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Cesium Carbonate-Mediated Reaction of Dichloronaphthoquinone Derivatives with O-Nucleophiles

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Summary. A cesium carbonate-mediated reaction of 2,3-dichloronaphthoquinone, 6,7-dichloro-5,8-quinolinedione, and -isoquinolinedione with oxygen nucleophiles has been described.

Keywords. Dichloronaphthoquinone; Nucleophilic substitution; Oxygen nucleophile; Cesium carbonate; Alkoxynaphthoquinone.

Introduction

The naphthoquinone skeleton is found in many natural products and has been employed as a synthesis intermediate for the preparation of numerous heterocyclic compounds with interesting biological properties, such as antitumor, antibacterial, antifungal, and anti-inflammatory agents [1, 2]. The quinoline alkaloids, such as streptonigrin, streptonigron, and lavendamycin, possess extraordinary cytotoxic activities, and the quinolinedione moiety is responsible for the antitumor activity because of its ability to degrade *DNA* [3–5]. This structural pattern is also observed in quinone antibiotics including mitomycin C, actinomycin, and rifamycin, a class of inhibitors of *DNA*-transcribing enzymes [6]. Thus, extensive studies on the nucleophilic substitution of quinones including naphthoquinone, quinolinequinone, and quinazolinequinone with aniline nucleophiles and their promising cytotoxic activities against human cancer cells have been described [7–11].

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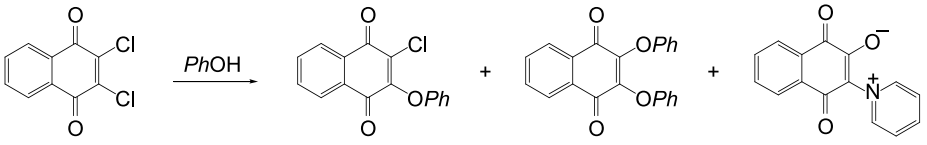
On the other hand, the reaction of naphthoquinones with alcohol derivatives has not found much attention in literature. Examples mainly include the synthesis of 3-alkoxy-1,4-naphthoquinones by treatment of 2,3-dichloronaphthoquinone with various alkoxides [12–15]. However, this approach is hampered by the poor yields and low chemoselectivity depending on the reaction parameters, such as reagents and reaction conditions. Notwithstanding the importance of this system, existing methods for the synthesis of alkoxynaphthoquinones are limited in their scope and generality. Thus, there is a need for the development of more flexible strategies that will accommodate a range of structural diversity. Here, we wish to report a cesium carbonate-mediated reaction of 2,3-dichloronaphthoquinone (**1**), 6,7-dichloro-5,8-quinolinedione (**5**), and -isoquinolinedione (**8**) with various oxygen nucleophiles.

Results and Discussion

Initially, we undertook mono-substitution of 2,3-dichloronaphthoquinone (**1**) with phenol under various conditions, as shown in Table 1. An attempted reaction in refluxing *Et*OH showed no conversion. Whereas K_2CO_3 and pyridine gave mainly the Zwitterion **4**, at elevated temperature it accelerated the displacement of both chlorines resulting in the formation of 2,3-dialkoxynaphthoquinone **3** [1, 16]. Even though $CeCl_3 \cdot 7H_2O$ was successfully employed in the amine displacement with various dihalo-

Table 1. Base-promoted substitution of 2,3-dichloronaphthoquinone (**1**) with phenol



1 **2a** **3** **4**

Entry	Conditions	Yield of **2a** (**3**, **4**)/%
1	*Et*OH, reflux, 32 h	NR
2	$CeCl_3 \cdot 7H_2O$, *Et*OH, rt, 48 h	NR
3	K_2CO_3, pyridine, rt, 2 h	24 (6, 48)
4	Et_3N, *THF*, rt, 76 h	66
5	Cs_2CO_3, *THF*, rt, 76 h	93

naphthoquinones [10, 11], in this case, surprisingly, it did not react at all. After examining a number of bases, we found the mono-substitution was greatly increased by adding Cs_2CO_3 in *THF* at room temperature, and thus we obtained 2-chloro-3-phenoxy-1,4-naphthoquinone (**2a**) in 92% yield without any side-product. With this promising result, we studied mono-substitution reactions of **1** under mediation of Cs_2CO_3 with various alcoholic substrates to secure synthesis of alkoxynaphthoquinone derivatives with structural diversity.

