Continuous *In Situ* Electrogeneration of *o*-Benzoquinone in Microreactor: Application to High Yield Reaction with Benzenethiols

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We have successfully demonstrated that a microflow reactor is extremely useful in controlling reactions involving an unstable *o*-benzoquinone. As a model reaction, Michael addition reaction between *o*-benzoquinone generated from electrochemical oxidation of catechol and benzenethiols was employed. This reaction system enables selective oxidation of catechol avoiding the oxidation of benzenethiol, although these oxidation potentials are close to each other. The examination of several reaction conditions indicated that the key features of the method are an effective *o*-benzoquinone generation and its rapid use for the following reaction without decomposition in a microflow system. In addition, cyclic voltammetry measurements elucidated that catechol concentration and selection of anode material were crucial factors for effective *o*-quinone generation.

Keywords: electrosynthesis, *o*-quinone, Michael addition, unstable compound, diphenylsulfide synthesis

1. Introduction

Generation and controlling of reactive species (including short-lived molecules) are one of the most important issues in organic reaction. Temperature, solvent, reaction time, additives, etc. have been commonly examined for this purpose. On the other hand, recent progress of organic synthesis in flow condition opened a new reaction system controlling highly reactive species. The key feature of the system is that the fast generation and consumption of the reactive species. Chemically generated reactive species have been employed for the several organic synthetic systems in flow conditions [1]. Although electrochemically generated species can be also employed for organic reactions in flow conditions [2], the application of the species has been limited so far.

Electrosynthetic reaction is regarded as an environmentally friendly method to activate organic molecules [3]. Since anode and cathode act as oxidant and reductant respectively, the method does not need redox reagents in principle. However, selectivity of electrosynthetic reaction strongly depends on the redox potentials of substrates combination. Although several techniques have been developed to overcome this problem [4], the feature of continuous flow synthesis has a possibility to provide a new system to control the electrosynthesis reaction in highly efficient and selective manner.

We recently reported that a microflow reactor is extremely useful in controlling reactions involving an unstable *o*-quinone [5]. Our system employed Michael addition reaction between *o*-benzoquinone generated from electrochemical oxidation of catechol and benzenethiols as a model reaction (Figure 1). *o*-Quinones are attractive molecules from a synthetic point of view, since they can react with various reagents and then afford corresponding substituted catechols, benzofurans and so on [6–19]. In this regard, *o*-quinones would be considered as useful and important synthetic building blocks in organic and medicinal chemistry. However, *o*-quinones are too reactive and unstable to store and not easy to handle because of their lability. In fact, decomposition, isomerization, or polymerization often occur during storage. Therefore, these *o*-quinones are usually prepared by the in situ oxidation of the corresponding catechols in the presence of a reaction partner [19,20]. However, the oxidation potentials of the reaction partners, especially nucleophiles, are often the same or lower than those of the corresponding catechols, and therefore the presence of the partners would prevent the desired oxidation of the catechols [19]. To avoid the decomposition of *o*-quinones and competing oxidation, catechols must be oxidized in the absence of organic substrate and then used immediately for the following reaction. To achieve the model reaction in high efficient manner, an electrochemical microreactor was fabricated. The microflow reactor fabricated for the model reaction consists of two parts, an electrolysis part for the generation of *o*-benzoquinone and a chemical reaction part for its rapid use for Michael addition reaction. The electrochemical generation of *o*-benzoquinone capitalized on the oxidation of catechol [19]. This method enables rapid generation of *o*-benzoquinone and does not require the use of a chemical oxidant that can complicate downstream processes.

The successful preliminary results prompted us to perform a systematic study of the Michael addition reaction. Herein, we wish to report the details of our study of Michael addition reaction between electrogenerated *o*-benzoquinone and benzenethiols in microflow reactors. Especially, electrochemical behavior of catechol on the electrodes was focused because the electrogeneration of *o*-benzoquinone is a key step of this model reaction.

