesis of *p*-quinones. At first, various combinations were examined for the oxidation of 1-methoxynaphthalene **1** (Table 1). The combination of Oxone® and cyclic hypervalent iodine oxidants, such as 2-iodoxybenzoic acid (IBX) and 2-iodosobenzoic acid (IBA), gave the target *p*-naphthoquinone **2** in low-to-moderate yields (entries 2 and 3), while no products were obtained without Oxone®. Interestingly, IBA showed higher activity than pentavalent IBX, which is in marked contrast to the fact that oxidation power of IBX is generally higher than that of IBA. This result can be explained by the influence of the solubility of the hypervalent iodine oxidants in MeCN/H_2O (1/1) mixture. Indeed, the use of 2-iodobenzoic acid (2-IB), having relatively high solubility in water, smoothly generated IBA in the presence of Oxone®, resulting in improvement of the reaction rate (entry 4). Furthermore, the amount of Oxone® could be reduced by extending the reaction time (entries 5 and 6). Although addition of H_2O_2 and/or V_2O_5 increased the yield (entries 7–9), they were not an important factor in reducing the amount of Oxone® required. Due to their roles in the *p*-quinone-forming process to work collaboratively with IBA generated from 2-IB by Oxone®, it seems that the peroxo-vanadium species produced by the activation of V_2O_5 with H_2O_2 would show strong oxidizing ability towards a variety of organic substrates [50–53]. To our delight, the production of 2-carboxycinnamic acid **4** was suppressed to below 3% by using 2-IB in the Oxone® oxidation system (entry 9), whereas this byproduct was the main product (64% yield) in the absence of 2-IB (see Scheme 4) [49]. Notably, only *p*-naphthoquinone **2** was selectively obtained under our conditions and the structural isomer, *o*-naphthoquinone **3**, was not detected at all. The results shown in Table 1 indicate that the combination of Oxone® and a hypervalent iodine precursor, 2-IB, for selective *p*-quinone synthesis is superior to Oxone® itself.

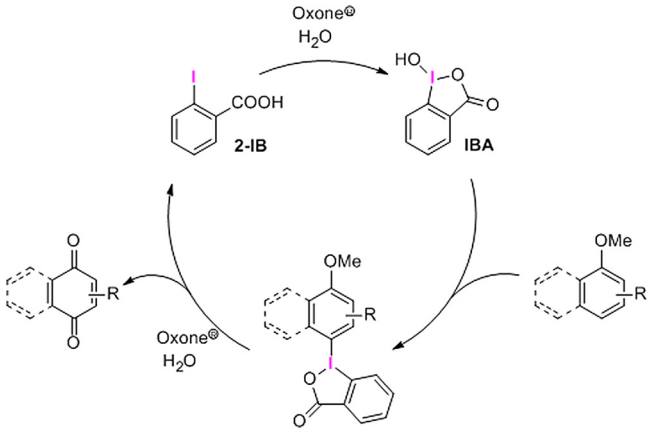
Although the combination of H_2O_2 (5 equiv) and V_2O_5 (0.1 equiv) gave the *p*-quinone **2** in 60% yield (entry 9), the use of excess amounts of Oxone® (10 equiv) is not suitable for practical use. Similarly, the use of H_2O_2 (5 equiv) (entry 7) appeared to provide no significant advantage over the conditions without H_2O_2 (entries 5 and 6). Comparison of the isolated yields of *p*-quinone **2** in entries 5 and 6 suggested that the MeCN/H_2O (2/3) medium was relatively better than MeCN/H_2O (1/1). This result was also ascertained by the investigation of the influence on water content in MeCN for the oxidation of 1,3-dimethoxybenzene **5** to 2-methoxybenzoquinone **6** (Fig. 1a). Furthermore, using a smaller proportion of MeCN is desirable because *p*-quinones are sometimes azeotroped when removing the solvents under reduced pressure during isolation. Thus, metal-free conditions with the combination of Oxone® and 2-IB in MeCN/H_2O (2/3) medium (entry 6) were used for experiments to test the substrate scope. The oxidation reaction did not proceed at all in the absence of water, suggesting that

Table 2
Screening of different anisole derivatives as substrates.



