Synthesis A. Hamsath et al. Special Topic

Quinone C–H Alkylations via Oxidative Radical Processes

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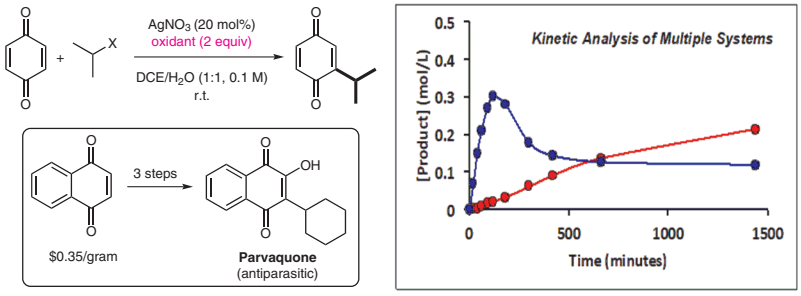

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Abstract A brief survey of radical additions to quinones is reported. Carboxylic acids, aldehydes, and unprotected amino acids are compared as alkyl radical precursors for the mono- or bis- C–H alkylation of several quinones. Two methods for radical initiation are discussed comparing inorganic persulfates and Selectfluor as stoichiometric oxidants. Kinetic analysis reveals dramatic differences in the rate of radical initiation depending on the identity of the radical precursor and oxidant. Synthetic strategies for efficiently producing alkyl-quinones are discussed in the context of selecting optimum radical precursors and initiators depending on quinone identity and functional groups present.

Key words quinones, radicals, alkylation, Selectfluor, kinetics

Quinones are versatile reagents that have been used as oxidants, synthetic intermediates, and chemotherapeutics.[1] Because of their highly reducing nature, quinones have shown notable activity in the context of enzymatic electron transfers, affecting the levels of reactive oxygen species and oxidative stress in biological tissues.[2] As shown in Figure 1, a variety of quinone structures display useful biological activity.[3] Remarkably, even very simple alkyl-quinones such as thymoquinone display an impressive range of biological activity, including anticancer properties.[4] Studies have shown that subtle changes to the quinone structure greatly affect therapeutic efficacy, and so synthetic methods for the assembly of diverse quinone libraries would be useful for assessing structure–activity relationships.[5] Traditional methods for quinone functionalization have relied on transition-metal catalysis, although recent advances in free-radical chemistry have provided attractive alternatives.[6] Boronic acids and esters have been popular as bench-stable radical precursors for quinone arylation, although alkylation is also possible from organoboron reagents and carboxylic acids.[7] More recently, 1,4-dihydropyridines have been utilized as aldehyde equivalents for photocatalyzed quinone alkylation, further establishing radical C–H functionalization as a robust alternative to precious-metal catalysis.[8]