The Cs-mediated substitution was successfully applicable to the synthesis of 3-phenoxynaphthoquinone derivatives from **1** with an array of phenolic nucleophiles (Table 2, entries 2–11) in the presence of Cs_2CO_3 at ambient temperature. The substitution uniformly provided 3-phenoxynaphthoquinone derivatives **2b**–**2k** in good to excellent yield. We could extend this method to the readily available benzyl (entry 12) and aliphatic alcohols (entries 13–16), without any problem. The reaction gener-

Table 2. Synthesis of 3-alkoxynaphthoquinone derivatives

Entry	*R*OH	Time/h	**2** (yield/%)
1	*Ph*OH	76	**2a** (93)
2	2-O*Me*-*Ph*OH	20	**2b** (95)
3	3-O*Me*-*Ph*OH	20	**2c** (98)
4	4-O*Me*-*Ph*OH	76	**2d** (92)
5	4-O*Et*-*Ph*OH	96	**2e** (73)
6	4-*Me*-*Ph*OH	76	**2f** (95)
7	4-*Et*-*Ph*OH	96	**2g** (88)
8	4-NO_2-*Ph*OH	72	**2h** (84)
9	2,3-(O*Me*)$_2$-*Ph*OH	72	**2i** (95)
10	3,5-(O*Me*)$_2$-*Ph*OH	48	**2j** (86)
11	2-NO_2-4-O*Me*-*Ph*OH	96	**2k** (67)
12	*Ph*CH_2OH	180	**2l** (65)
13	*Me*$(CH_2)_3$OH	180	**2m** (34)
14	*Et*$_2$N$(CH_2)_2$OH	180	**2n** (43)
15	1-(2-Hydroxyethyl)piperidine	180	**2o** (62)
16	4-(2-Hydroxyethyl)morpholine	180	**2p** (52)

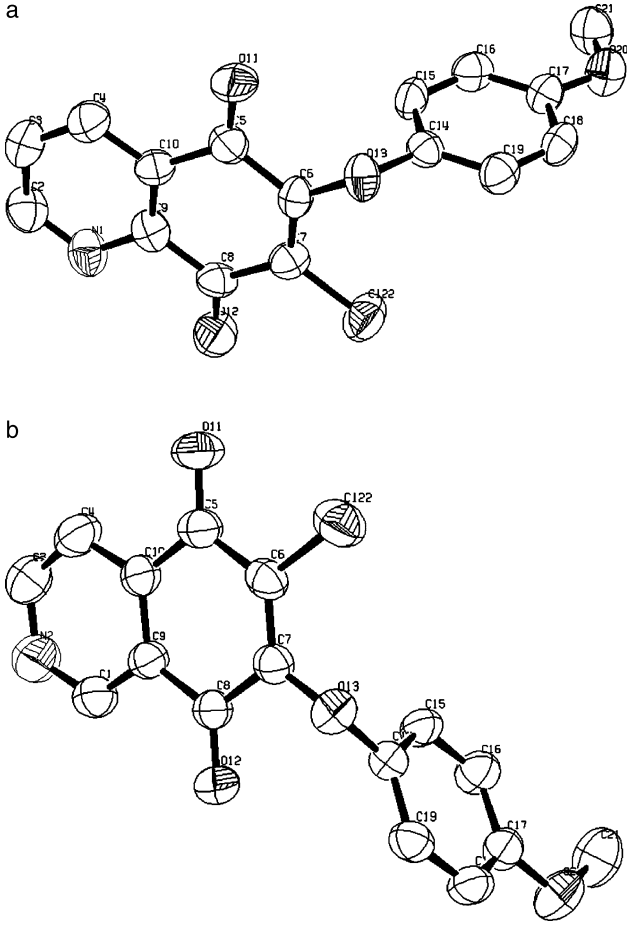


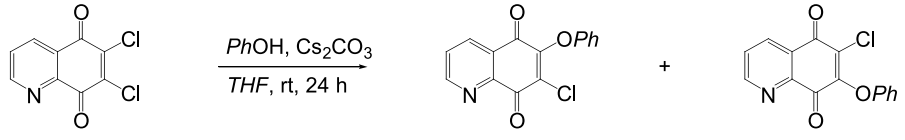
Fig. 1. Crystal structures of a) 6-(4-methoxyphenyloxy)-7-chloroquinolinedione (**6b**) and b) 6-chloro-7-(4-methoxyphenyloxy)isoquinolinedione (**10c**)