Entry	Substrate		Product		Time	Yield
1		**13a**		**14a**	1 h	59%
2		**13b**		**14b**	2 h	68%
3		**13c**		**14c**	1 h	82%
4		**13d**		**14d**	1 h	90%
5		**13e**		**14e**	1 h	52%
6		**13f**		**14f**	1 h	60%

Scheme 9. Catalytic activity of 2-IB in the *p*-quinone synthesis.
a) 20 mol% of 2-IB



Scheme 10. Plausible catalytic cycle for the *p*-quinone synthesis.

water plays an important role in the reaction mechanism. Indeed, water was required for generation of IBA, which is in accord with the present oxidation reaction to produce IBA. The use of MeOH, 2,2,2-trifluoroethanol (TFE), or hexafluoro-2-propanol (HFIP), instead of water was not beneficial for the oxidation reaction. After optimization of reaction temperature, the reaction at 40 °C resulted in the best yield of the oxidation product (Fig. 1b).

A proposed reaction mechanism for the *p*-selective oxygenation using 2-IB and Oxone® system is shown in Scheme 5. 2-IB was initially *in-situ* transformed into IBA by the reaction with Oxone® in the presence of water. IBA can then react with 1-methoxynaphtalene **1** at the 4-position to generate ***Int*-2** rather than at the 2-position for giving ***Int*-3**, which controlled the regioselective oxidation. Indeed, IBA is known to react with anisole regioselectively at the *para*-position to form diaryliodonium(III) salt [54–61]. The resulting **Int-2** was converted into *p*-naphthoquinone **2** in the presence of Oxone® and water.

3.2. Substrate scope

Several 1-methoxynaphthalene derivatives with electron-donating groups were examined as substrates in our metal catalyst-free oxidation. 1,3-Dimethoxynaphthalene **7a** and 1,2-dimethoxynaphthalene **7b** could both produce 2-methoxy-1,4-naphthoquinone **8** in 70% and 7% yields, respectively (Scheme 6). The low yield of *p*-quinone in the latter case would suggest that the quinone-forming reaction is relatively faster than the oxygenation of the aromatic ring, which is probably the rate-determining step. The generation of *o*-quinone **9** by oxygenation of the *ortho* aromatic position was suppressed during the oxidation of 1,3-dimethoxynaphthalene **7a**.

The oxidation of functionalized 1,7-dimethoxynaphthalene **10a** afforded 6-methoxy-1,4-naphthoquinone **11a** in 52% yield (Scheme 7). This yield is over twice that of the oxidation using Oxone® as the sole oxidant (25%) [49]. Oxidation of 1-acetamide-5-methoxynaphthalene **10b** produced 5-acetamido-1,4-naphthoquinone **11b** in 71% yield based on recovery of the starting material (BRSM).

Next, the reactions of monocyclic anisole derivatives were investigated. The oxidations of 1,3-dimethoxybenzene **5** for 1.5 h and 1,2-dimethoxybenzene **12** for 3 h gave the corresponding *p*-quinone **6** in 52% and 37% yields, respectively (Scheme 8). The higher productivity for the former case appears to be the same as that observed for the

naphthalenes (see Scheme 6), with the corresponding *o*-quinone competitively produced from the *ortho*-dimethoxy aromatics. Nonetheless, the oxidation of 1,2-dimethoxybenzene **12** using Oxone® without any additive did not produce the same product **6** [62]. The results of further investigation using various substituted anisoles **13a-f** as substrates are shown in Table 2. Comparison between 1,3-dimethoxybenzene **5** and the methyl-substituted derivatives **13a-c** on the reaction (entries 1–3) suggested the positive effect of the electron-donating group on the yield of the corresponding *p*-quinones **14a-c**. This comparison also showed that oxygenation of the 5-methyl isomer **13c** was more productive than those of the 6-methyl isomer **13a** and the 2-methyl isomer **13b** (entries 1–3). Thus, methoxyarene **13c** having an electron-donating methyl group at the *ortho* position of the reaction site increased the reactivity for oxidation to afford the quinone product **14c** in a higher yield. The oxidation of 1,3,5-trimethoxybenzene **13d** using the combination of Oxone® and 2-IB gave the corresponding quinone **14d** in 90% yield (entry 4), whereas the treatment of the substrate **13d** with phenyliodine (III) bis(trifluoroacetate) (PIFA) in the absence of Oxone® alternatively formed phenyl(2,4,6-trimethoxyphenyl)iodonium(III) trifluoroacetate salt in 79% yield without producing the *p*-quinone **14d** [16]. These results clearly support the superiority of 2-IB as a mediator in the *p*-quinone synthesis using Oxone®. The oxidations of 1,3,5-trisubstituted benzenes **13c** and **13d** affording the corresponding *p*-quinones in high yields (entries 3 and 4, respectively) proved the utility of the *p*-quinone synthesis for 3,5-difunctionalized anisoles. On the other hand, the oxidations of 2,3,5-trifunctionalized anisoles, **13e** and **13f**, gave the corresponding *p*-quinones **14e** and **14f** in moderate yields (entries 5 and 6, respectively). The yield of *p*-quinone **14e** was relatively lower than that having multiple methyl groups **14f** due to the partial formation of the corresponding *o*-quinone by the presence of the methoxy group at the 2-position, despite the enhancement of electron density of the aromatic ring.