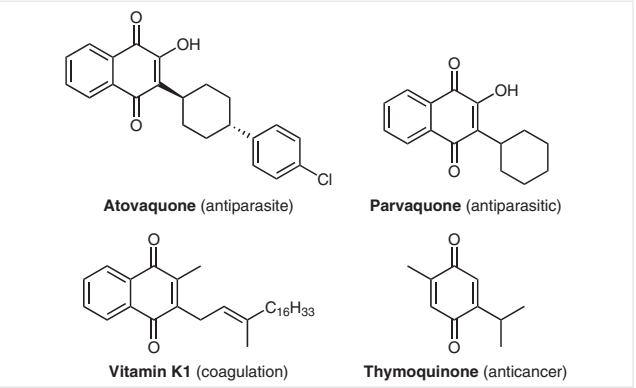


Figure 1 Biologically active alkyl-quinones

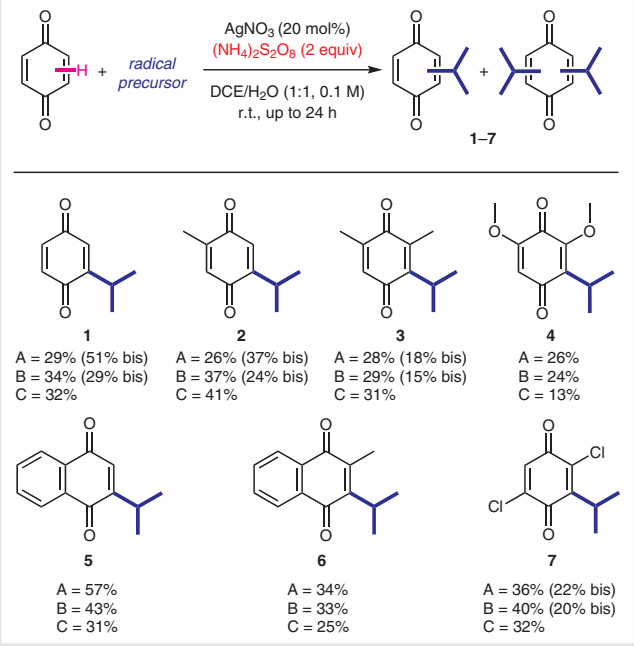
Our lab has been interested in free-radical chain processes using simple and inexpensive radical precursors under mild reaction conditions. Our initial entry into radical C–H alkylation involved Ag(I)-catalyzed Strecker degradation of unprotected amino acids to produce nucleophilic radicals.[9] Although this method was suitable to functionalize a variety of electron-deficient heteroarenes, our method required elevated temperatures and strongly oxidizing conditions, limiting functional group compatibility. Through our subsequent work on radical fluorination, we discovered that Selectfluor was a suitable oxidant to promote Ag(I)-catalyzed decarboxylation for heteroarene or quinone C–H alkylation under mild conditions.[10] Through the development of this method, we noted significant differences in reactivity comparing Selectfluor and inorganic persulfates as oxidants, most notably in the rate of radical initiation. We

became interested in exploring how this rate difference affects the efficiency of C–H alkylation of quinones depending on the identity of the oxidant, the radical precursor, and the quinone.

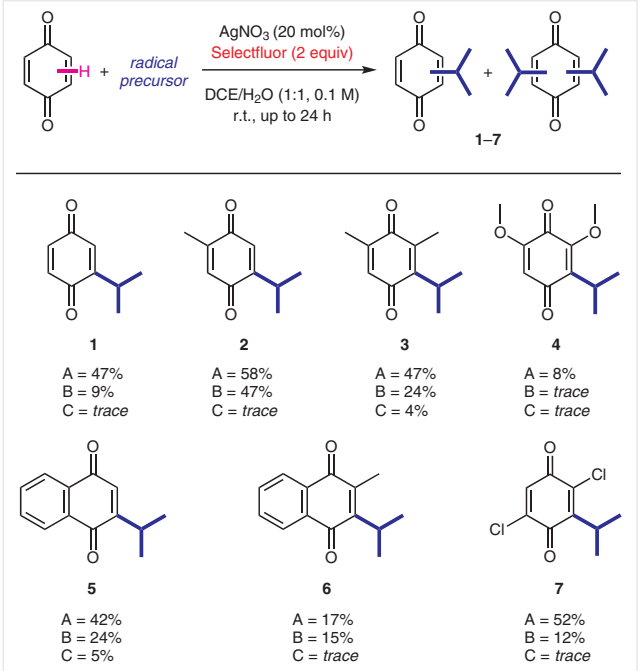
Our initial efforts focused on comparing several simple, and widely available, radical precursors for Ag(I)-catalyzed quinone alkylation using ammonium persulfate [$(NH_4)_2S_2O_8$] as an oxidant (Scheme 1). Based on our previous work, we identified the isopropyl radical as being optimum for comparing nucleophilic radical additions to conjugated electrophiles.[9] Isobutyric acid, isobutyraldehyde, and valine are all capable of quinone alkylation at room temperature under identical experimental conditions. Because all the radical precursors examined produce the isopropyl radical as the reactive species, differences in conversion or selectivity may be attributed to differences in the rate of radical formation. Electron-neutral (**1**, **5**), electron-rich (**2**–**4**, **6**), and electron-poor (**7**) quinones are all suitable reaction partners, although the nucleophilic nature of alkyl radicals typically renders electron-poor quinones the most reactive. Under these strongly oxidizing conditions (Scheme 1), several quinones yield a mixture of mono- and bis-alkylated products with isobutyric acid and isobutyraldehyde, but not with valine.

