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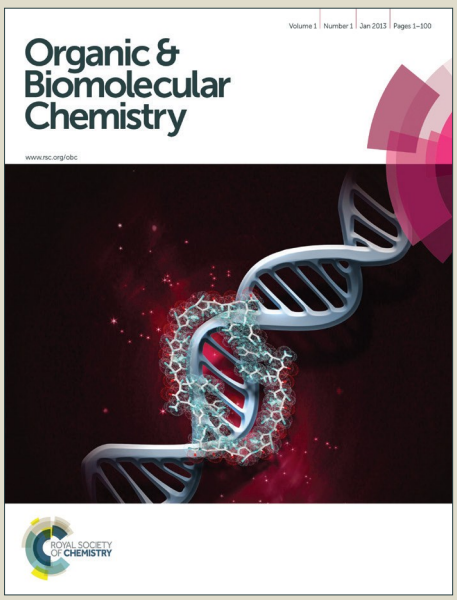

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ARTICLE

ONO-Pincer Ruthenium Complex-Bound Norvaline for Efficient Catalytic Oxidation of Methoxybenzenes with Hydrogen Peroxide

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The enhanced catalytic activity of ruthenium complex-bound norvaline Boc-L-[Ru]Nva-OMe **1**, in which the ONO-pincer ruthenium complex Ru(pydc)(terpy) **2** is tethered to the α-side chain of norvaline, has been demonstrated for the oxidation of methoxybenzenes to *p*-benzoquinones with a wide scope of substrates and unique chemoselectivity.

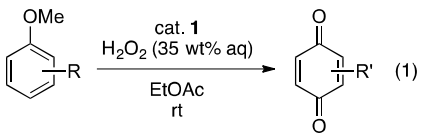
Introduction

Bioorganometallic compounds, which are hybrids of biologically important molecules and organometallic molecules,[1] have attracted much attention as efficient platforms for multifunctional materials. The inherent properties of these molecular components can provide various functions, such as self-assembly,[2] molecular recognition,[3] photochemical[4] and electrochemical properties,[5] and catalytic activity, in an individual or more importantly an emergent manner.[6] To develop such functional molecules, numerous efforts have been devoted to finding appropriate conjugation of transition-metal complexes with various biomolecules, such as DNAs,[7] sugars,[8] amino acids,[9] peptides,[10] and proteins.[11] Among these, conjugation with amino acids, so-called metalated amino acids, have the longest history, as ferrocene-conjugated alanine and phenylalanine were first reported by Schlögl in 1957.[12] Various types of metalated amino acids and their peptide-congeners have been synthesized with the aim of developing bioprobes and biolabeling agents, for example, peptide-tethered Gd and Tc complexes are used as contrast agents in MRI and SPECT imaging.[13] Photo- and electrochemical functional material applications[14] have also been demonstrated based on the cooperative interaction of multiple metal centers on peptide backbones. However, catalysis using metalated amino acids and peptides has been explored limitedly, despite the wide spread application of transition-metal complexes as catalysts in organic chemistry. We have reported NCN- and PCP-pincer Pd complex-bound norvaline and the corresponding peptides.[15] These systems showed unique self-assembly properties, affording well-regulated Pd arrays. Moreover, the cyclization of alkynoic acids[16] and Suzuki–Miyaura-type 1,4-additions[17] were successfully catalyzed using these Pd-bound norvaline-supramolecular gels. Interestingly, the catalytic efficiency of the supramolecular gels was substantially increased compared with those of both the non-assembled phase and the parent Pd complex alone.

Various ruthenium complex-bound amino acids[18] and peptides[18,19] have been recently developed with a focus on the applications of ruthenium as catalysts,[20] photo/electrochemical materials,[21] and bio-markers in chemical biology.[22] However, only a few examples of Ru-bound amino acid-catalyzed reaction have been reported:[23] Gilbertson and Robinson independently reported an NHC-Ru complex-bound peptide-catalyzed olefin metathesis reaction. A hybrid of an NHC-Ru complex and protein for ring-closing metathesis was developed by Hilvert. Furthermore, Albrecht synthesized histidine-based NHC-Ru complexes and examined their catalytic activity in transfer hydrogenation of benzophenone.

We have recently succeeded in synthesizing an ONO-pincer ruthenium complex[24]-bound norvaline, Boc-L-[Ru]Nva-OMe **1**[25] (Fig. 1, [Ru] = Ru(pydc)(terpy)[26] **2**, developed by Nishiyama [27]). The excellent catalytic activity of **2** in various oxidation reactions has been reported by Nishiyama[27] and Beller.[28] We demonstrated that metalated amino acid **1** catalyzed the oxidation of alcohols with H_2O_2, and the catalytic activity of **1** was much higher than that of the parent ruthenium complex **2**.

By further focusing on the catalytic activity of **1**, we have found that it shows excellent catalytic activity toward the oxidation of methoxybenzenes to *p*-benzoquinones with a wide substrate scope and unique chemoselectivity (Eq. 1). This type of reaction is well-known as an important class of enzymatic metabolism of phenol derivatives. Moreover, *p*-benzoquinones are biologically and pharmaceutically important molecules. Therefore, considerable



(1)

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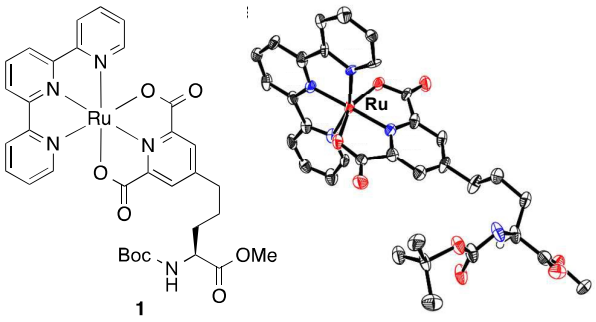


Fig. 1 The ruthenium complex-bound norvaline **1** and its single crystal structure.

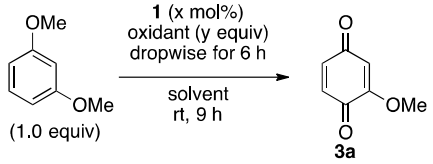
effort has been expended to develop more efficient and versatile syntheses of *p*-benzoquinone derivatives, especially through oxidative transformation of arenes using stoichiometric oxidants[29-36] and transition metal catalysts, such as iron,[37] vanadium,[38] ruthenium,[39] chromium,[40] and rhenium.[41] However, challenges in developing more practical and environmentally friendly reactions remain to be addressed: Development of more active and selective catalysts to reduce catalyst loading, replacement of expensive and harmful oxidants with molecular O_2 or H_2O_2, and avoidance of toxic solvents. Herein, we report the highly efficient and environmentally benign oxidative transformation of methoxybenzenes to *p*-benzoquinones with only a small amount of catalyst **1** using H_2O_2 as the terminal oxidant.