3.3. Catalytic function

Finally, the catalytic activity of 2-IB was investigated (Scheme 9). At 5 mol% loading of 2-IB, the oxidation reaction of 3,5-dimethoxytoluene **13c** and trimethoxybenzene **13d** proceeded to successfully give 2-methoxy-6-methyl-1,4-benzoquinone **14c** and 2,6-dimethoxybenzene **14d** in 62% and 86% yields, respectively. This result indicates that 2-IB possesses good catalytic function. Plausible catalytic cycle of the present reaction is shown in Scheme 10 [63–65]. 2-IB was first oxidized by Oxone® in the presence of water to generate IBA, which reacted with substrates affording the iodonium(III) intermediate [54]. Subsequently, this reaction intermediate was further oxidized by Oxone® to give quinone along with the regeneration of 2-IB. 2-IB was reactivated into IBA through the re-oxidation with Oxone® in an aqueous solution during the *p*-quinone formation. The details of this unique catalytic system are under investigation with further optimization of the catalyst structure.

4. Conclusions

In summary, we have established a new metal-catalyst-free direct *p*-quinone synthesis system from monomethoxyarenes using the combination of Oxone® and hypervalent iodine compound at room temperature in an aqueous medium. The cyclic hypervalent iodine(III) compound, IBA, generated from the corresponding organoiodine compound, 2-IB, by *in-situ* oxidation with Oxone® was shown to mediate site-selective oxygenation as a specific catalytic species. Thus, this methodology is an attractive metal-catalyst-free oxidation system for the selective *p*-quinone synthesis from monomethoxyarenes, which cannot be achieved without the present system. The use of the easily available organocatalyst as a replacement of metal oxidants is also the significant advantage of our reaction system.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research B and C (JSPS KAKENHI (B) Grant Number 18H02014 and JSPS KAKENHI (C) Grant Number 19K05466) from JSPS. T.D. acknowledges the research fund of the Asahi Glass Foundation and support from the Ritsumeikan Global Innovation Research Organization (R-GIRO) project. H.S. thanks The Pharmaceutical Society of Japan (PSJ) for support of the Nagai Memorial Research Encouragement.