2. Result and Discussion

2.1. Comparison of Reactor Type. First of all, the model reaction was performed in a conventional batch type cell using 4-isopropylbenzenethiol as a nucleophile (Table 1, entry 1). When catechol and 4-isopropylbenzenethiol were mixed in the same electrolytic cell (in-cell method), the yield of **3a** was 13%. According to *I–E* curves of catechol and 4-isopropylbenzenethiol, oxidation potentials of both catechol and 4-isopropylbenzenethiol were relatively close to each other (Figure 2). Hence, the competing oxidation that most likely occurred is an issue for this reaction.

Subsequently, 4-isopropylbenzenethiol was added to the batch type electrolytic cell after the catechol electrochemical oxidation (ex-cell method) to prevent the competing oxidation (Table 1, entry 2). In this case, the yield of **3a** was improved to 32% since competing oxidation of the catechol and 4-isopropylbenzenethiol would be avoided. However, black precipitates were confirmed before addition of 4-isopropylbenzenethiol. The formation of the precipitate indicated decomposition of the *o*-benzoquinone [21] during the extended electrolysis time needed to accumulate sufficient quantities of the intermediate. On the other
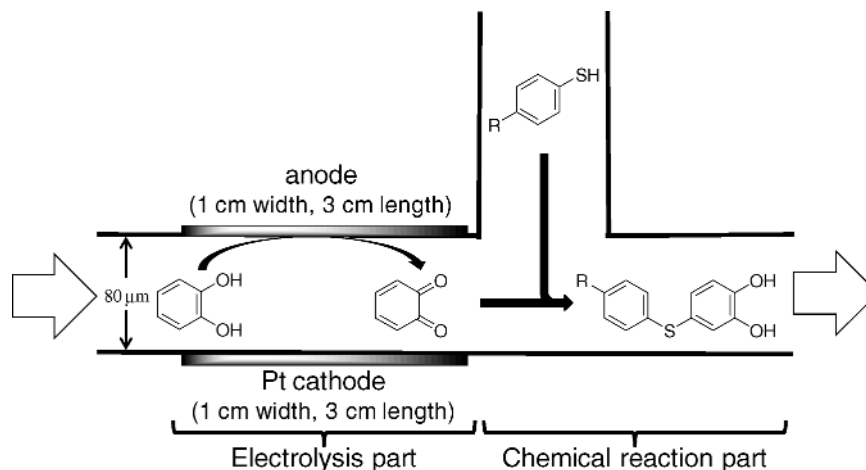
Figure 1. Schematic representation of the electrogeneration of *o*-benzoquinone and the following reaction with a benzenethiol in the microflow reactor

hand, by using the microflow reactor, the yield of **3a** was significantly improved to 88% (the productivity was 13.8 mg/h). This result apparently suggests that *o*-benzoquinone could be generated effectively without interference of the thiol oxidation, and in addition the generated *o*-benzoquinone could be used rapidly for the reaction with 4-isopropylbenzenethiol without decomposition (Table 1, entry 3).

In the next, various reaction conditions were examined to figure out the behavior of this model reaction.

2.2. Effect of Anode Material. The electrode material is an important factor in selecting the course of an electrode reaction and in controlling the efficiency of a reaction. Since the initial step of this model reaction is electrogeneration of *o*-benzoquinone, the effect of anode materials of the microreactor on the yield of **3a** was examined. On the other hand, a Pt plate was commonly employed as a cathode material of the microreactor since a cathodic process in the electrosynthesis is hydrogen evolution.

Table 2 shows chemical yields of product **3a** after electrolysis of 0.01 M catechol in acetonitrile solution using a microreactor with various anode materials. Both glassy carbon and graphite electrodes exhibited relatively good performance, and especially, graphite electrode gave the best result. On the other hand, platinum electrode exhibited lower performance compared to that of carbon electrodes. To evaluate and figure out the efficiency of *o*-quinone generation on all electrode materials used, cyclic voltammetry measurements were carried out (Figure 3). Cyclic voltammograms of catechol indicated that the graphite electrode has lower over potential for oxidation of catechol compared with other electrodes as shown in Figure 3a. Moreover, graphite electrode has large superficial area in a specific size, which would reduce the

Table 1. Chemical yields of **3a** in the sequential reaction using a batch type cell and microreactor[a]

Entry	Reactor type	Yield (%)[c]
1	Batch type cell (In-cell)	13
2	Batch type cell (ex-cell)	32
3	Microflow reactor[b]	88

[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; current density, 1.5 mA cm^{-2}; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM NaClO$_4$; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine.
[b] Electrode distance, 80 μm; flow rate, 0.1 mL/min.
[c] Determined by HPLC.