We postulated that formation of an isopropyl radical from valine would limit the rate of C–H alkylation due to a multistep initiation process, allowing unfavorable termination pathways to compete with a second alkylation. Furthermore, whereas carboxylic acids or aldehydes theoretically only require one equivalent of oxidant for alkylation, the Strecker degradation of unprotected amino acids presumably consumes several equivalents of oxidant per alkyl radical generated, minimizing the likelihood of bis-alkylation.[11] It is interesting to note that decreasing the stoichiometry of isobutyric acid or isobutyraldehyde decreased the prevalence for bis-alkylation, but did not suitably improve the overall conversion into mono-alkylated product. Across the scope of the quinones examined, isobutyric acid and isobutyraldehyde were viewed as comparable radical precursors when using ammonium persulfate as a strong oxidant.

We next sought to compare the same set of isopropyl radical precursors under identical experimental conditions by replacing ammonium persulfate with Selectfluor as the stoichiometric oxidant. As shown in Scheme 2, only mono-alkylated products were observed regardless of the identity of the radical precursor. Across the range of quinones studied, isobutyric acid was shown to be the superior radical



Scheme 1 Comparison of precursors for radical alkylation with ammonium persulfate. *Reagents and conditions*: quinone (0.2 mmol), radical precursor (0.4 mmol), ammonium persulfate (0.4 mmol), $AgNO_3$ (0.04 mmol) in DCE/H_2O (2 mL, 1:1) at room temperature for up to 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Method 'A' radical precursor is isobutyric acid. Method 'B' radical precursor is isobutyraldehyde. Method 'C' radical precursor is valine.



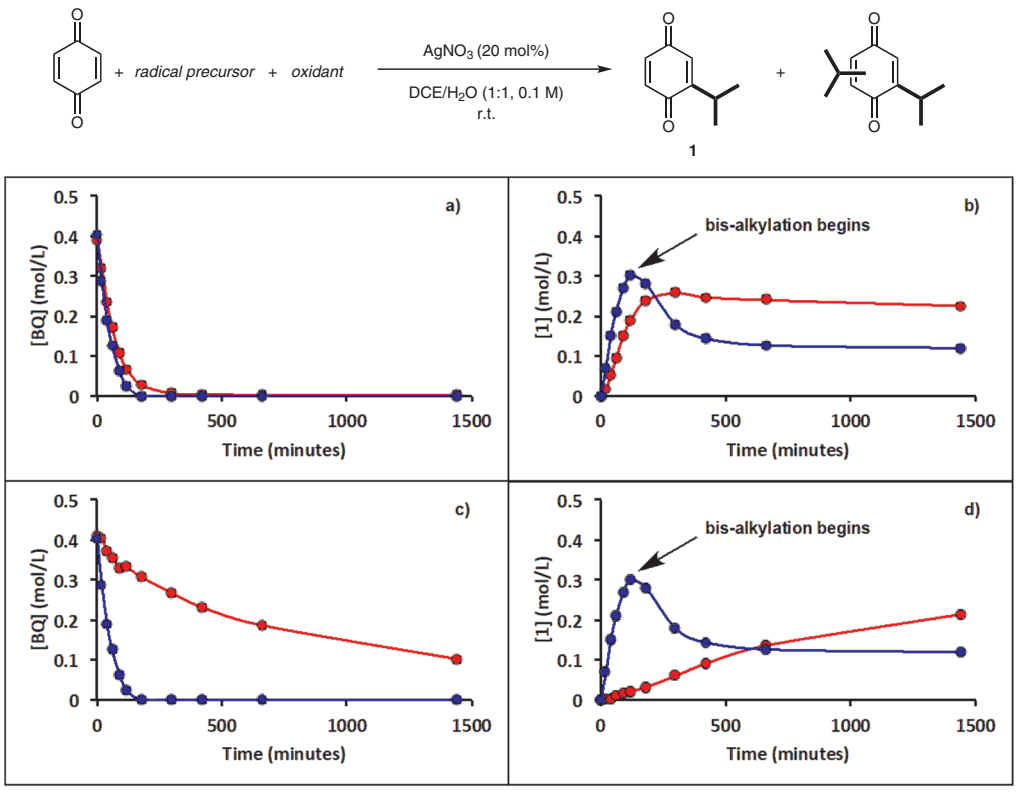
Scheme 2 Comparison of precursors for radical alkylation with Selectfluor. *Reagents and conditions*: quinone (0.2 mmol), radical precursor (0.4 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol) in DCE/H_2O (2 mL, 1:1) at room temperature for up to 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Method 'A' radical precursor is isobutyric acid. Method 'B' radical precursor is isobutyraldehyde. Method 'C' radical precursor is valine.

precursor, whereas valine was essentially ineffective. These results suggested that highly reactive quinones are more effectively mono-alkylated using Selectfluor as an oxidant with carboxylic acids as radical precursors.