References

[1] I. Abraham, R. Joshi, P. Pardasani, R.T. Pardasani, J. Braz. Chem. Soc. 22 (2011) 385–421.
[2] J.L. Bolton, T. Dunlap, Chem. Res. Toxicol. 30 (2017) 13–37.
[3] G.G. Dias, A. King, F. de Moliner, M. Vendrell, E.N. da Silva Jr, Chem. Soc. Rev. 47 (2018) 12–27.
[4] P.M. Cheuka, G. Mayoka, P. Mutai, K. Chibale, Molecules 22 (2017), https://doi.org/10.3390/molecules22010058.
[5] K. Xu, P. Wang, L. Wang, C. Liu, S. Xu, Y. Cheng, Y. Wang, Q. Li, H. Lei, Chem. Biodivers. 11 (2014) 341–363.
[6] K.W. Wellington, RSC Adv. 5 (2015) 20309–20338.
[7] S.B. Kim, R.D. Pike, D.A. Sweigart, Acc. Chem. Res. 46 (2013) 2485–2497.
[8] Y. Wu, R. Zeng, J. Nan, D. Shu, Y. Qiu, S.-L. Chou, Adv. Energy Mater. 7 (2017) 1700278.
[9] M. Miroshnikov, K.P. Divya, G. Babu, A. Meiyazhagan, L.M.R. Arava, P.M. Ajayan, G. John, J. Mater. Chem. A Mater. Energy Sustain. 4 (2016) 12370–12386.
[10] J. Moussa, H. Amouri, Angew. Chem. Int. Ed. 47 (2008) 1372–1380.
[11] J.A. Reingold, S.U. Son, S.B. Kim, C.A. Dullaghan, M. Oh, P.C. Frake, G.B. Carpenter, D.A. Sweigart, Dalton Trans. (2006) 2385-2398.
[12] C.C. Nawrat, C.J. Moody, Angew. Chem. Int. Ed. 53 (2014) 2056–2077.
[13] Q.H. Luu, S. Mito, Tetrahedron 71 (2015) 895–916.
[14] S. Akai, Y. Kita, Org. Prep. Proced. Int. 30 (1998) 603–629.
[15] W.M. Owton, J. Chem. Soc. Perkin Trans. I 1 (1999) 2409–2420.
[16] H. Tohma, H. Morioka, Y. Harama, M. Hashizume, Y. Kita, Tetrahedron Lett. 42 (2001) 6899–6902.
[17] A. Wu, Y. Duan, D. Xu, T.M. Penning, R.G. Havey, Tetrahedron 66 (2010) 2111–2118.
[18] H. Hussain, I.R. Green, I. Ahmed, Chem. Rev. 113 (2013) 3329–3371.
[19] T. Yakura, Y. Tian, Y. Yamauchi, M. Omoto, T. Konishi, Chem. Pharm. Bull. 57 (2009) 252–256.
[20] T. Yakura, T. Konishi, Synlett (2007) 765–768.
[21] T. Yakura, Y. Yamauchi, Y. Tian, M. Omoto, Chem. Pharm. Bull. 56 (2008) 1632–1634.
[22] T. Yakura, M. Omoto, Y. Yamauchi, Y. Tian, A. Ozono, Tetrahedron 66 (2010) 5833–5840.
[23] MMP/Fe(III)-porphyrin: I. Artaud, K.B. Aziza, C. Chopard, D. Mansuy, J. Chem. Soc., Chem. Commun (1991) 31-33.
[24] Ru(TPP)CO/HBr: T. Higuchi, C. Satake, M. Hirobe, J. Am. Chem. Soc. 117 (1995) 8879-8880.
[25] [Ru(III) (Me3tacn)(CF3COO)2(H2O)]CF3COO/tBuOOH: W.-H. Cheung, W.-P. Yip, W.-Y. Yu, C.-M. Che, Can. J. Chem. 83 (2005) 521-526.
[26] [Ru(IV) (2,6-Cl2tpp)Cl2]/2,6-Cl2pyNO: J.-L. Zhang, C.-M. Che, Chem. Eur. J. 11 (2005) 3899-3914.
[27] Ru(II)(pybox-dh)(pydic)/H2O2: S. Iwasa, A. Fakhruddin, H.S. Widagdo, H. Nishiyama, Adv. Synth. Catal. 347 (2005) 517-520.
[28] CH3ReO3/ H2O2: R. Bernini, E. Mincione, M. Barontini, F. Crisante, G. Fabrizi, A. Gambacorta, Tetrahedron 63 (2007) 6895-6900.
[29] [Fe(qpy)](ClO4)2/oxone, P. Liu, Y. Liu, E.L.-M. Wong, S. Xiang, C.-M. Che, Chem. Sci. 2 (2011) 2187–2195.
[30] R. Yoshida, K. Isozaki, T. Yokoi, N. Yasuda, K. Sadakane, H. Takaya, M. Nakamura, Org. Biomol. Chem. 14 (2016) 7468–7479.
[31] G. Labat, J.-L. Seris, B. Meunier, Angew. Chem. Int. Ed. 29 (1990) 1471–1473.
[32] A. Sarkar, S.K. Pal, M.E. Itkis, P. Liao, F.S. Tham, B. Donnadieu, R.C. Haddon, Chem. Mater. 21 (2009) 2226–2237.
[33] K. Grudzień, M. Barbasiewicz, Appl. Organometal. Chem. 29 (2015) 322–327.
[34] A.M. Johansson, C. Mellin, U. Hacksell, J. Org. Chem. 51 (1986) 5252–5258.
[35] R.L. de Carvalho, G.A.M. Jardim, A.C.C. Santos, M.H. Araujo, W.X.C. Oliveira, A.C.S. Bombaça, R.F.S. Menna-Barreto, E. Gopi, E. Gravel, E. Doris, E.N. de Silva Jr, Chem. Eur. J. 24 (2018) 15227–15235.
[36] C. Abate, M. Niso, E. Lacivita, P.D. Mosier, A. Toscano, R. Perrone, J. Med. Chem. 54 (2011) 1022–1032.
[37] H. Miyamura, M. Shiramizu, R. Matsubara, S. Kobayashi, Angew. Chem. Int. Ed. 47 (2008) 8093–8095.
[38] M.O. Ratnikov, L.E. Farkas, E.C. McLaughlin, G. Chiou, H. Choi, S.H. El-Khalafy, M.P. Doyle, J. Org. Chem. 76 (2011) 2585–2593.
[39] N. Lebrasseur, G.-J. Fan, M. Oxoby, M.A. Looney, S. Quideau, Tetrahedron 61 (2005) 1551–1562.
[40] T. Ogata, I. Okamoto, E. Kotani, T. Takeya, 60 (2004) 3941-3948.
[41] L.J. Mitchell, W. Lewis, C.J. Moody, Green Chem. 15 (2013) 2830–2842.
[42] O. Suchard, R. Kane, B.J. Roe, E. Zimmermann, C. Jung, P.A. Waske, J. Mattay, M. Oelgemöller, Tetrahedron 62 (2006) 1467–1473.