Results and Discussion

The optimization of various conditions for **1**-catalyzed oxidation of methoxybenzenes using 1,3-dimethoxybenzene as a model compound is shown in Table 1. Reactions were typically carried out in the presence of catalyst **1** with dropwise addition of the oxidants. In the presence of 0.01 mol% of **1**, the substrate was completely consumed to afford 2-methoxy-*p*-benzoquinone (**3a)** in 96% yield by addition of 3.0 equivalents of H_2O_2 (entry 1). We found that the addition procedure and amounts of H_2O_2 affected the yield of **3a**. The yield was decreased by the addition of H_2O_2 in one portion (entry 2). The observed yield decreasing can be ascribed to not only the decomposition of H_2O_2 caused by the reaction with high-valent Ru species[42], but also catalyst decomposition in the presence of excess amount of H_2O_2 as described later. When 2.0 equivalents of H_2O_2 were added, the yield of **3a** was also decreased (entry 3). Under the conditions that catalyst loading was reduced to 0.005 and 0.001 mol%, the yields were drastically decreased (entries 4 and 5). The reaction could also be conducted in solvents such as CH_2Cl_2 and toluene with moderate yields (entries 6 and 7).

Among the oxidants screened, Oxone alone gave product **3a** in low yield, whereas its aqueous solution was much more effective (entries 8 and 9). Upon treatment with urea-H_2O_2, iodosobenzene, and 2,6-dichloropyridine *N*-oxide, 1,3-dimethoxybenzene was hardly oxidized to **3a** and no other product was obtained (entries 10–12). Using a CH_2Cl_2 solution of *m*-CPBA and aqueous *tert*-butyl hydroperoxide, the conversion of 1,3-dimethoxybenzene was 62% and 28%, respectively, although only a trace amount and 5% yield of **3a** were obtained, respectively (entries 13 and 14).

Table 1 The ruthenium complex-bound norvaline **1**-catalyzed oxidation of 1,3-dimethoxybenzene under various conditions



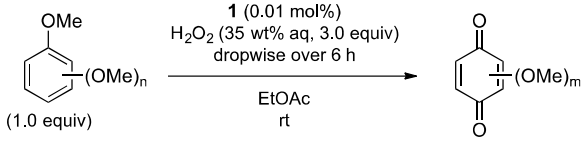
entry	x	oxidant	y	solvent	yield[a]
1	0.01	H_2O_2 (35 wt% aq)	3.0	EtOAc	96[b]
2	0.01	H_2O_2 (35 wt% aq)[c]	3.0	EtOAc	86[d]
3	0.01	H_2O_2 (35 wt% aq)	2.0	EtOAc	85
4	0.005	H_2O_2 (35 wt% aq)	2.0	EtOAc	12
5	0.001	H_2O_2 (35 wt% aq)	2.0	EtOAc	3
6	0.01	H_2O_2 (35 wt% aq)	3.0	CH_2Cl_2	73
7	0.01	H_2O_2 (35 wt% aq)	3.0	toluene	59
8	0.01	oxone[e,f]	3.0	EtOAc	15
9	0.01	oxone[f] (1.00 M aq)	3.0	EtOAc	81
10	0.01	urea-H_2O_2[e]	3.0	EtOAc	<1
11	0.01	PhIO[e]	3.0	EtOAc	<1
12	0.01	2,6-Cl_2Py N-oxide[e]	3.0	EtOAc	<1
13	0.01	*m*-CPBA (1.00 M in CH_2Cl_2)	3.0	EtOAc	<1
14	0.01	t-BuOOH (70 wt% aq)	3.0	EtOAc	5

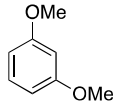
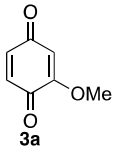
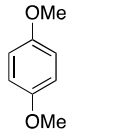
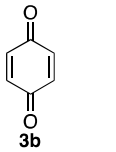
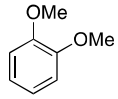
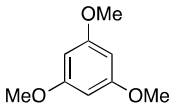
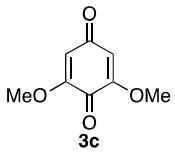
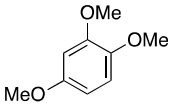
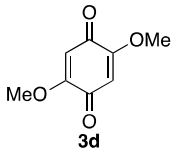
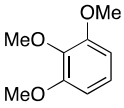
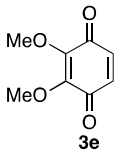
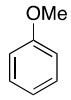
[a] Determined by calibrated GC analysis using methyl nonanoate as an internal standard. [b] In the presence of 0.01 mol% of Ru(pydc)(terpy) **2** as a catalyst, **3a** was obtained in 40% yield. [c] Added in one portion. [d] In the presence of 0.01 mol% of Ru(pydc)(terpy) **2** as a catalyst, **3a** was obtained in 29% yield. [e] Solid-state reagents were added portionwise over 6 h. [f] $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$.

The oxidation of 1,3-dimethoxybenzene catalyzed by the parent ruthenium complex **2** gave **3a** in lower yield (40%) than that obtained by using catalyst **1** under the same conditions as entry 1. Further decreasing of the product yield was also observed under the condition of one-portion addition of H_2O_2, where the reaction almost stopped after 3 h, affording **3a** in 29% yield.[43] In the **2**-catalyzed reaction, the color of the aqueous phase of the reaction mixture turned pale red, indicating the formation of high oxidation state ionic Ru species derived from ligand dissociation followed by over oxidation as described in our previous paper.[25] These results indicate the amino acid moiety of **1** influences positively to suppress undesired deactivation of the catalyst by excess amount of H_2O_2.

The oxidation of several methoxybenzenes were studied (Table 2) under the optimal condition described in Table 1, entry 1. The yields of *p*-benzoquinones depended greatly on the substitution pattern of methoxy groups on the aromatic ring. Efficient oxidation of 1,3- and 1,4-dimethoxybenzene took place to afford **3a** and *p*-benzoquinone (**3b)** in 92% and 67% isolated yields, respectively (entries 1 and 2). On the other hand, 1,2-dimethoxybenzene gave **3a** in only 5% yield (entry 3). Trisubstituted methoxybenzenes also showed good reactivities, similar to those of the dimethoxybenzenes, despite their higher steric hindrance (entries 4 and 5). However, the proximally trisubstituted 1,2,3-trimethoxybenzene showed poor reactivity, giving the corresponding *p*-benzoquinones **3e** in 15%

Table 2 The ruthenium complex-bound norvaline **1**-catalyzed oxidation of various methoxybenzenes