Based on the proposed mechanism for Ag(I)-catalyzed radical alkylation with carboxylic acids, we believed that the lower reduction potential of Selectfluor (E° = –0.04 V) compared to ammonium persulfate (E° = 2.01 V) would slow the production of alkyl radicals available to react with quinones.[12] This kinetic difference could explain the propensity for mono-alkylation via the Selectfluor method and should be easily tested by comparing global reaction progressions. It has previously been shown that 1,4-benzoquinone is an excellent radical electrophile, and so the rate of C–H alkylation is likely to be most affected by the rate of alkyl radical formation.[13] We sought to provide experimental evidence for this hypothesis by comparing the global rates of 1,4-benzoquinone alkylation when using either ammonium persulfate or Selectfluor as oxidants.

Due to the heterogeneity of the reaction medium, manual sampling was used to determine reaction progressions. As shown in Scheme 3, 1,4-benzoquinone is consumed within three hours with ammonium persulfate as the oxidant (plot 'a'). Under these conditions, the rate of product formation is higher using isobutyric acid as a radical precursor compared to isobutyraldehyde (plot 'b'). This result suggests that oxidative decarboxylation is faster than decarbonylation as all elementary mechanistic steps are expected to be identical after formation of the isopropyl radical.[14] It is interesting to note that for isobutyric acid, formation of the bis-alkylated product is not observed until nearly all of the 1,4-benzoquinone starting material is consumed (the point indicated by the arrow in plot 'b'). This suggests that the slightly electron-rich 2-isopropyl-1,4-benzoquinone (**1**) is a less effective electrophile, consistent with the data shown in Scheme 1.

Because the conversions shown in Scheme 2 were generally lower with isobutyraldehyde, we compared the rates of C–H alkylation with ammonium persulfate or Selectfluor using isobutyric acid as the sole radical precursor. Dramatic differences in the rate of C–H alkylation were observed between the two oxidants. Whereas persulfate-mediated initiation consumes 1,4-benzoquinone in approximately three hours, the Selectfluor-mediated reaction still contains 25%



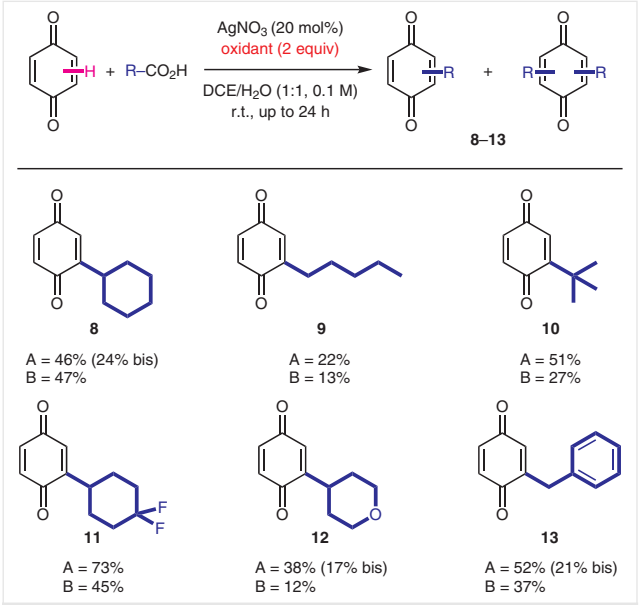
Scheme 3 Rate comparisons for isobutyric acid and isobutyraldehyde using ammonium persulfate and Selectfluor. *Reagents and conditions*: 1,4-benzoquinone (0.4 mmol), radical precursor (0.8 mmol), oxidant (0.8 mmol), $AgNO_3$ (0.08 mmol) in DCE/H_2O (4 mL, 1:1) at room temperature for up to 24 h. Using a glass microsyringe, 10 µL aliquots were taken from the organic phase at specified time points. Conversions were determined by GCMS against 4-*tert*-butylbenzene as an internal standard. Each data point represents the average value of three runs under identical conditions. Plots a) and b), $(NH_4)_2S_2O_8$ as the oxidant, blue data is isobutyric acid as the radical precursor, red data is isobutyraldehyde as the radical precursor. Plots c) and d), isobutyric acid as the radical precursor, blue data is $(NH_4)_2S_2O_8$ as the oxidant, red data is Selectfluor as the oxidant.