ally allowed the introduction of a wide range of hydroxyl group-containing nucleophiles, and the results are summarized in Table 2. However, carboxyl group-containing nucleophiles, such as acetic and benzoic acid did not react at all.

The substitution works very effectively for the mono-alkoxylation of naphthoquinone. So far, we examined its applicability to similarly related structures, quinolinedione and isoquinolinedione, with oxygen nucleophiles. Reaction of 6,7-dichloro-5,8-quinolinedione (**5**) with 4-methoxyphenol gave two regioisomeric products at the 1:1 molar ratio, which, in turn, were very difficult to isolate by conventional separation. To confirm the regiochemistry of the products, we tried to prepare a single crystal for X-ray crystallography. Fortunately, we were able to obtain a crystal of one isomer, and the X-ray crystal diffraction analysis proved its constitution as 6-(4-methoxyphenyloxy)-7-chloroquinolinedione (**6b**), as depicted in Fig. 1a.

Based on the crystal data, these two isomers could be distinguished by means of chemical shifts of the ^{1}H NMR spectra in $CDCl_3$. Although C2-H and C3-H protons rather centers at $\delta = 9.09$–9.04 and 7.73–7.71 ppm regardless of the regioisomers, the differences between the chemical shifts of C4-H protons showed distinctive values as shown in Table 3. The spectrum of the isomeric mixtures displayed two sets of peaks around $\delta = 8.53$–8.52 and 8.39–8.37 ppm, attributed to the C4-H for each isomer. The spectral data of these isomers showed that the C4-H chemical shifts of the C7-quinolinediones **7** were considerably

Table 3. Reaction of 6,7-dichloro-5,8-quinolinedione (**5**) with phenols

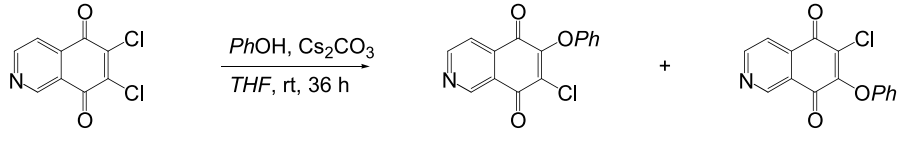


5 **6** **7**

Entry	*Ph*OH	$\delta_{C4\text{-}H}$/ppm[a]		Yield/%[b,c]
		6	**7**	
1	4-*Et*-*Ph*OH (**a**)	8.39	8.53	87
2	4-O*Me*-*Ph*OH (**b**)	8.37	8.53	86
3	4-O*Et*-*Ph*OH (**c**)	8.38	8.52	87

[a] ^{1}H NMR recorded in $CDCl_3$; [b] combined yield of the regioisomers **6** and **7** at 1:1 molar ratio; [c] trace of disubstituted quinolinedione was observed

Table 4. Reaction of 6,7-dichloro-5,8-isoquinolinedione (**8**) with phenols



8 **9** **10**

Entry	*Ph*OH	$\delta_{C1\text{-}H}$/ppm[a]		$\delta_{C4\text{-}H}$/ppm[a]		Yield/%[b,c]
		9	**10**	**9**	**10**	
1	3-*Me*-*Ph*OH (**a**)	9.46	9.29	7.84	8.00	80
2	4-*Et*-*Ph*OH (**b**)	9.46	9.26	7.83	7.99	86
3	4-O*Me*-*Ph*OH (**c**)	9.47	9.29	7.83	8.00	85
4	4-O*Et*-*Ph*OH (**d**)	9.45	9.28	7.82	9.99	81

[a] ^{1}H NMR recorded in $CDCl_3$; [b] combined yield of the regioisomers **9** and **10** at ~1:5 molar ratio; [c] in each case $\leq$10% of disubstituted isoquinolinedione **11** was isolated

moved downfield with respect to those of the C6-isomers **6**. This phenomenon agreed nicely with the previous results observed in amine cases [8].