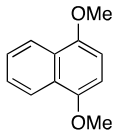
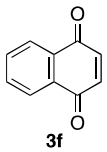
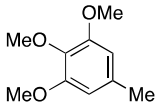
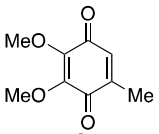
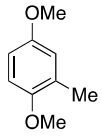
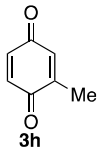
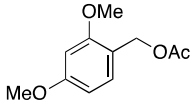
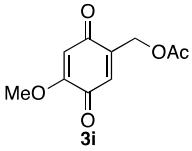
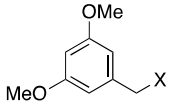
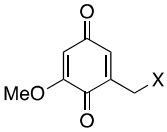
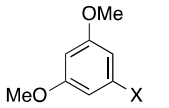
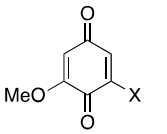
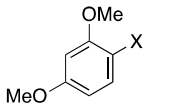
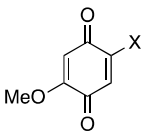
entry	substratre	product	time [h]	yield[a] [%]
1		 **3a**	9	92
2		 **3b**	9	67
3		**3a**	12	5
4		 **3c**	6	98
5[b]		 **3d**	9	69
6		 **3e**	12	15
7[c]		**3b**	12	32

[a] Isolated yield. [b] As a side product, **3a** was obtained in 14% yield. [c] As a side product, **3a** was obtained in 9% yield.

yield (entry 6). Previously reported oxidation of monomethoxybenzene, anisole was often sluggish, giving less than 10% yield of products, even with the use of strong oxidizing agents;[44] however, the oxidation of anisole gave **3b** in 32% yield along with formation of **3a** in 9% yield under the present reaction conditions (entry 7).

The substrate scope has been explored to examine the utility of this reaction for producing biologically and pharmaceutically important synthetic intermediates. The oxidation of multifunctionalized methoxybenzenes was conducted by using catalyst **1** (Table 3). Under the optimal condition described in Table

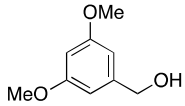
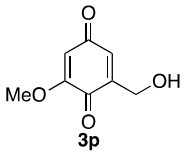
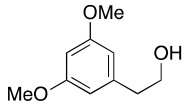
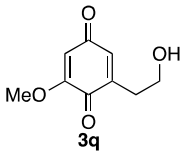
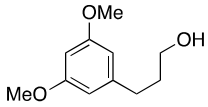
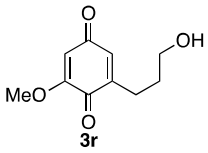
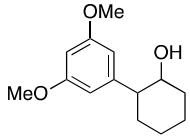
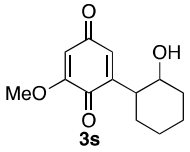
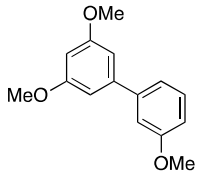
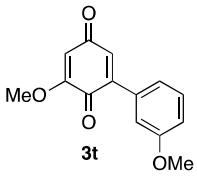
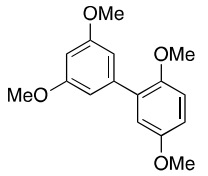
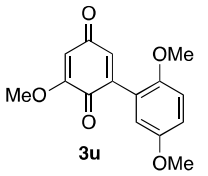
Table 3 The ruthenium complex-bound norvaline **1**-catalyzed oxidation of multi-functionalized methoxybenzenes[a]

entry	substratre	product		yield[b] [%]
1[c]		 **3f**		90
2		 **3g**		71
3		 **3h**		74
4		 **3i**		73
5 6			X = Cl **3j** X = Br **3k**	92 49
7[d] 8[d]			X = Cl **3l** X = Br **3m**	70 82
9[d] 10[d]			X = Cl **3n** X = Br **3o**	58 47

[a] Reactions were carried out under the conditions described in Table 1, entry 1, unless otherwise noted. [b] Isolated yield. [c] 50 °C. [d] Ru-cat: 0.05 mol%.

1, entry 1, 1,4-dimethoxy naphthalene was oxidized to *α*-naphthoquinone (**3f**), which is a simple model structure of vitamin K, in 90% yield (entry 1). Methyl-substituted methoxybenzenes were efficiently converted to corresponding *p*-benzoquinones **3g** and **3h**, which are analogues of coenzyme Q_n (entries 2 and 3). Dimethoxybenzene bearing a benzyl acetate group was selectively oxidized to 2-methoxy-5-acetoxymethyl-*p*-benzoquinone **3i** without benzylic oxidation (entry 4). Similar selectivity of functional groups on the aromatic ring was also observed for 1-halomethyl-3,5-dimethoxybenzenes, which afforded 6-halomethyl-2-methoxy-*p*-benzoquinones **3j** and **3k** without halogen elimination or benzylic oxidation (entries 5 and 6), although a small amount of 2-bromo-1-(bromomethyl)-3,5-dimethoxybenzene was obtained (14%, NMR

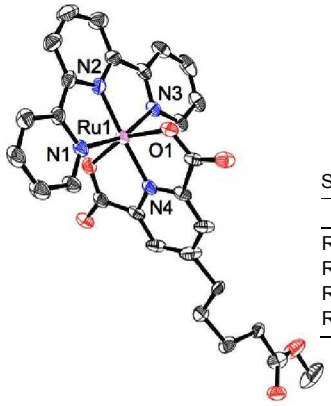
Table 4 The ruthenium complex-bound norvaline **1**-catalyzed intramolecular competitive oxidation of methoxybenzenes.[a]

entry	substrate	product	yield[b] [%]
1		 **3p**	93
2		 **3q**	94
3		 **3r**	93
4		 **3s**	80
5[c]		 **3t**	62
6[c]		 **3u**	81

[a] Reactions were carried out under the conditions described in Table 1, entry 1, unless otherwise noted. [b] isolated yield. [c] 5.0 equiv of H_2O_2 (35 wt% aq) was added.

yield) from 1-(bromomethyl)-3,5-dimethoxybenzene (entry 6). Obtained **3j** could be useful intermediate for coenzyme Q_n and vitamin K derivatives via nickel-catalyzed cross-coupling reactions.[45] Excellent chemoselectivity was also observed in the oxidation of halogen-substituted 1,3-dimethoxybenzenes. The corresponding halogen-substituted *p*-benzoquinones were exclusively obtained in good yields (entries 7–10). The resulting bromo-*p*-benzoquinone derivatives were reported as useful synthetic intermediates for polycyclic quinones, such as indolequinones[46] and naphthoquinones.[47]

The unique chemoselectivity was further demonstrated for the intramolecular competitive oxidation of hydroxyalkyl-substituted dimethoxybenzenes and polymethoxy biphenyls (Table 4). The selective oxidation of the dimethoxy-substituted aromatic ring of 1-hydroxymethyl-3,5-dimethoxybenzene proceeded to give corresponding *p*-benzoquinones **3p** without any benzylic oxidation (entry 1). It is noteworthy that Nishiyama and Beller reported ONO-pincer Ru(II) complexes-catalyzed efficient oxidation reaction of alcohols in the presence of iodosobenzene or H_2O_2, respectively.[26, 28] Selective oxidation of dimethoxy-substituted aromatic rings was also observed in the reaction of 1,3-dimethoxybenzene derivatives bearing primary and secondary alcohols, exclusively affording the corresponding *p*-benzoquinones **3q**–**3s** (entries 2–4). Interestingly, similar selectivities were reported in CAN-mediated reactions; however, the types of substrates are limited to 1,4-



Selected bond length [Å]

	6	*cf.* **2** [50]
Ru1–N1	2.052(4)	2.060(5)
Ru1–N2	1.945(4)	1.964(5)
Ru1–N4	1.967(4)	1.979(6)
Ru1–O1	2.105(2)	2.111(3)

Fig. 2 Single crystal X-ray structure of **6**.