unreacted starting material after 24 hours (plot 'c'). Comparing the initial rates of product formation for the two methods reveals that persulfate-mediated alkylation occurs approximately 30 times faster than when using Selectfluor as an oxidant (plot 'd'). This data is consistent with our hypothesis that the formation of bis-alkylation products is largely controlled by the rate of alkyl radical formation, which is directly related to the strength of the stoichiometric oxidant.

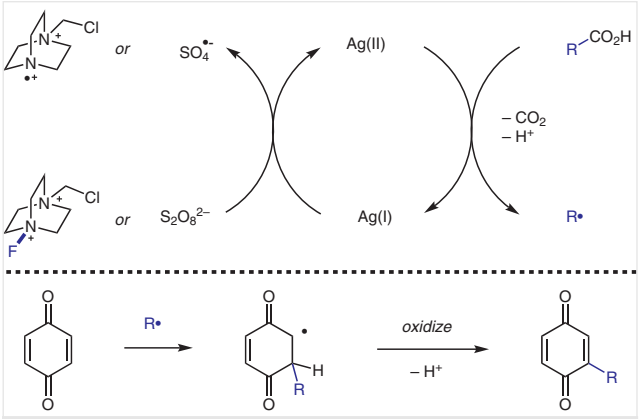
The kinetic data shown in Scheme 3 suggests that powerful oxidants, such as ammonium persulfate, rapidly generate alkyl radicals via decarboxylation of carboxylic acids. For highly reactive electrophiles this influx of reactive species can lead to over-alkylation, a problem that is not easily overcome by altering reactant stoichiometry. Conversely, slow formation of alkyl radicals using Selectfluor as a mild oxidant leads to suitable conversion of exclusively mono-alkylated products over longer reaction times. This assessment is true in the context of the isopropyl radical where high levels of nucleophilicity ensure efficient reaction with 1,4-benzoquinone. However, we have shown that several alkyl carboxylic acids are suitable radical precursors for quinone alkylation using Selectfluor as an oxidant.[10b] In many cases, the stability and nucleophilicity of the generated alkyl radical play large roles in reaction efficiency, and the choice of oxidant depends on predicting the efficacy of the nucleophilic radical generated. As shown in Scheme 4, for highly reactive quinones such as 1,4-benzoquinone, simple secondary alkyl radicals **8** produce higher yields of mono-alkylation when using Selectfluor as an oxidant. The poor stability of primary radicals **9** renders them inefficient with either oxidant, but the stable *tert*-butyl radical **10** is more efficient with a stronger oxidant, likely due to steric effects slowing the nucleophilic addition. Because of their decreased nucleophilicity, deactivated secondary radicals **11** are more efficient when rapidly formed using ammonium persulfate. Stabilized benzylic radicals **13** are reactive enough to produce bis-alkylation with ammonium persulfate, but still yield a suitable amount of the mono-alkylated product.

A possible mechanism for the radical alkylation of quinones is shown in Scheme 5. Single-electron oxidation of Ag(I) by either persulfate or Selectfluor would produce Ag(II). Oxidation of the carboxylate by Ag(II) would lead to radical decarboxylation, liberating a nucleophilic alkyl radical (R•). Reaction with a quinone would produce a substituted quinone radical species that likely undergoes an oxidation/deprotonation sequence to form the expected alkylated quinone product.