Analogously, reaction of 6,7-dichloro-5,8-isoquinolinedione (**8**) with 4-methoxyphenol (entry 3, Table 4) gave two regioisomers at a ratio of 1:5 (^{1}H NMR). The X-ray crystal diffraction analysis of the major isomer proved the 6-chloro-7-(4-methoxyphenyloxy)isoquinolinedione (**10c**) as depicted in Fig. 1b. One possible explanation for the preference of the C7-substitution (such as **10**) is that the C5-carbonyl group, which is *para* to the nitrogen, is more electronegative than the C8-carbonyl in resonance structures, in terms of charge separation. Thus, 1,4-addition might be expected to be dominated by the C5-carbonyl group [7]. The chemical shifts of C1-H and C4-H protons are greatly affected by the regioselectivity between C6- and C7-substitution patterns. Although C2-H proton rather centers at $\delta = 9.12$–9.10 ppm regardless of the regioisomers, the differences between the chemical shifts of C2-H and C4-H protons showed distinctive values as shown in Table 4. The spectral data of these isomers showed that the C4-H chemical shifts of the C7-quinolinediones **10** were considerably moved downfield with respect to those of the C6-isomers **9**, whereas the C1-H chemical shifts of the C7-quinolinediones moved upfield. Such phenomena are very consistent, and could be useful criteria for assigning regioselectivity of similarly related structures.

In conclusion we developed a method that provides an efficient synthesis of alkoxynaphthoquinone derivatives with structural diversity. Central to this strategy is the application of Cs_2CO_3-mediated substitution of 2,3-dichloronaphthoquinone, 6,7-dichloroquinolinedione, and 6,7-dichloroisoquinolinedione with oxygen nucleophiles. The reaction is shown to be quite general for a wide array of aryl and aliphatic alcohols. It is noteworthy that the chemical shifts of phenyl protons are greatly affected by the substitution patterns in quinolinedione and isoquinolinedione.

Experimental

6,7-Dichloro-5,8-quinolinedione (**5**) and -isoquinolinedione (**8**) were prepared according to Refs. [7, 17]. Other chemicals were purchased from Aldrich and used without further purification. Melting points were measured on a Barnstead Electrothermal IA9100 apparatus. Mass spectra were recorded on a Varian 1200 GC/MS operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance 300 ultrashield at 300.12 and 75.03 MHz. The data for X-ray structure determination was collected on graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å) equipped with a Bruker SMART Apex II X-ray diffractometer.

Typical Procedure as Exemplified for the Synthesis of 2-Chloro-3-(4-methoxyphenoxy)-1,4-naphthoquinone (**2d**, $C_{17}H_{11}ClO_4$)
To a solution of 227 mg **1** (1 mmol) and 149 mg 4-methoxyphenol (1.2 mmol) in 10 cm^3 *THF* was added 325 mg Cs_2CO_3 (1 mmol). The reaction mixture was stirred for 76 h at room temperature. The mixture was partitioned with H_2O and ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue. This residue was purified by column chromatography on silica gel (*n*-hexane/*Et*O*Ac* = 9/1) to afford 289 mg (92%) **2d**. Mp 113°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (dd, 1H, $J = 9.0$, 2.2 Hz), 8.03 (dd, 1H, $J = 9.0$, 2.3 Hz), 7.79–7.75 (m, 2H), 6.97 (d, 2H, $J = 6.0$ Hz), 6.85 (d, 2H, $J = 6.0$ Hz), 3.79 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 178.9$, 178.6, 156.5, 154.3, 150.8, 134.9, 134.7, 133.4, 131.6, 131.1, 127.7, 127.5, 118.3, 115.1, 56.0 ppm; EIMS (70 eV): m/z (%) = 316 (M^+, 10), 314 (M^+, 28), 251 (13), 191 (13), 163 (24), 135 (26), 123 (12), 99 (31), 76 (58), 63 (100), 50 (100).