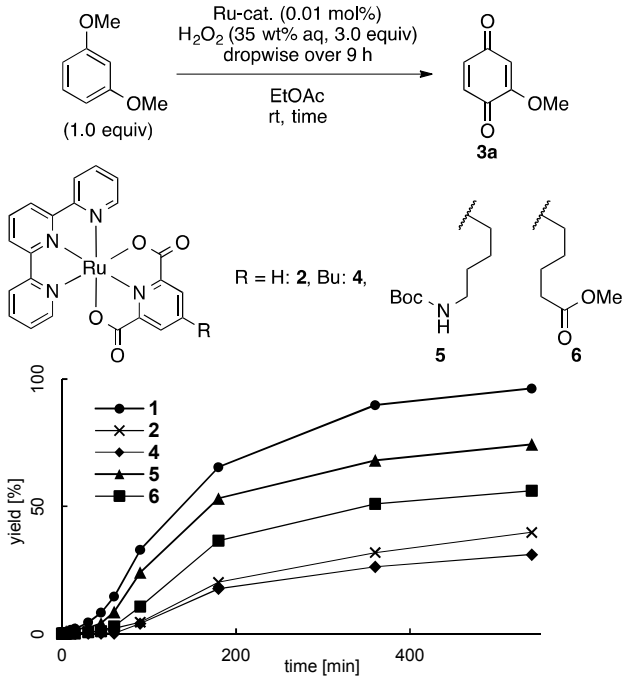


Fig. 3 Ruthenium complexes-catalyzed oxidation reactions of 1,3-dimethoxybenzene and the time-course profiles for yield of the product.

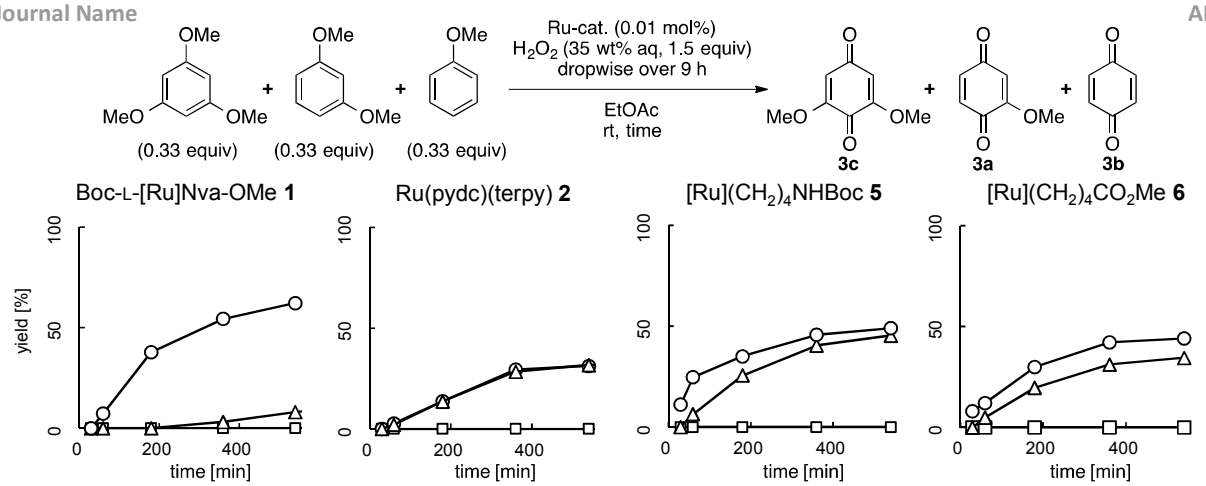


Fig. 4 Competitive oxidation between mono-, di-, and trimethoxybenzenes. Quinones: circle: **3c**, triangle: **3a**, square: **3b**.

dimethoxybenzene derivatives[31,45,48]. The order of reactivity was investigated by examining the oxidation of polymethoxy biphenyls (entries 5 and 6). Excellent intramolecular chemoselectivity was achieved on biaryl platforms such as 3,3′,5-trimethoxy-1,1′-biphenyl and 2,3′,5,5′-tetramethoxy-1,1′-biphenyl to afford aryl-substituted *p*-benzoquinones **3t** and **3u** as the results of preferable oxidation of the more electron-rich aromatic ring. Such selective oxidation of 1,3-dimethoxyphenyl groups has also been reported by Hirobe in their Ru-porphyrin-catalyzed oxidation reactions.[39] Note that higher yields were observed for all of the substrates compared with those for the parent **2**-catalyzed reactions.[49]

To investigate the role of the amino acid moieties on the catalytic activity of ruthenium complex-bound norvaline **1** compared with the parent complex **2**, various analogues of **1** were prepared and their catalytic activities for the oxidation of 1,3-dimethoxybenzene were compared. The ruthenium complexes **4**–**6** were readily synthesized by a Suzuki–Miyaura cross-coupling reaction between Ru(pydc-Br)(terpy) and the corresponding boranes prepared *in situ*, as in the synthesis of **1**.[27] The molecular structure of **6** was unambiguously determined by single crystal X-ray structure analysis. In this structure, the bond lengths in parent complex **2** are well preserved, as shown in Fig. 2.[50]

As illustrated in Fig. 3, the catalytic activities of **1**, **2**, and **4**–**6** were assessed for the oxidation of 1,3-dimethoxybenzene. Catalyst **1** showed the highest activity and gave **3a** in an optimal yield (96% by GC). Ru(pydc)(terpy) complexes possessing a 4-(*tert*-butoxycarbonyl)aminobutyl group and a 4-(methoxycarbonyl)butyl group (**5** and **6**), which have the partial *N*- and *C*-terminal substituents of **1**, were found less active compared with **1**, but had higher activities (**5**: 74% and **6**: 56% yield after 9 h) than that of the parent complex **2** and *n*-butyl-substituted complex **4** (**2**: 40% and **4**: 31% yield after 9 h). The higher solubility of **4**–**6** in organic solvents compared with that of **2** suggests that phase transfer ability in water/organic biphasic solvent systems would be key to the enhancement of reaction efficiency induced by amino acid moieties (*vide infra*).[25]

The amino acid moieties also influence the selectivity of the catalyst towards the competitive oxidation between multiple substrates remarkably. Fig. 4 shows the reaction profiles for the reactions of an equimolar mixture of 1,3,5-trimethoxybenzene, 1,3-dimethoxybenzene, and anisole catalyzed by **1**, **2**, **5**, and **6**. Interestingly, the **1**-catalyzed reaction predominantly gave 2,6-dimethoxy-*p*-benzoquinone **3c** in 62% yield from 1,3,5-trimethoxybenzene. On the other hand, both **3c** and **3a** were obtained from 1,3,5-trimethoxybenzene and 1,3-dimethoxybenzene, respectively, with the use of catalysts **2** (32% and 32%), **5** (49% and 45%), and **6** (44% and 35%). This reactivity showed the particular effect of the amino acid moiety conjugated with the oxidation catalyst.