Table 2. Effect of anode material on the yield of **3a**[a]

Entry	Anode material	Yield[b] (%)
1	Platinum	9
2	Glassy carbon	80
3	Graphite	88

[a] Experimental conditions: cathode, Pt plate; current density, 1.5 mA cm^{-2}; charge passed, 2.8 F/mol; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM NaClO$_4$; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine; electrode distance, 80 μm; flow rate, 0.1 mL/min.
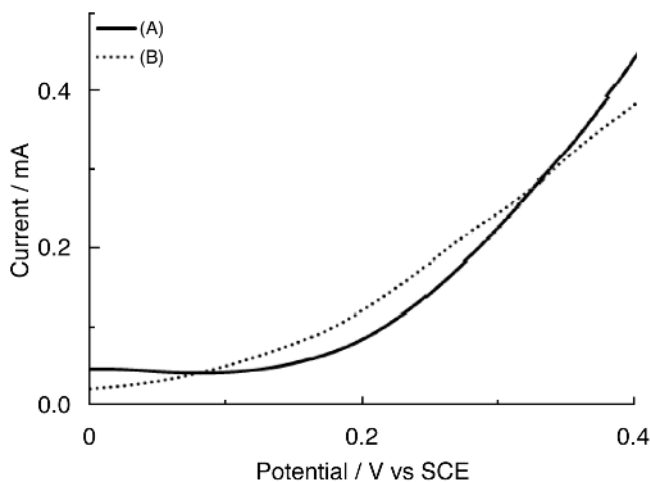[b] Determined by HPLC.

actual current density to oxidize the catechol in mild condition. These features might improve the efficiency of catechol oxidation. On the other hand, despite the platinum and glassy carbon electrodes showed similar behavior for catechol oxidation on positive direction in cyclic voltammograms (Figure 3b and c), platinum electrode gave low yield in preparative electrolysis (see Table 2). In cyclic voltammograms recorded at graphite and glassy carbon electrodes, the cathodic response corresponding to *o*-quinone reduction seems to be comparable to the anodic response corresponding to catechol oxidation (Figure 3a and b). However, the cathodic response recorded on platinum electrode almost disappeared (Figure 3c). These results indicate that *o*-quinone generated on platinum electrode is unstable. In other words, *o*-quinone would undergo side reaction to give non-reduction active compound. Therefore, effective preparative electrolysis might be difficult using platinum electrode.

Figure 2. *I–E* curves of (A) 10 mM catechol and (B) 10 mM 4-isopropylbenzenethiol at a graphite disk anode (4 mm ϕ) in 100 mM NaClO$_4$ + 10 mM 2,6-lutidine acetonitrile solution
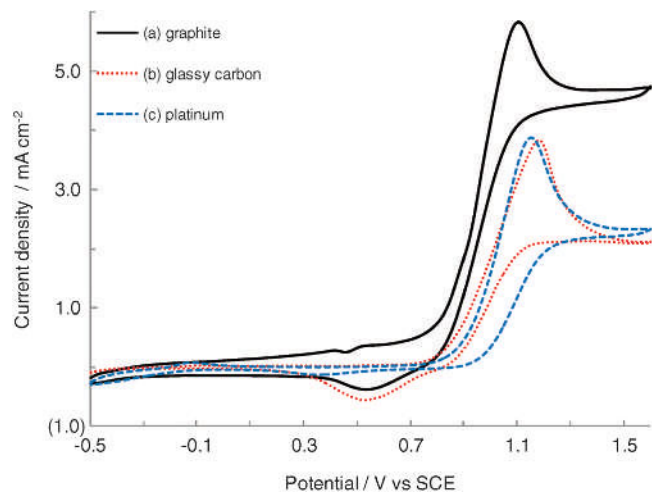
Figure 3. Cyclic voltammograms of 10 mM catechol in 100 mM NaClO₄ solution recorded at (a) graphite disk (5 mm ϕ), (b) glassy carbon disk (3 mm ϕ), and (c) platinum disk (3 mm ϕ) electrodes. Scan rate is 30 mV/s