2-Chloro-3-phenoxy-1,4-naphthoquinone (**2a**, $C_{16}H_9ClO_3$)
Mp 138–139°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.22$ (dd, 1H, $J = 9.0$, 2.1 Hz), 8.06 (dd, 1H, $J = 9.0$, 2.1 Hz), 7.80–7.76 (m, 2H), 7.34 (t, 2H, $J = 7.8$ Hz), 7.16 (d, 1H, $J = 7.5$ Hz), 7.02 (d, 2H, $J = 8.1$ Hz) ppm; EIMS: m/z (%) = 286 (M^+, 22), 284 (M^+, 65), 249 (52), 221 (40), 165 (44), 123 (29), 77 (97), 51 (100).

2-Chloro-3-(2-methoxyphenoxy)-1,4-naphthoquinone (**2b**, $C_{17}H_{11}ClO_4$)
Mp 145–146°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (dd, 1H, $J = 9.0$, 1.8 Hz), 8.02 (dd, 1H, $J = 8.7$, 1.8 Hz), 7.77–7.73 (m, 2H), 7.11 (t, 2H, $J = 6.9$ Hz), 6.95 (t, 2H, $J = 7.2$ Hz), 3.75 (s, 3H) ppm; EIMS: m/z (%) = 316 (M^+, 24), 314 (M^+, 100), 279 (39), 261 (31), 206 (40), 163 (54), 135 (100), 121 (96), 99 (89), 77 (81).

2-Chloro-3-(3-methoxyphenoxy)-1,4-naphthoquinone (**2c**, $C_{17}H_{11}ClO_4$)
Mp 91–92°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.22$ (dd, 1H, $J = 9.0$, 2.4 Hz), 8.06 (dd, 1H, $J = 9.0$, 2.4 Hz), 7.80–7.76 (m, 2H), 7.21 (t, 1H, $J = 8.4$ Hz), 6.70–6.41 (m, 3H), 3.80 (s, 3H) ppm; EIMS: m/z (%) = 316 (M^+, 34), 314 (M^+, 65), 279 (87), 251 (68), 223 (43), 152 (26), 123 (36), 92 (66), 77 (92), 63 (100), 50 (53).

2-Chloro-3-(4-ethoxyphenoxy)-1,4-naphthoquinone (**2e**, $C_{18}H_{13}ClO_4$)
Mp 145–146°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (dd, 1H, $J = 9.0$, 2.1 Hz), 8.04 (dd, 1H, $J = 9.0$, 2.4 Hz), 7.79–7.75 (m, 2H), 6.96 (d, 2H, $J = 6.6$ Hz), 6.84 (d, 2H, $J = 6.9$ Hz), 4.00 (q, 2H, $J = 6.9$ Hz), 1.40 (t, 3H, $J = 6.9$ Hz) ppm; EIMS: m/z (%) = 328 (M^+, 66), 299 (31), 264 (30), 236 (28), 190 (29), 162 (46), 135 (51), 99 (100), 75 (92), 64 (88).

2-Chloro-3-(p-tolyloxy)-1,4-naphthoquinone (**2f**, $C_{17}H_{11}ClO_3$)
Mp 146–147°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (dd, 1H, $J = 9.0$, 2.1 Hz), 8.04 (dd, 1H, $J = 9.0$, 2.4 Hz), 7.79–7.75 (m, 2H), 7.13 (d, 2H, $J = 8.4$ Hz), 6.91 (d, 2H, $J = 8.4$ Hz), 2.33 (s, 3H) ppm; EIMS: m/z (%) = 300 (M^+, 37), 298 (M^+, 100), 263 (85), 235 (22), 207 (64), 179 (54), 163 (29), 135 (58), 123 (58), 99 (67), 91 (73), 65 (92).

2-Chloro-3-(4-ethylphenoxy)-1,4-naphthoquinone
(**2g**, $C_{18}H_{13}ClO_3$)
Mp 121–122°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.22$ (dd, 1H, $J = 9.0$, 2.1 Hz), 8.05 (dd, 1H, $J = 9.0$, 2.4 Hz), 7.80–7.76 (m, 2H), 7.15 (d, 2H, $J = 8.4$ Hz), 6.93 (d, 2H, $J = 6.9$ Hz), 2.63 (q, 2H, $J = 7.5$ Hz), 1.23 (t, 3H, $J = 7.5$ Hz) ppm; EIMS: m/z (%) = 314 (M^+, 29), 312 (M^+, 77), 297 (100), 277 (29), 191 (34), 163 (61), 135 (38), 99 (74), 77 (99), 51 (35).