Detailed mechanistic studies of the oxidation of 1,3-dimethoxybenzene revealed that **1**-catalyzed oxidation of methoxybenzenes proceeds via two-step oxidation where the first step gives phenol intermediate via single electron transfer (SET) from electron-rich substrate and nucleophilic addition of H_2O, and the second oxidation of phenol intermediate proceeds to afford the corresponding *p*-benzoquinones along with elimination of methanol.

To assess the H_2O addition mechanism of the oxygenation step, ^{18}O-labeling experiments were carried out using $H_2{}^{16}O_2$ (35 wt% in

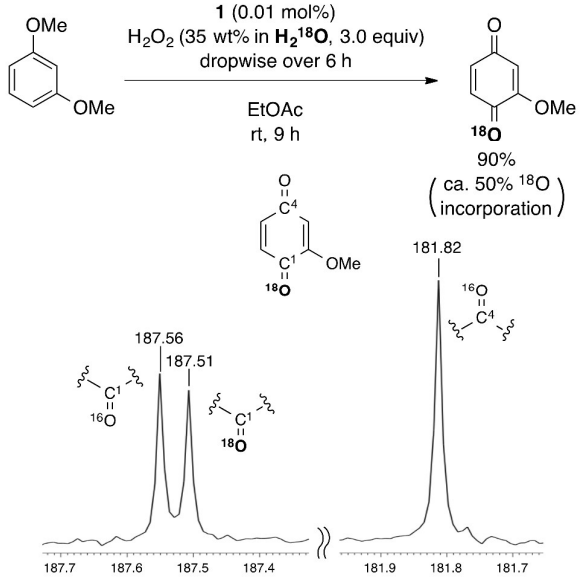
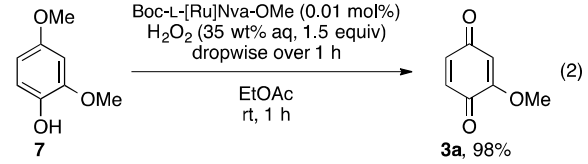


Fig. 5 Isotope labeling experiment with $H_2{}^{16}O_2/H_2{}^{18}O$. The carbonyl region of the ^{13}C NMR spectrum of the product in $CDCl_3$ is shown.

$H_2{}^{18}O$; denoted as $H_2{}^{16}O_2/H_2{}^{18}O$).[51] The catalytic oxidation of 1,3-dimethoxybenzene with $H_2{}^{16}O_2/H_2{}^{18}O$ proceeded smoothly in the presence of a catalytic amount of **1** to give the ^{18}O-labeled 2-methoxy-*p*-benzoquinone as shown in Fig. 5. The formation of a singly ^{18}O-incorporated product was confirmed by GC-MS analysis,[52] in which were detected only [M] and [M+2] ion peaks. Further incorporation of ^{18}O was not observed so that doubly labeled [M+4] ion peak was not detected by the GC-MS analysis. ^{13}C NMR[53] and ^1H–^{13}C HMQC analyses[52] revealed, by comparison with the NMR spectra of the parent compound **3a**, that the incorporation of ^{18}O took place selectively at the C^1-carbonyl of 2-methoxy-*p*-benzoquinone. The observed $^{16}O/^{18}O$ ratio of 50/50 at the C^1 position was in good agreement with the $^{16}O/^{18}O$ ratio in the starting $H_2{}^{16}O_2/H_2{}^{18}O$ solution.[51] This result indicates that nucleophilic addition of H_2O to the aromatic ring is involved in the reaction pathway.

The formation of phenol intermediates was detected in the oxidation of anisole at the early stage (30 min) of the reaction, where the careful GC-MS analysis indicated the formations of 4- and 2-methoxyphenol (ca. 1%). To evaluate the second oxidation step, we conducted the oxidation of 2,4-dimethoxyphenol **7**, which is the expected intermediate of 1,3-dimethoxybenzene oxidation (Eq. 2). Actually, this model reaction of the second step proceeded smoothly under the same reaction conditions to give the corresponding **3a** in 98% yield.

A plausible catalytic cycle based on these experimental results is described in Fig. 6. This reaction can be explained by assuming a Ru(IV)=O species as a reactive intermediate generated by oxidation of the starting Ru(II) complex with H_2O_2.[54] SET from methoxybenzenes to Ru(IV)=O **A** followed by the nucleophilic attack of H_2O to the resulting radical cation **B** affords intermediate **C** in a similar manner to metal salt-induced aromatic substitution.[55] SET from electron-rich arenes has been proposed in the reactions



with high-valent or photo-excited Ru species[56] and also in the oxidation of methoxybenzenes by lignin peroxidase or Fe-porphyrin catalysts with H_2O_2.[57] Proton-coupled electron transfer (PCET) then gives the corresponding *p*-methoxyphenol intermediate **D** and regenerate the Ru(II) species.[58] The second oxidation step proceeds presumably through a phenoxy radical intermediates **E** and **E'** generated by PCET from **D** to **A**. SET from the phenoxy radicals to Ru(III)-OH **F** affords the ionic pair **G** and **H**. Finally, the formation of the corresponding *p*-benzoquinones can proceed via anionic $[Ru(II)–OH]^-$ **H** attacks the carbonyl carbon of **G** with formation of the corresponding hemiketal intermediate followed by spontaneous methanol elimination to give the product *p*-benzoquinones.

It is noteworthy that similar two-step oxidation mechanism for methoxybenzenes was proposed in cytochrome P450 and Ru-porphyrin-catalyzed oxidation. Hirobe and co-workers suggested a mechanism via the generation of corresponding *p*-methoxyphenols, which are readily oxidized to the *p*-benzoquinones along with by-production of methanol via hemiketal intermediate.[39,59,60]

Although the exact role of the amino acid moiety has not yet been clarified, our previous study on the oxidation of alcohols catalyzed by **1**[25] suggests that the formation of micellar aggregates through the self-assembly of **1** in the H_2O–EtOAc biphasic reaction system can account for the observed enhancement of catalytic activity: The aggregates of **1** are capable of facilitating the transportation of H_2O_2 and substrates between the aqueous and organic phases to accelerate the generation of Ru(IV)=O active species **A** and the reaction of **A** with methoxybenzenes. In addition, we consider that the aggregates