2.3. Effect of Catechol Concentration. The substrate concentration is also an important factor for both chemical and lectro-chemical reaction. Therefore, the effect of catechol concentration on the yield was investigated. As shown in Table 3, yield of **3a** was increased with a decrease in the catechol concentration. This

Table 3. Effect of catechol concentration on the yield of **3a**[a]

Entry	Catechol concentration (mM)	Yield[b] (%)
1	5	90
2	10	88
3	20	58
4	100	14

[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; current density, 1.5 mA cm^{-2}; charge passed, 2.8 F/mol; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM NaClO₄; nucleophile, 1 equivalent of 4-isopropylbenzenethiol; base, 1 equivalent of 2,6-lutidine; electrode distance, 80 µm.
[b] Determined by HPLC.

Table 4. Effect of the flow rate and current density on yield of **3a**[a]

Entry	Flow rate (mL/min)	Current density (mA cm^{-2})	Yield[b] (%)
1	0.01	1.5	8
2	0.05	1.5	48
3	0.10	1.5	88
4	0.14	1.5	66
5	0.10	1.1	48
6	0.10	3.0	48
7	0.10	6.0	32

[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; electrode distance, 80 µm; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM NaClO₄; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine.
[b] Determined by HPLC.

can be ascribed to the decomposition of *o*-quinone at higher catechol concentrations. Indeed, black precipitate was observed in such higher catechol concentration conditions.

According to the cyclic voltammograms obtained from low catechol concentration condition, the cathodic response corresponding to *o*-quinone reduction seems to be comparable to the anodic response corresponding to catechol oxidation (Figure 4a–c). On the other hand, the cathodic response recorded in high catechol concentration condition was diminished relative to the anodic response (Figure 4d). These results suggested that generated *o*-quinone could be decomposed in a high catechol concentration condition. As a plausible side reaction, *o*-quinone may react with catechol to give dimer or polymer. Hence, a low catechol concentration condition would be desirable to avoid the side reaction of *o*-quinone electrogenerated [21].

2.4. Effect of Current Density and Flow Rate. Then the influence of the flow rate and current density on the model sequential reaction using the microflow reactor was examined (Table 4). The yield of **3a** increased with an increase in the flow rate, and the highest value was obtained at 0.1 mL/min (Table 4, entries 1, 2, and 3). At lower flow rates, the decomposition and overoxidation of *o*-benzoquinone occurred due to a longer residence time in the reactor. In fact, black precipitates could be observed in these cases. On the other hand, at 0.14 mL/min of the flow rate (Table 4, entry
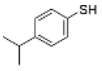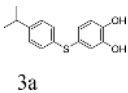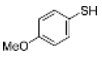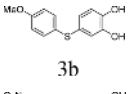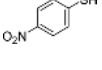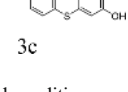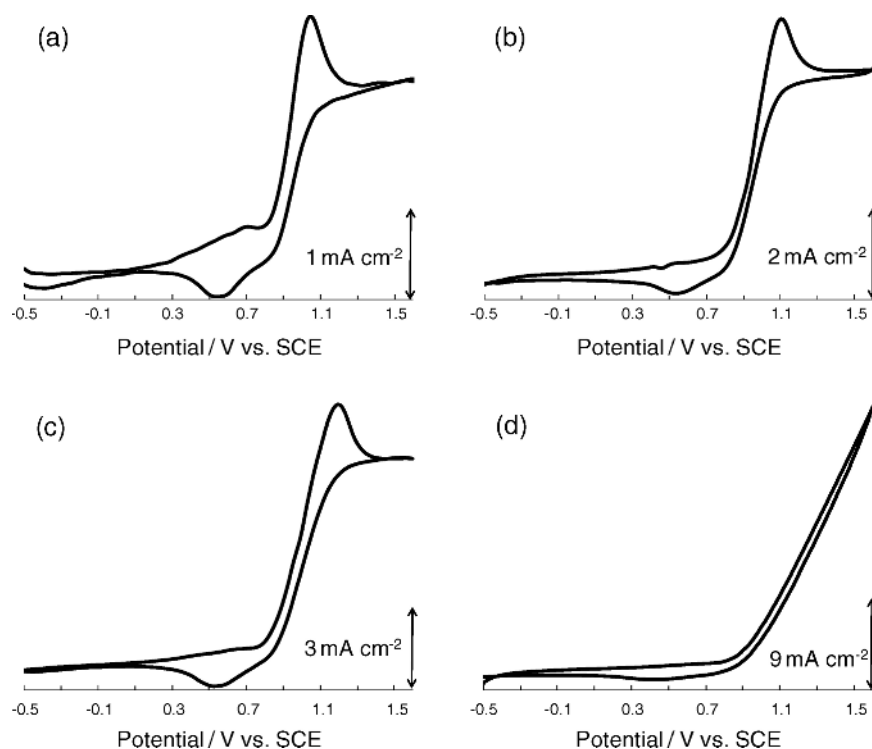