2-Chloro-3-(4-nitrophenoxy)-1,4-naphthoquinone
(**2h**, $C_{16}H_8ClNO_5$)
Mp 181–182°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.28$–8.25 (m, 3H), 8.02 (dd, 1H, $J = 9.0$, 2.7 Hz), 7.87–7.79 (m, 2H), 7.11 (d, 2H, $J = 9.0$ Hz) ppm; EIMS: m/z (%) = 331 (M^+, 25), 329 (M^+, 51), 301 (20), 220 (26), 191 (18), 163 (53), 135 (30), 99 (51), 76 (100), 63 (41), 50 (65).

2-Chloro-3-(2,3-dimethoxyphenoxy)-1,4-naphthoquinone
(**2i**, $C_{18}H_{13}ClO_5$)
Mp 123–125°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.19$ (dd, 1H, $J = 8.4$, 1.5 Hz), 8.02 (dd, 1H, $J = 8.4$, 1.5 Hz), 7.79–7.72 (m, 2H), 7.06 (t, 1H, $J = 8.4$ Hz), 6.81 (d, 1H, $J = 8.4$ Hz), 6.74 (d, 1H, $J = 8.4$ Hz), 3.87 (s, 3H), 3.72 (s, 3H) ppm; EIMS: m/z (%) = 346 (M^+, 18), 344 (M^+, 83), 329 (19), 313 (21), 251 (10), 206 (12), 163 (33), 135 (48), 99 (53), 95 (75), 76 (40), 51 (100).

2-Chloro-3-(3,5-dimethoxyphenoxy)-1,4-naphthoquinone
(**2j**, $C_{18}H_{13}ClO_5$)
Mp 118–119°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (dd, 1H, $J = 9.0$, 2.4 Hz), 8.07 (dd, 1H, $J = 9.0$, 2.4 Hz), 7.83–7.74 (m, 2H), 6.24–6.01 (m, 3H), 3.76 (s, 3H), 3.75 (s, 3H) ppm; EIMS: m/z (%) = 346 (M^+, 14), 344 (M^+, 43), 309 (100), 294 (85), 265 (16), 172 (25), 133 (51), 99 (51), 63 (62).

2-Chloro-3-(4-methoxy-2-nitrophenoxy)-1,4-naphthoquinone
(**2k**, $C_{17}H_{10}ClNO_6$)
Mp 123–124°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (dd, 1H, $J = 8.7$, 1.5 Hz), 7.98 (dd, 1H, $J = 8.9$, 1.7 Hz), 7.80–7.74 (m, 2H), 7.60 (d, 1H, $J = 2.9$ Hz), 7.13–7.07 (m, 2H), 3.89 (s, 3H) ppm; EIMS: m/z (%) = 359 (M^+, 2), 313 (40), 235 (3), 163 (27), 151 (38), 135 (59), 123 (97), 99 (48), 75 (82), 63 (100), 51 (82).

2-Benzyloxy-3-chloro-1,4-naphthoquinone (**2l**, $C_{17}H_{11}ClO_3$)
Mp 78–80°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$–8.07 (m, 2H), 7.74 (dd, 2H, $J = 9.0$, 3.0 Hz), 7.43 (d, 2H, $J = 7.5$ Hz), 7.38–7.35 (m, 3H), 5.65 (s, 2H) ppm; EIMS: m/z (%) = 300 (M^+, 15), 298 (M^+, 58), 263 (13), 181 (10), 123 (15), 91 (88).