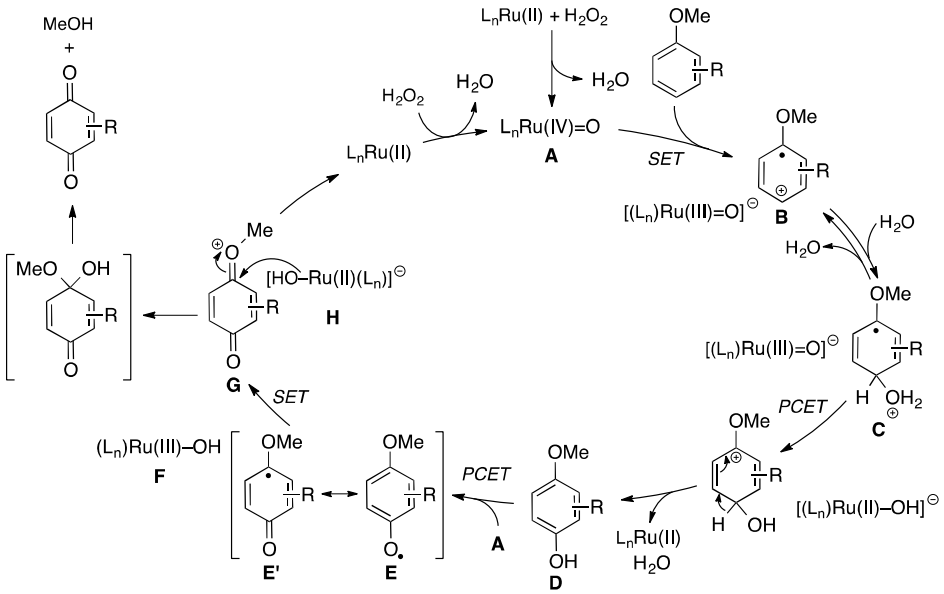


Fig. 6 A plausible mechanism for the oxidation of methoxybenzene.

of **1** stabilizes the catalyst to suppress the undesirable decomposition of ruthenium complex moiety caused by over oxidation in the presence of excess H_2O_2, which is described in the reaction optimization part. Further detailed investigations of the proposed phase-transfer and stabilization mechanism are ongoing based on small angle X-ray and neutron scattering experiments to confirm the formation of the self-assemblies of **1** in the reaction mixture.

Conclusions

We have developed a novel efficient catalytic oxidation of methoxybenzenes using ONO-pincer ruthenium complex-bound norvaline **1** as catalyst with H_2O_2. The use of only 0.01 mol% of catalyst **1** and 3.0 equivalents of H_2O_2 allows the oxidation reaction proceed smoothly at room temperature to give a wide variety of the corresponding *p*-benzoquinones in good to excellent yields. The unique selectivity of this reaction was highlighted by the intramolecular competitive oxidation of various methoxybenzenes, even for the reaction of those bearing reactive functional groups, such as hydroxy and halogen groups. The substantially large enhancement of catalytic activity of **1** compared with the parent complex **2** was achieved for all substrates with unique chemoselectivity in competitive reaction between multiple methoxybenzenes, which has not been observed in the precedented Ru-bound amino acids.[10,18,19,23] These results successfully demonstrate the emergent effect in metalated amino acid induced by the appropriate conjugation of amino acid and organometallic complex. The reaction profiles observed in the **1**-catalyzed oxidation implied the role and effect of amino acid moiety as an mediator of self-assembly of micelle-like aggregates,[25] which act as phase-transfer catalyst with preventing decomposition of the ruthenium complex.

We believe that the observed unique catalytic properties of **1** will contribute to provides a new mild and efficient method for *p*-benzoquinones synthesis, and also contribute for the design of a new class of bio-inspired organometallic catalysts, such as peptide-based artificial metalloenzymes.

Experimental

General. All the reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel equipped with J. Young valve under a positive pressure of high-purity argon (99.999%). Commercially available reagents and solvents for all the reactions were purified by distillation or recrystallization before use. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-ECS400 spectrometer at 392 MHz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL JNM-ECS400 spectrometer at 98.5 MHz or Bruker Avance III 800US Plus NMR system at 800 MHz. The proton chemical shift values are reported in perts per million (ppm, δ scale) downfield from tetramethylsilane (δ 0.00). The chemical shift values for carbon are also reported in perts per million and referenced to the carbon resonance of $CDCl_3$ (δ 77.16). Data are presented as chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet and/or multiplet resonance, br = broad), coupling constant in heltz (Hz), signal area integration in natural numbers, and assignment (*italic*).

General procedure for Ru-catalyzed oxidation of methoxybenzenes (Table 1–4, Fig. 3, and Eq. 2)

The CH_2Cl_2 solution of **1**, **2**, **5**, or **6** (1.0 mM, 0.10 mL, 1.0×10^{-4} mmol) was placed in a 10 mL of Schlenk flask. After removing CH_2Cl_2 in vacuo, the resulting violet powder was dissolved into ethyl acetate (0.300 mL) and followed by the addition of substrate (1.00 mmol) and an internal standard of methyl nonanoate (86.2 mg, 0.500 mmol). To the resulting mixture, an oxidant was added dropwise (solution) or portionwise (powder) over 6 hours at room temperature, unless otherwise noted. After the stirring for several hours, the organic phase of the mixture was extracted with ethyl acetate (4.0 mL) three times and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography or recrystallization.

2-(chloromethyl)-6-methoxy-*p*-benzoquinone (3j). Prepared according to the general procedure using 1-chloromethyl-3,5-dimethoxybenzene (187 mg, 1.00 mmol) as a starting material and H_2O_2 aq (35 wt%, 0.286 mL, 3.0 mmol) as a terminal oxidant for 9 hours. The crude product was purified by silica gel column chromatography in hexane/EtOAc (7/3 in v/v) to afford **3j** (172 mg, 92% yield) as a yellow powder; mp: 102–105 ºC; IR (neat): 3065, 2947, 1676, 1654, 1631, 1603, 1457. 1440, 1409, 1316, 1256, 1231, 1174, 1043, 943, 919, 895, 805, 787, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 392 MHz) δ 6.86 (dt, 2.2 Hz, 1.8 Hz, 1H, -C(CH_2Cl)=C*H*-), 5.96 (d, 2.2 Hz, 1H, -C(OMe)=C*H*-), 4.42 (d, 1.8 Hz, 2H, -C*H*$_2$Cl), 3.85 (s, 3H, -O*Me*); ^{13}C NMR ($CDCl_3$, 98.5 MHz) δ 186.7 –C(OMe)*C*(=O)-), 180.6 (-CH*C*(=O)-), 158.8 (-CH=*C*(OMe)-), 142.1 (-CH=*C*(CH_2Cl)-), 134.7 (-C(CH_2Cl)=*C*H-), 107.9 (-C(OMe)=*C*H-), 56.7 (-O*Me*), 39.1 (-*C*H_2Cl); HRMS (EI) (*m/z*): M^+ calcd for $C_8H_7ClO_3$, 186.0084; found, 186.0085; Anal. calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78; found, C, 51.52; H, 3.83.