Figure 4. Cyclic voltammograms of (a) 5 mM, (b) 10 mM, (c) 20 mM, and (d) 100 mM catechol. in 100 mM NaClO₄ solution recorded at graphite disk electrode (5 mm ϕ). Scan rate is 30 mV/s

Table 5. Michael addition reactions between *o*-benzoquinone generated from electrooxidation of catechol and benzenethiols[a]

Nucleophile	Product	Reactor type	Yield[b] (%)
	3a	Microflow reactor[b]	88
		Batch type cell	13
	3b	Microflow reactor[b]	79
		Batch type cell	n.d.
	3c	Microflow reactor[b]	81
		Batch type cell	7

[a] Experimental conditions: anode, graphite plate; cathode, Pt plate; electrode distance, 80 μm; current density, 1.5 mA cm^{-2}; flow rate, 0.1 mL/min; charge passed, 2.8 F/mol; solvent, AcCN; substrate, 10 mM catechol; supporting electrolyte, 100 mM NaClO$_4$; nucleophile, 10 mM 4-isopropylbenzenethiol; base, 10 mM 2,6-lutidine.
[b] Determined by HPLC.
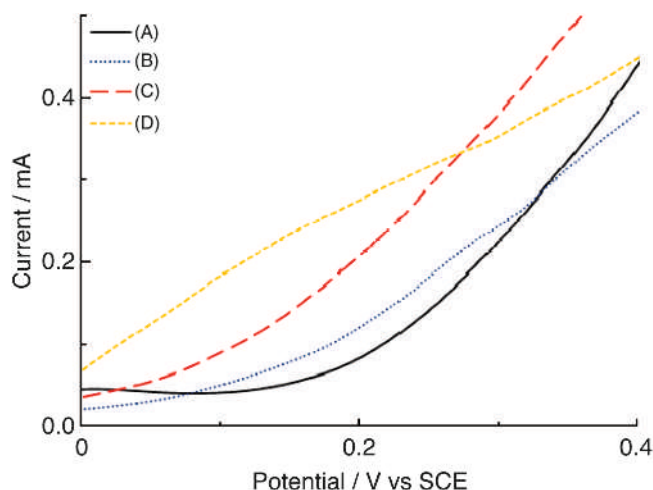
Figure 5. *I–E* curves of (A) 10 mM catechol, (B) 10 mM 4-isopropylbenzenethiol, (C) 10 mM 4-methoxybenzenethiol, and (D) 10 mM 4-nitrobenzenethiol at a graphite disk anode (4 mm ϕ) in 100 mM NaClO$_4$ + 10 mM 2,6-lutidine acetonitrile solution

4), the yield decreased again. This can be explained by an insufficient bulk conversion due to a higher flow rate. Actually, ca. 30% of the starting material was recovered in this case. At 1.1 mA cm^{-2} of the current density (Table 4, entry 5), the yield was less than 50% due to an insufficient bulk conversion. On the other hand, at higher current densities (Table 4, entries 6 and 7), the yield was 50% or worse since overoxidation took place. Black precipitates were actually confirmed in these cases.

2.5. Effect of Substituent of Benzenethiols on the Yield. Finally, to demonstrate the generality of this methodology, we also investigated Michael addition reactions between *o*-benzoquinone generated from electrochemical oxidation of catechol and other benzenethiols using the microflow reactor, and compared with those using the batch type electrolytic cell (in-cell method). In addition, oxidation potentials of catechol and benzenethiols were measured to figure out the sequence of oxidation of two substrates in the in-cell method.