2-Butoxy-3-chloro-1,4-naphthoquinone (**2m**, $C_{14}H_{13}ClO_3$)
A semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$ (dd, 1H, $J = 9.0$, 2.7 Hz), 8.08 (dd, 1H, $J = 9.0$, 2.4 Hz), 4.57 (t, 2H, $J = 6.3$ Hz), 1.79 (quintet, 2H, $J = 6.6$ Hz), 1.52 (sextet, 2H, $J = 7.5$ Hz), 0.98 (t, 3H, $J = 7.5$ Hz) ppm; EIMS: m/z (%) = 266 (M^+, 16), 264 (M^+, 40), 221 (10), 208 (100), 180 (98), 173 (24), 123 (44).

2-Chloro-3-(2-diethylaminoethoxy)-1,4-naphthoquinone
(**2n**, $C_{16}H_{18}ClNO_3$)
A semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.14$ (dd, 1H, $J = 9.0$, 2.7 Hz), 8.09–8.03 (m, 1H), 7.73–7.70 (m, 2H), 4.80 (t, 2H, $J = 4.8$ Hz), 2.90 (t, 2H, $J = 4.8$ Hz), 2.58 (q, 4H, $J = 6.9$ Hz), 0.87 (t, 6H, $J = 6.9$ Hz) ppm; EIMS: m/z (%) = 310 (M^+, 1), 308 (M^+, 3), 250 (3), 149 (22), 111 (26), 97 (39), 83 (43), 71 (53), 57 (100).

2-Chloro-3-(2-piperidin-1-ylethoxy)-1,4-naphthoquinone
(**2o**, $C_{17}H_{18}ClNO_3$)
A semi-solid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$ (dd, 1H, $J = 9.0$, 2.1 Hz), 8.02 (dd, 1H, $J = 9.0$, 2.1 Hz), 4.71 (t, 2H, $J = 4.8$ Hz), 2.61 (t, 2H, $J = 4.8$ Hz), 2.30 (br s, 4H), 2.01 (s, 4H), 0.88–0.76 (m, 2H) ppm; EIMS: m/z (%) = 321 (M^+, 38), 319 (M^+, 100), 279 (43), 167 (9), 149 (11), 98 (32).

2-Chloro-3-(2-morpholin-4-ylethoxy)-1,4-naphthoquinone
(**2p**, $C_{16}H_{16}ClNO_4$)
Mp 104–105°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$ (dd, 1H, $J = 8.9$, 2.4 Hz), 8.09 (dd, 1H, $J = 8.9$, 2.3 Hz), 7.77–7.73 (m, 2H), 4.77 (t, 2H, $J = 4.6$ Hz), 3.26 (t, 4H, $J = 4.1$ Hz), 2.69 (t, 2H, $J = 4.6$ Hz), 2.39 (t, 4H, $J = 4.5$ Hz) ppm; EIMS: m/z (%) = 323 (M^+, 9), 321 (M^+, 37), 208 (3), 163 (3), 113 (6), 100 (100), 56 (12).

Typical Procedure as Exemplified for the Synthesis of 7-Chloro-6-(4-methoxyphenoxy)-5,8-quinolinedione (**6b**, $C_{16}H_{10}ClNO_4$) *and 6-Chloro-7-(4-methoxyphenoxy)-5,8-quinolinedione*
(**7b**, $C_{16}H_{10}ClNO_4$)
To a solution of 100 mg **5** (0.44 mmol) and 60 mg 4-methoxyphenol (0.48 mmol) in 5 cm^3 *THF* was added 143 mg Cs_2CO_3 (0.44 mmol) at room temperature. The reaction mixture was stirred for 24 h. The mixture was partitioned with H_2O and ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. This residue was purified by column chromatography on silica gel (*n*-hexane/*EtOAc* = 3/1) to afford 119 mg (86%) of two regioisomeric products (**6b** and **7b**). Each analytical sample was obtained by repeated column chromatography and then recrystallization (*n*-hexane-CH_2Cl_2) of the enriched isomer, respectively.

6b: Mp 181°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.07$ (dd, 1H, $J = 4.8$, 1.5 Hz), 8.37 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.72 (dd, 1H, $J = 7.8$, 4.8 Hz), 6.98 (d, 2H, $J = 10.2$ Hz), 6.85 (d, 2H, $J = 10.2$ Hz), 3.79 (s, 3H) ppm; EIMS: m/z (%) = 317 (M^+, 18), 315 (M^+, 46), 192 (12), 164 (18), 136 (66), 100 (61), 92 (47), 77 (79), 63 (100), 50 (74).