2-(bromomethyl)-6-methoxy-*p*-benzoquinone (3k). Prepared according to the general procedure using 1-bromomethyl-3,5-dimethoxybenzene (231 mg, 1.00 mmol) as a starting material and H_2O_2 aq (35 wt%, 0.286 mL, 3.0 mmol) as a terminal oxidant for 9 hours. The crude product was purified by silica gel column chromatography in hexane/EtOAc (7/3 in v/v) to afford **3k** (118 mg, 49% yield) as a yellow powder; mp: 113.5–116.8 ºC; IR (neat): 3066, 1679, 1647, 1628, 1599, 1456, 1436, 1380, 1319, 1234, 1186, 1058, 923, 910, 879, 863, 813, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 392 MHz) δ 6.79 (dt, 2.2 Hz, 1.1 Hz, 1H, -C(CH_2Br)=C*H*-), 5.94 (d, 2.2 Hz, 1H, -C(OMe)=C*H*-), 4.23 (d, 1.1 Hz, 2H, -C*H*$_2$Br), 3.82 (s, 3H, -O*Me*); ^{13}C NMR ($CDCl_3$, 98.5 MHz) δ 186.7 (-C(OMe)*C*(=O)-), 180.6 (-CH*C*(=O)-), 158.8 (-CH=*C*(OMe)-), 142.1 (-CH=*C*Br-), 134.7 (-CBr=*C*H-), 107.9 (-C(OMe)=*C*H-), 56.7 (-O*Me*), 39.1 (-CH_2Br); HRMS (EI) (*m/z*): M^+ calcd for $C_8H_7BrO_3$, 229.9579; found, 229.9576; Anal. calcd for $C_8H_7BrO_3$: C, 41.59; H, 3.05; found, C, 41.73; H, 3.13.

6-(3-hydroxypropyl)-2-methoxy-*p*-benzoquinone (3r). Prepared according to the general procedure using 3-(3,5-dimethoxyphenyl)-1-propanol (196 mg, 1.00 mmol) as a

starting material and H_2O_2 aq (35 wt%, 0.286 mL, 3.0 mmol) as a terminal oxidant for 9 hours. The crude product was purified by recrystallization from EtOAc and hexane to afford **3r** (183 mg, 93% yield) as a yellow solid: mp: 96–98 ºC; IR (neat): 3466, 3070, 2941, 1680, 1648, 1617, 1597, 1444, 1362, 1335, 1323, 1241, 1181, 1060, 1033, 913, 893, 882, 851, 804, 791, 742, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 392 MHz) δ 6.53 (dt, *J* = 2.2, 1.4 Hz, 1H, -C($CH_2CH_2CH_2OH$)=C*H*-, 5.89 (d, *J* = 2.2 Hz, 1H, -C(OMe)=C*H*-), 3.82 (s, 3H, -O*Me*), 3.69 (q, *J* = 5.8 Hz, 2H, -$CH_2CH_2CH_2OH$), 2.56 (td, *J* = 7.6, 1.4 Hz, 2H, -$CH_2CH_2CH_2OH$), 1.79 (tt, *J* = 7.6, 5.8 Hz, 2H, -$CH_2CH_2CH_2OH$) 1.79 (t, *J* = 5.8 Hz, 1H, -O*H*); ^{13}C NMR ($CDCl_3$, 98.5 MHz) δ 187.6 (-C(OMe)*C*(=O)-), 182.3 (-CH*C*(=O)-), 159.0 (-CH=*C*($CH_2CH_2CH_2OH$)-), 147.1 (-CH=*C*(OMe)-), 133.4 (-C($CH_2CH_2CH_2OH$)=*C*H-), 107.3 (-C(OMe)=*C*H-), 61.8 (-$CH_2CH_2CH_2OH$), 56.5 (-O*Me*), 30.9 (-$CH_2CH_2CH_2OH$), 25.4 (-$CH_2CH_2CH_2OH$); HRMS (EI) (*m/z*): M^+ calcd for $C_{10}H_{12}O_4$, 196.0736; found, 196.0740; Anal. calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17; found, C, 61.28; H, 6.20.

***trans*-6-(2-hydroxycyclohexyl)-2-methoxy-*p*-benzoquinone (3s).** Prepared according to the general procedure using *trans*-2-(3,5-dimethoxyphenyl)cyclohexanol (236 mg, 1.00 mmol) as a starting material and H_2O_2 aq (35 wt%, 0.286 mL, 3.0 mmol) as a terminal oxidant for 9 hours. The crude product was purified by recrystallization from EtOAc and hexane to afford **3s** (189 mg, 80% yield) as a yellow crystal; mp: 146–147 ºC; IR (neat): 3537, 3071, 2928, 2861, 1667, 1646, 1626, 1599, 1458, 1447, 1397, 1325, 1274, 1233, 1198, 1181, 1121, 1085, 1071, 1048, 977, 933, 913, 867, 854, 809, 731, 689, 663 cm^{-1}; ^1H NMR ($CDCl_3$, 392 MHz) δ 6.54 (d, *J* = 2.2 Hz, 1H, -C($C_6H_{11}OH$)=C*H*-), 5.89 (d, *J* = 2.2 Hz, 1H, -C(OMe)=C*H*-), 3.82 (s, 3H, -O*Me*), 3.53 (td, *J* = 10, 4.0 Hz, 1H, -C*H*(OH)-), 2.77 (td, *J* = 10, 3.1 Hz, 1H, -CH(OH)C*H*-), 2.15–2.04 (m, 1H, -CH(OH)CH_2-), 1.92–1.70 (m, 3H, -CH(OH)CH_2(CH_2)$_3$-), 1.69–1.52 (br, 1H, -O*H*) 1.46–1.25 (m, 4H, -CH(OH)(CH_2)$_4$-); ^{13}C NMR ($CDCl_3$, 98.5 MHz) δ 187.8 (-C(OMe)*C*(=O)-), 182.4 (-CH*C*(=O)-), 159.1 (-CH=*C*(OMe)-), 149.4 (-CH=*C*($C_6H_{11}OH$)-), 132.6 (-C($C_6H_{11}OH$)=*C*H-), 107.1 (-C(OMe)=*C*H-), 74.2 (-*C*H(OH)-), 56.5 (-O*Me*), 44.3 (-CH(OH)*C*H-), 36.4 (-CH(OH)*C*H_2), 31.5 (-CH(OH)$CH_2CH_2CH_2CH_2$-), 25.6 (-CH(OH)$CH_2CH_2CH_2CH_2$-), 25.0 (-CH(OH)$CH_2CH_2CH_2CH_2$-); HRMS (EI) (*m/z*): M^+ calcd for $C_{13}H_{16}O_4$, 236.1049; found, 236.1050; Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; found, C, 65.82; H, 6.90. Fully assigned ^1H and ^{13}C NMR spectra are shown as Fig. S67 and S68.