As shown in Table 5, the yields in all cases were higher for reactions run with the microflow reactor. The generation amount of *o*-benzoquinone in the first electrochemical oxidation step of the microreactor process should be the same for all the reactions since the electrolysis part of the reactor is the same. Therefore, overall yields for the two-step sequence are reflection of the Michael addition. Since the nucleophilicity of all three thiols studied is roughly equivalent, the three reactions led to similar yields. On the other hand, in batch processes (in-cell method), product yields would be dependent on the oxidation potential of benzenethiols used because catechol and benzenethiols are mixed in the same electrolytic cell in these cases. In fact, as shown in Figure 5, the oxidation potential of all benzenethiols was lower than that of cathechol, and hence the yields for all batch processes are all low because of competitive oxidation of the thiol nucleophile.

3. Conclusion

In conclusion, we have developed an effective method for the generation and reaction of *o*-benzoquinone using a microflow system. The key features of the method are an effective *o*-benzoquinone generation and its rapid use for the following reaction in the microflow system. Cyclic voltammetry measurements elucidated that catechol concentration and selection of anode material played crucial role for effective *o*-quinone
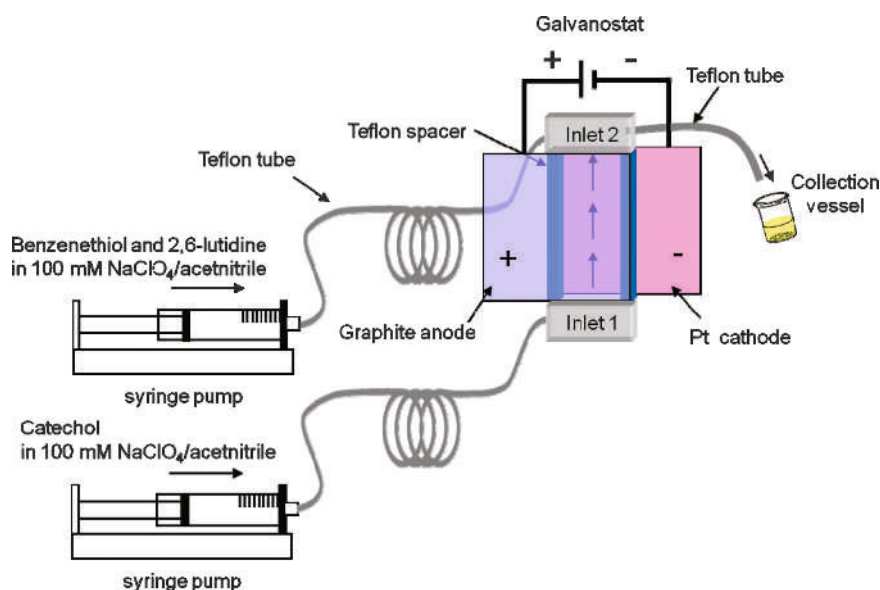
Figure 6. Schematic illustration of the microflow system

generation without causing its decomposition. It is hoped that this facile and novel reaction system will highlight the utility of flow reactors for optimizing reactions involving sensitive intermediates.

4. Experimental

4.1. Instrumentation. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were measured on JEOL JNM EX-270 spectrometer operating at 270 MHz (^{1}H NMR), 67.8 MHz (^{13}C NMR) in CDCl_3. All ^{1}H NMR chemical shifts were reported in ppm relative to internal references of TMS at δ 0.00. ^{13}C NMR chemical shifts were reported in ppm relative to carbon resonance in chloroform-d_1 at δ 77.00. EI mass spectra were measured with a Shimadzu GCMS-QP5050A mass spectrometer. IR spectra were recorded on a Shimadzu FTIR-8100A spectrometer. Cyclic voltammetry was performed by using a computer-controlled electrochemical analyzer (ALS/CH Instruments 630C). Preparative electrolyses were carried out with a HOKUTO DENKO HA-501 Potentiostat/Galvanostat.