7b: Mp 170°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.04$ (dd, 1H, $J = 4.8$, 1.5 Hz), 8.53 (dd, 1H, $J = 7.8$, 1.5 Hz),

7.73 (dd, 1H, $J = 7.8$, 4.8 Hz), 6.98 (d, 2H, $J = 10.5$ Hz), 6.84 (d, 2H, $J = 10.5$ Hz), 3.78 (s, 3H) ppm; EIMS: m/z (%) = 317 (M^+, 14), 315 (M^+, 60), 280 (16), 136 (63), 100 (73), 77 (66), 64 (100), 50 (65).

Crystallographic Data for ***6b***

Empirical formula, $C_{16}H_{10}ClNO_4$; formula weight, 315.70; crystal system, orthorhombic; space group, $P2(1)2(1)2(1)$; unit cell dimensions, $a = 5.1790(4)$ Å, $b = 8.1796(7)$ Å, $c = 32.047(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; volume, 1357.56(19) $Å^3$; density (calculated), 1.545 Mg/m^3; reflections collected, 8026; final R indices [$I > 2\sigma(I)$], $R1 = 0.0653$, $wR2 = 0.1394$; R indices (all data), $R1 = 0.1667$, $wR2 = 0.1809$. Atomic coordinates and crystallographic parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 639461). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Typical Procedure as Exemplified for the Synthesis of 6-Chloro-7-(4-methoxyphenoxy)-5,8-isoquinolinedione (**10c**, $C_{16}H_{10}ClNO_4$) *and 6,7-Bis(4-methoxyphenoxy)-5,8-isoquinolinedione* (**11c**, $C_{23}H_{17}NO_6$)

To a solution of 23 mg **8** (0.1 mmol) and 14 mg 4-methoxyphenol (0.11 mmol) in 1 cm^3 *THF* was added 33 mg Cs_2CO_3 (0.1 mmol) at room temperature. The reaction mixture was stirred for 36 h. The mixture was partitioned with H_2O and ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the residue. The residue was purified by column chromatography on silica gel (*n*-hexane/*EtOAc* = 9/1) to afford 27 mg (85%) of two regioisomeric products (**9c** and **10c**) and 4 mg (10%) **11c**. An analytical sample of the major isomer **10c** was obtained by repeated column chromatography followed by recrystallization (*n*-hexane-CH_2Cl_2).

10c: Mp 132°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.29$ (s, 1H), 9.11 (d, 1H, $J = 5.1$ Hz), 8.00 (d, 1H, $J = 5.1$ Hz), 6.98 (d, 2H, $J = 9.0$ Hz), 6.87 (d, 2H, J = 9.0 Hz), 3.80 (s, 3H) ppm; EIMS: m/z (%) = 317 (M^+, 40), 315 (M^+, 61), 44 (37), 43 (37), 40 (100).

11c: Mp 114°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.34$ (s, 1H), 9.08 (d, 1H, $J = 5.0$ Hz), 7.89 (d, 1H, $J = 5.0$ Hz), 6.86–6.74 (m, 8H), 3.75 (s, 6H) ppm; EIMS: m/z (%) = 403 (M^+, 100), 375 (5), 252 (8), 240 (8), 196 (5), 169 (6), 135 (38), 123 (24), 92 (30), 40 (41).

Crystallographic Data for ***10c***

Empirical formula, $C_{16}H_{10}ClNO_4$; formula weight, 315.70; crystal system, monoclinic; space group, $P2(1)/c$; unit cell dimensions, $a = 5.3200(2)$ Å, $b = 19.5179(7)$ Å, $c = 13.6253(4)$ Å, $\alpha = 90°$, $\beta = 99.946(2)°$, $\gamma = 90°$; volume, 1393.52(8) $Å^3$; density (calculated), 1.505 Mg/m^3; reflections collected, 13993; final R indices [$I > 2\sigma(I)$], $R1 = 0.0505$, $wR2 = 0.1027$; R indices (all data), $R1 = 0.1382$, $wR2 = 0.1351$. Atomic coordinates and crystallographic parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 639462). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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