6-(3-methoxyphenyl)-2-methoxy-*p*-benzoquinone (3t). Prepared according to the general procedure using 3,3',5-trimethoxy-1,1'-biphenyl (244 mg, 1.00 mmol) as a starting material and H_2O_2 aq (35 wt%, 0.477 mL, 5.0 mmol) as a terminal oxidant for 9 hours. The crude product was purified by silica gel column chromatography in hexane/EtOAc (8/2 in v/v) to afford **3t** (152 mg, 62% yield) as an orange powder; mp: 101–103 ºC; IR (neat): 2942, 1679, 1639, 1626, 1596, 1484, 1438, 1369, 1319, 1307, 1281, 1229, 1206, 1174, 1105, 1094, 1044, 1003, 893, 870, 840, 811, 779, 761, 706, 682 cm^{-1}; ^1H NMR ($CDCl_3$, 392 MHz) δ 7.35 (m, 1H, Ar-*H*), 7.05 (dt, *J* = 7.6, 1.4 Hz, 1H, Ar-*H*), 7.01 (d, *J* = 0.90 Hz, 1H, Ar-*H*), 7.00 (ddd, *J* = 7.6, 2.7, 0.90 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 2.2 Hz, 1H, -CAr=C*H*-), 6.00 (d, *J* = 2.2 Hz, 1H, -C(OMe)=C*H*-), 3.87 (s, 3H, -O*Me*), 3.83 (s, 3H, -O*Me*); ^{13}C NMR ($CDCl_3$, 98.5 MHz) δ 187.3 (-C(OMe)*C*(=O)-), 181.1 (-CHC(=O)-), 159.6 (-*Ar*OMe), 158.9 (-CH=*C*(OMe)-), 144.3 (-CH=*C*Ar-), 133.8 (-CH=C*Ar*-), 133.6 (-CAr=*C*H-), 129.7 (-*Ar*), 121.6 (-*Ar*), 116.0 (-*Ar*), 114.6 (-*Ar*), 107.3 (-C(OMe)=*C*H-), 56.6 (ArO*Me*), 55.5 (-CH=C(O*Me*)-); HRMS (EI) (*m/z*): M^+ calcd for $C_{14}H_{12}O_4$, 244.0736; found, 244.0741; Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95; found, C, 68.57; H, 5.05.

6-(2,5-dimethoxyphenyl)-2-methoxy-*p*-benzoquinone (3u). Prepared according to the general procedure using 2,3',5,5'-tetramethoxy-1,1'-biphenyl (275 mg, 1.00 mmol) as a starting material and H_2O_2 aq (35 wt%, 0.477 mL, 5.0 mmol) as a terminal oxidant for 9 hours. The crude product was purified by silica gel column chromatography in hexane/EtOAc (8/2 in v/v) to afford **3u** (222 mg, 81% yield) as a red powder; mp: 130–132 ºC; IR (neat): 2942, 2841, 1686, 1640, 1622, 1596, 1500, 1455, 1419, 1362, 1327, 1297, 1273, 1229, 1179, 1141, 1091, 1044, 1026, 1009, 924, 894, 880, 825, 810, 728, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 392 MHz) δ 6.95 (dd, *J* = 9.0, 2.7 Hz, 1H, Ar-*H*), 6.90 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.73 (d, *J* = 3.1 Hz, 1H, Ar-*H*), 6.72 (d, *J* = 2.7 Hz, 1H, -CAr=C*H*-), 5.97 (d, *J* = 2.2 Hz, 1H, -C(OMe)=C*H*-), 3.86 (s, 3H, -CH=C(O*Me*)-), 3.78 (s, 3H, -ArO*Me*), 3.83 (s, 3H, -ArO*Me*); ^{13}C NMR ($CDCl_3$, 98.5 MHz) δ 187.6 (-C(OMe)*C*(=O)-), 180.2 (-CH*C*(=O)-), 159.2 (-CH=*C*(OMe)-), 153.6 (-*Ar*OMe), 151.5 (-*Ar*OMe), 144.2 (-CH=*C*Ar-), 135.1 (-CAr=*C*H-), 123.2 (-*Ar*), 116.1 (-*Ar*), 112.7 (-*Ar*), 107.3 (-C(OMe)=*C*H-), 56.5 (-ArO*Me*), 56.5 (-ArO*Me*), 56.0 (-CH=C(O*Me*)-); HRMS (EI) (*m/z*): M^+ calcd for $C_{14}H_{12}O_4$, 244.0736; found, 244.0741; Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95; found, C, 68.57; H, 5.05.

Procedure for Ru-catalyzed oxidation of methoxybenzenes mixture (Fig. 4)

The CH_2Cl_2 solution of complex **1**, **2**, **5**, or **6** (1.0 mM, 0.10 mL, 1.0×10^{-4} mmol) was placed in a 10 mL of Schlenk flask. After removing CH_2Cl_2 in vacuo, the resulting violet powder was suspended into ethyl acetate (0.500 mL) followed by the addition of 1,3,5-trimethoxybenzene (55.4 mg, 0.33 mmol), 1,3-dimethoxybenzene (45.5 mg, 0.33 mmol), anisole (35.6 mg, 0.33 mmol), and an internal standard of methyl nonanoate (86.2 mg, 0.500 mmol). To the resulting mixture, aqueous H_2O_2 (35 wt%, 0.286 mL, 3.00 mmol) was added dropwise over 6 hours at room temperature under argon. For GC analysis of time-course of the reaction, an aliquot of the reaction mixture was taken at certain intervals and analyzed after dissolved into ethyl acetate and filtered with $MgSO_4$ and florisil.

Preparation of H_2O_2 in $H_2{}^{18}O$ (35 wt%)

H_2O_2 (50 wt% aq) was distilled at 70 ºC under the reduced pressure of 9 torr for three times. The distilled H_2O_2 (1.16 g, 88 wt% aq confirmed by ^1H NMR in CD_3CN) was mixed with $H_2{}^{18}O$ (98.7% ^{18}O, 1.74 g) to prepare H_2O_2 in $H_2{}^{18}O$ (35 wt%).

Procedure for oxidation reaction using H_2O_2 in $H_2{}^{18}O$ (Fig. 5)

The CH_2Cl_2 solution of **1** in CH_2Cl_2 (1.0 mM, 0.10 mL, 1.0×10^{-4} mmol) was placed in a 10 mL of Schlenk flask. After

removing CH_2Cl_2 in vacuo, the resulting violet powder was suspended into ethyl acetate (0.300 mL) followed by the addition of 1,3-dimethoxybenzene (138 mg, 1.00 mmol) and an internal standard of methyl nonanoate (86.2 mg, 0.500 mmol). To the resulting mixture, H_2O_2 in $H_2{}^{18}O$ (35 wt%, 0.291 mL, 3.00 mmol) was added dropwise over 6 hours at room temperature under argon. The organic phase of the mixture was extracted with ethyl acetate (4.0 mL) three times and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography.

Further information of detailed procedure for the experiments and the analytical and spectral data of compounds are described in supplementary information.

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