4.2. Materials. Acetonitrile and 4-isopropylbenzenethiol were purchased from Wako PureChemical Industries and used as received. Catechol, 4-methoxybenzenethiol, 4-nitrobenzenethiol, and 2,6-lutidine were purchased from Tokyo Chemical Industry and used as received. Sodium perchlorate was purchased from Kanto Chemical and used as purchased.

4.3. Microflow Reactor. Figure 6 shows schematic illustration of the electrochemical microflow reactor. The reactor was constructed from platinum (Pt) plate (3-cm width, 3-cm length) and graphite (G) plate (3-cm width, 3-cm length). A spacer (NITOFLON® 80-μm thickness adhesive tape, Nitto Denko) was used to leave a rectangular channel exposed, and the two electrodes were simply sandwiched together (area of the two electrodes: 1×3 cm^2). After connecting Teflon tubing to inlets and outlet, the cell was sealed with epoxy resin. As shown in Figure 6, the inlets 1 and 2 were provided for introducing the catechol and benzenethiol solutions, respectively.

4.4. Voltammetry Measurement. I–E curve measurements for the oxidation of catechol and benzenethiols, and cyclic voltammetry measurements of catechol were performed by using a computer-controlled electrochemical analyzer (ALS/CH Instruments 630C). I–E curves were recorded at a temperature of 25 ± 2 °C using an undivided cell equipped with a working electrode (graphite disk electrode), an auxiliary electrode (Pt plate, 2×2 cm^2), and a saturated calomel reference electrode (SCE).

4.5. General Procedure for Preparative Electrolysis Using Microflow Reactor. Bulk electrolysis of catechol (10 mM) in acetonitrile was conducted with a constant current (1.5 mA cm^{-2}) and solution flowing through the electrolysis cell. The solution containing 4-isopropylbenzenethiol (10 mM) and 2,6-lutidine (10 mM) was introduced at the inlet 2 in Figure 6. The flow rates of two solutions were fixed at 0.1 mL/min. The flow rates were controlled by using syringe pump (KD Scientific model 100). Reaction mixture was collected and then analyzed by high-performance liquid chromatography (HPLC) to determine the product yield. HPLC analysis was performed by an external standard method with a Shimazu 880-PU equipped with UV detector (875-UV, Shimazu) and an ODS column (Inertsil ODS-4, GL Science).

4.6. General Procedure for Preparative Electrolysis Using Bath Type Reactor. As for in-cell method, bulk electrolysis was carried out using an undivided cell equipped with a working electrode (graphite plate, 1×3 cm^2) and an auxiliary electrode (Pt plate, 1×3 cm^2) in 100 mM NaClO_4/acetonitrile solution (10 mL) containing catechol (10 mM), 4-isopropylbenzenethiol (10 mM), and 2,6-lutidine (10 mM). Constant current (1.5 mA

cm^{-2}) was applied for the electrolysis. After the charge was passed (2.8 F/mol), reaction mixture was analyzed by HPLC to determine the product yield. As for ex-cell method, bulk electrolysis was carried out using an undivided cell equipped with a working electrode (graphite plate, 1×3 cm^2) and an auxiliary electrode (Pt plate, 1×3 cm^2) in 100 mM NaClO_4/acetonitrile solution (10 mL) containing catechol (10 mM). Constant current (1.5 mA cm^{-2}) was applied for the electrolysis. After the charge was passed (2.8 F/mol), 4-isopropylbenzenethiol (10 mM) and 2,6-lutidine (10 mM) in acetonitrile solution (10 mL) were added followed by stirring for 10 min. Reaction mixture was analyzed by HPLC to determine the product yield.

4.7. Synthesis and Characterization of Authentic Samples for HPLC Analysis

4.7.1. 4-(4-Isopropyl-phenylsulfanyl)-benzene-1,2-diol (3a). A solution of catechol (0.2 g, 1.8 mmol) and Ag_2O (0.85 g, 3.7 mmol) in acetonitrile (10 mL) were stirred for 10 min. Ag_2O was removed from solution by gravity filtration. The resulting filtrate was added to the solution of 4-isopropyl benzenethiol (0.27 g, 1.8 mmol) and 2,6-lutidine (1.9 g, 17.7 mmol) in acetonitrile (10 mL) and stirred for 1 h at room temperature. Resulting mixture was then acidified with 1 M HCl and extracted with diethyl ether. The organic layer was dried with sodium sulfate and diethyl ether was removed by rotary evaporation. Crude product was purified by silica gel column chromatography (Hex/EtOAc) to give viscous yellow oil (16% yield).