To demonstrate the utility of quinone C–H alkylation, we sought to develop a short synthesis of parvaquone from unfunctionalized 1,4-naphthoquinone as a simple and inexpensive starting material (Scheme 6). Although 2-hydroxy-1,4-naphthoquinone is commercially available, the electron-donating hydroxy renders nucleophilic radical addition ineffective, regardless of the oxidant used. In addition, 2-hydroxy-1,4-naphthoquinone is more than four times the cost of naphthoquinone, and the hydroxy group is easily installed through the quinone alkene using straightforward chemistry. Either ammonium persulfate or Selectfluor may be used as the oxidant for the initial reaction, although bis-alkylation is sterically unfavored and so ammonium persulfate was chosen as the cost-effective option. This simple synthetic sequence could easily be applied to producing structural analogues of parvaquone simply by substituting cyclohexanecarboxylic acid for an alternative radical precursor. In this way, radical alkylation could be

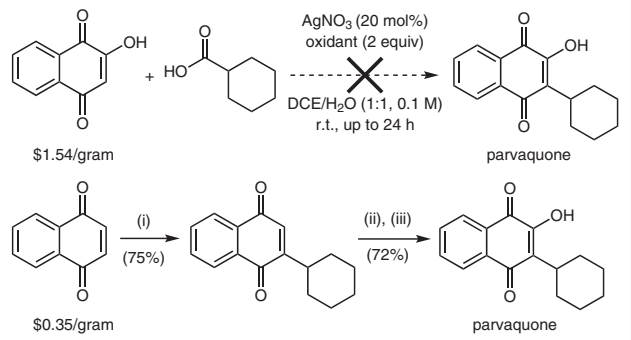


Scheme 4 1,4-Benzoquinone alkylation from various carboxylic acids. *Reagents and conditions*: quinone (0.2 mmol), carboxylic acid (0.4 mmol), oxidant (0.4 mmol), $AgNO_3$ (0.04 mmol) in DCE/H_2O (2 mL, 1:1) at room temperature for up to 24 h. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Method 'A' oxidant is $(NH_4)_2S_2O_8$. Method 'B' oxidant is Selectfluor.



Scheme 5 Proposed mechanism for quinone alkylation

used to generate a library of substituted quinones to screen for structure–activity relationships in the search for a more potent compound.



Scheme 6 A short synthesis of parvaquone. Price comparison for a 100-gram bottle from Sigma-Aldrich. *Reagents and conditions*: (i) 1,4-naphthoquinone (0.2 mmol), cyclohexanecarboxylic acid (0.4 mmol), $(NH_4)_2S_2O_8$ (0.4 mmol), $AgNO_3$ (0.04 mmol) in DCE/H_2O (20 mL, 1:1) at room temperature for 24 h, 75% isolated yield; (ii) 30% H_2O_2, Na_2CO_3, 80 °C, 1 h, 93% isolated yield; (iii) concentrated H_2SO_4, 57% yield.[15]

In conclusion, we have described a brief survey of multiple strategies for quinone C–H alkylation via radical processes. Carboxylic acids, aldehydes, and unprotected amino acids are all suitable alkyl radical precursors, although carboxylic acids were deemed to be the most generally effective. Kinetic comparisons showed that carboxylic acids produce alkyl radicals faster than aldehydes, and ammonium persulfate is much more reactive than Selectfluor as a stoichiometric oxidant. Depending on the quinone substrate, the optimum radical precursor and oxidant could be selected by assessing the nucleophilic character of the expected radical. Finally, we demonstrated the utility of radical alkylation by providing a short and inexpensive synthesis of a biologically active quinone, parvaquone. We look forward to applying such strategies for library synthesis of simple alkyl-quinones in the future.

Reagents and solvents were purchased at the highest commercial quality and used without purification. NMR yields were calculated by selecting proton peaks from products that were previously isolated. Trimethoxybenzene was used as the NMR standard. The yields describe the result of a single experiment. Reactions were monitored by NMR spectroscopy; the spectra were recorded on a Varian-INOVA 400 MHz or 500 MHz spectrometer and calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR 7.26 ppm, ^{13}C NMR 77.16 ppm). The following abbreviations are used to explain multiplicities (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). High-resolution mass spectrometry (HRMS) was performed using a ThermoFisher Q-Exactive instrument. Kinetic data were obtained by GCMS (Agilent Technologies 5975 Series MSD GCMS) with *tert*-butylbenzene as the standard.