[43] A. van der Klei, R.L.P. de Jong, J. Lugtenburg, A.G.M. Tielens, Eur. J. Org. Chem. (2002) 3015–3023.
[44] H.M.L. Davies, X. Dai, M.S. Long, J. Am. Chem. Soc. 128 (2006) 2485–2490.
[45] C.-L. Lee, C.-H. Huang, H.-C. Wang, D.-W. Chuang, M.-J. Wu, S.-Y. Wang, T.-L. Hwang, C.-C. Wu, Y.-L. Chen, F.-R. Chang, Y.-C. Wu, Org. Biomol. Chem. 9 (2011) 70–73.
[46] D. Deffieux, I. Fabre, A. Titz, J.-M. Léger, S. Quideau, J. Org. Chem. 69 (2004) 8731–8738.
[47] C. Boullais, C. Rannou, E. Réveillère, C. Mioskowski, Eur. J. Org. Chem. (2000) 723–727.
[48] K. Möller, G. Wienhöfer, K. Schröder, B. Join, K. Junge, M. Beller, Chem. Eur. J. 16 (2010) 10300–10303.
[49] K.N. Parida, J.N. Moorthy, J. Org. Chem. 80 (2015) 8354–8360.
[50] R. Gopinath, A.R. Paital, B.K. Patel, Tetrahedron Lett. 43 (2002) 5123–5126.
[51] A. Butler, M.J. Clague, G.E. Meister, Chem. Rev. 94 (1994) 625–638.
[52] V. Conte, F. Di Furia, G. Modena, J. Org. Chem. 53 (1988) 1665–1669.
[53] M. Hubert, S. Lucien, D. Eric, P. Michele, F. Jean, W. Raymond, J. Am. Chem. Soc. 105 (1983) 3101–3110.
[54] T. Kitamura, K. Nagata, H. Taniguchi, Tetrahedron Lett. 36 (1995) 1081–1084.
[55] Other trivalent hypervalent iodine reagents can also selectively react at the para-position of alkoxyarenes. See: T. Dohi, T. Hayashi, S. Ueda, T. Shoji, K. Toshitaka, K. Komiyama, H. Takeuchi, Y. Kita, Tetrahedron 75 (2019) 3617-3627.
[56] T. Dohi, N. Yamaoka, Y. Kita, Tetrahedron 66 (2010) 5775–5785.
[57] T. Dohi, M. Ito, K. Morimoto, Y. Minamitsuji, N. Takenaga, Y. Kita, Chem. Commun. (Camb.) 40 (2007) 4152–4154.
[58] N.S. Soldatova, P.S. Postnikov, M.S. Yusubov, T. Wirth, Eur. J. Org. Chem. (2019) 2081–2088.
[59] M. Zhu, N. Jalalian, B. Olofsson, Synlett (2008) 592–596.
[60] M. Bielawski, M. Zhu, B. Olofsson, Adv. Synth. Catal. 349 (2007) 2610–2618.
[61] T. Kitamura, J. Matsuyuki, K. Nagata, R. Furuki, H. Taniguchi, Synthesis 10 (1992) 945-946 and see also ref. 16.
[62] S.L. Collom, P.T. Anastas, E.S. Beach, R.H. Crabtree, H. Hazari, T.J. Sommer, Tetrahedron Lett. 54 (2013) 2344–2347.
[63] For the concept of catalytic utilization of hypervalent iodine reagents, see: T. Dohi, Y. Kita, Chem. Commun. (2009) 2073-2085.
[64] R.D. Richardson, T. Wirth, Angew. Chem. Int. Ed. 45 (2006) 4402–4404.
[65] M. Ochiai, K. Miyamoto, Eur. J. Org. Chem. (2008) 4229–4239.