^{1}H-NMR (270 kHz; CDCl_3): δ 7.12–6.98 (m, 6H), 6.84 (t, 1H), 2.84 (m, $J = 7.02$ Hz, 1H), 1.21 (d, $J = 7.02$ Hz, 6H)

^{13}C-NMR (270 kHz; CDCl_3): δ 23.84, 33.60, 117.17, 121.24, 127.46, 144.304, 147.372

IR (neat NaCl ν/cm^{-1}) 3415, 2960, 2930, 2875, 1715, 1595, 1495, 1475, 1455, 1250, 1225, 1155, 1145, 1110

HRMS (ESI) m/z calculated for $C_{12}H_9NO_4S$ 260.0871, found 260.0873

4.7.2. 4-(4-Methoxy-phenylsulfanyl)-benzene-1,2-diol (3b). A solution of catechol (0.5 g, 4.5 mmol) and Ag_2O (2.13 g, 9.3 mmol) in acetonitrile (25 mL) were stirred for 10 min. Ag_2O was removed from solution by gravity filtration. The resulting filtrate was added to the solution of 4-methoxy benzenethiol (0.7 g, 5 mmol) and 2,6-lutidine (1.9 g, 17.7 mmol) in acetonitrile (10 mL) and stirred for 1 h at room temperature. Resulting mixture was then acidified with 1 M HCl and extracted with diethyl ether. The organic layer was dried with sodium sulfate and diethyl ether was removed by rotary evaporation. Crude product was purified by silica gel column chromatography (Hex/EtOAc) to give viscous yellow oil (15% yield).

^{1}H-NMR (270 kHz; CDCl_3): δ 7.15–7.09 (m, 2H), 6.98–6.88 (m, 2H), 6.72–6.78 (m, 3H)

^{13}C-NMR (270 kHz; CDCl_3): δ 158.45, 144.15, 143.85, 130.53, 126.34, 125.56, 120.73, 119.09, 116.70, 114.84, 55.25

IR (neat NaCl ν/cm^{-1}) 3410, 2980, 2930, 2830, 1700, 1595, 1495, 1455, 1360, 1325, 1285, 1245, 1175, 1025

HRMS (ESI) m/z calculated for $C_{13}H_{12}O_3S$ 248.0507, found 248.0515

4.7.3. 4-(4-Nitro-phenylsulfanyl)-benzene-1,2-diol (3c). A solution of catechol (0.5 g, 4.5 mmol) and Ag_2O (2.13 g, 9.3 mmol) in acetonitrile (25 mL) were stirred for 10 min. Ag_2O was removed from solution by gravity filtration. The resulting filtrate was added to the solution of 4-nitro benzenethiol (0.75 g, 4.8 mmol) and 2,6-lutidine (1.9 g, 17.7 mmol) in acetonitrile (25 mL) and stirred for 1 h at room temperature. Resulting mixture was then acidified with 1 M HCl and extracted with diethyl ether. The organic layer was dried with sodium sulfate and diethyl ether was removed by rotary evaporation. Crude product was purified by silica gel column chromatography (chloroform) and then

recrystallized from chloroform–acetone–hexane solution to give yellow crystal (20% yield).

^{1}H-NMR (270 kHz; CDCl$_3$): δ 7.00 (d, 3H), 7.22 (d, 2H), 8.10 (d, 2H)

^{13}C-NMR (270 kHz; CDCl$_3$): δ 207.21, 150.94, 148.07, 146.97, 128.66, 126.18, 124.50, 122.84, 119.36, 117.48

IR (neat KBr v/cm^{-1}) 3543, 3455, 2365, 1859, 1578, 1500, 1441, 1338, 1330, 1317, 1186, 1109

HRMS (ESI) *m/z* calculated for C$_{12}$H$_9$NO$_4$S 263.052, found 286.0147 (M+Na)$^+$

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