Functionalization of Quinones with $(NH_4)_2S_2O_8$ as the Oxidant; General Procedure A

To a vial containing a stir bar was added the quinone (0.2 mmol, 1 equiv), the radical precursor (0.4 mmol, 2 equiv) and $(NH_4)_2S_2O_8$ (91 mg, 0.4 mmol, 2 equiv) followed by dichloroethane (1 mL) and H_2O (0.9 mL). A solution of $AgNO_3$ (0.1 mL of a 0.4 M solution in H_2O, 0.04 mmol) was added in one portion. The reaction vial was capped with a screw cap and the contents stirred at room temperature for 24 h. Upon completion, the reaction was transferred to a test tube containing saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated in vacuo. Trimethoxybenzene (16.8 mg, 1 mmol) was added and the resulting crude material was dissolved in $CDCl_3$ for NMR yield analysis.

Functionalization of Quinones with Selectfluor as the Oxidant; General Procedure B

To a vial containing a stir bar was added the quinone (0.2 mmol, 1 equiv), the radical precursor (0.4 mmol, 2 equiv) and Selectfluor (142 mg, 0.4 mmol, 2 equiv) followed by dichloroethane (1 mL) and H_2O (0.9 mL). A solution of $AgNO_3$ (0.1 mL of a 0.4 M solution in H_2O, 0.04 mmol) was added in one portion. The reaction vial was capped with a screw cap and the contents stirred at room temperature for 24 h. Upon completion, the reaction was transferred to a test tube containing saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated in vacuo. Trimethoxybenzene (16.8 mg, 1 mmol) was added and the resulting crude material was dissolved in $CDCl_3$ for NMR yield analysis.

2-Isopropylcyclohexa-2,5-diene-1,4-dione (1), 2,6-Diisopropylcyclohexa-2,5-diene-1,4-dione (1-Bis-C2,C6), 2,5-Diisopropylcyclohexa-2,5-diene-1,4-dione (1-Bis-C2,C5) and 2,3-Diisopropylcyclohexa-2,5-diene-1,4-dione (1-Bis-C2,C3)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **1** (8.6 mg, 29%) as a yellow oil. The data matches those previously reported.[1] The same reaction also afforded an inseparable mixture of **1-Bis-C2,C6**, **1-Bis-C2,C5** and **1-Bis-C2,C3** (19.5 mg, 51%) as a yellow oil. When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **1** (34% NMR yield), **1-Bis-C2,C6** (13% NMR yield), **1-Bis-C2,C5** (13% NMR yield) and **1-Bis-C2,C3** (3% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **1** (32% NMR yield) with no bis product. The data for **1** matches those previously reported.[15]

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **1** (47% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **1** (9% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **1** (<2% NMR yield). The data for **1** matches those previously reported.[16]

Previously isolated NMR data were used as a reference to calculate NMR yields.

1-Bis-C2,C6 and 1-Bis-C2,C5

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (d, *J* = 1.2 Hz, 2 H), 6.47 (s, 2 H), 3.13–2.95 (m, 4 H), 1.12 (d, *J* = 6.9 Hz, 24 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 188.1, 187.0, 155.5, 154.4, 131.0, 129.9, 27.1, 26.6, 21.6, 21.5.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}O_2^+$: 193.1223; found: 193.1214 and 193.1213, respectively.

1-Bis-C2,C3

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (s, 2 H), 3.30–3.18 (m, 2 H), 1.27 (d, *J* = 7.1 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.3, 148.9, 136.6, 27.9, 21.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}O_2^+$: 193.1223; found: 193.1210.

2-Isopropyl-5-methylcyclohexa-2,5-diene-1,4-dione (2-C5), 2-Isopropyl-6-methylcyclohexa-2,5-diene-1,4-dione (2-C6), 2-Isopropyl-3-methylcyclohexa-2,5-diene-1,4-dione (2-C3), 2,3-Diisopropyl-5-methylcyclohexa-2,5-diene-1,4-dione (2-Bis-C5,C6) and 2,6-Diisopropyl-5-methylcyclohexa-2,5-diene-1,4-dione (2-Bis-C3,C5)

General procedure A was employed using 2-methyl-1,4-benzoquinone (24 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **2-C5** (9% NMR yield), **2-C6** (11% NMR yield), **2-C3** (6% NMR yield), **2-Bis-C3,C6** (19% NMR yield) and **2-Bis-C3,C5** (18% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **2-C5** (13% NMR yield), **2-C6** (16% NMR yield), **2-C3** (8% NMR yield), **2-Bis-C3,C6** (13% NMR yield) and **2-Bis-C3,C5** (11% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **2-C5** (14% NMR yield), **2-C6** (16% NMR yield), **2-C3** (11% NMR yield), with no bis product. The data for **2-C5**, **2-C6** and **2-C3** matches those previously reported.[10b]

General procedure B was employed using 2-methyl-1,4-benzoquinone (24 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **2-C5** (21% NMR yield), **2-C6** (23% NMR yield), **2-C3** (14% NMR yield), **2-Bis-C3,C6** (19% NMR yield) and **2-Bis-C3,C5** (19% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **2-C5** (14% NMR yield), **2-C6** (16% NMR yield) and **2-C3** (17% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **2-C5** (<2% NMR yield), **2-C6** (<2% NMR yield) and **2-C3** (<2% NMR yield). The data matches those previously reported.[10b]

Previously isolated NMR data were used as a reference to calculate NMR yields.

2-Bis-C3,C6 and 2-Bis-C3,C5

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (s, 1 H), 6.38 (s, 1 H), 3.17–3.07 (m, 2 H), 3.07–2.98 (m, 2 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 1.26 (dd, *J* = 7.1, 2.0 Hz, 12 H), 1.10 (dd, *J* = 6.9, 2.5 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8, 188.2, 187.7, 187.6, 155.1, 149.0, 145.3, 140.3, 137.4, 135.6, 134.0, 130.5, 53.6, 31.7, 28.9, 26.7, 22.8, 21.6, 20.5, 15.5, 14.3, 11.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}O_2^+$: 207.1380; found: 207.1350 and 207.1372 respectively.

2-Isopropyl-3,5-dimethylcyclohexa-2,5-diene-1,4-dione (3) and 2,6-Diisopropyl-3,5-dimethylcyclohexa-2,5-diene-1,4-dione (3-Bis)

General procedure A was employed using 2,6-dimethyl-1,4-benzoquinone (27 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **3** (28% NMR yield) and **3-Bis** (18% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **3** (29% NMR yield) and **3-Bis** (15% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **3** (31% NMR yield) with no bis product. The data for **3** matches those previously reported.[17]

General procedure B was employed using 2,6-dimethyl-1,4-benzoquinone (27 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **3** (47% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **3** (24% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **3** (4% NMR yield).

Previously isolated NMR data were used as a reference to calculate NMR yields.

3-Bis

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.13–3.03 (m, 2 H), 2.02 (s, 6 H), 1.25 (d, *J* = 7.1 Hz, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.9, 187.9, 149.3, 139.0, 28.9, 20.7, 11.9.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{22}O_2^+$: 221.1536; found: 221.1521.

2-Isopropyl-3,5-dimethoxycyclohexa-2,5-diene-1,4-dione (4)

General procedure A was employed using 2,6-dimethoxy-1,4-benzoquinone (34 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **4** (26% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **4** (24% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **4** (13% NMR yield).

General procedure B was employed using 2,6-dimethoxy-1,4-benzoquinone (34 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **4** (8% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **4** (3% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **4** (<2% NMR yield).

Previously isolated NMR data were used as a reference to calculate NMR yields.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (s, 1 H), 3.93 (s, 3 H), 3.78 (s, 3 H), 3.30–3.18 (m, 1 H), 1.20 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 178.9, 157.1, 154.9, 138.6, 107.6, 61.1, 56.5, 24.8, 20.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}O_4^+$: 211.0965; found: 211.0964.

2-Isopropylnaphthalene-1,4-dione (5)

General procedure A was employed using naphthoquinone (32 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **5** (57% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **5** (43% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **5** (31% NMR yield).

General procedure B was employed using naphthoquinone (32 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **5** (42% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **5** (24% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **5** (5% NMR yield).

Previously isolated NMR data were used as a reference to calculate NMR yields.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.03 (m, 2 H), 7.76–7.68 (m, 2 H), 6.77 (d, *J* = 1.0 Hz, 1 H), 3.31–3.19 (m, 1 H), 1.20 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.7, 185.0, 157.4, 133.9, 133.6, 132.7, 132.7, 132.1, 126.8, 126.1, 27.3, 21.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}O_2^+$: 201.0910; found: 201.0913.

2-Isopropyl-3-methylnaphthalene-1,4-dione (6)

General procedure A was employed using 2-methylnaphthoquinone (34 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **6** (34% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **6** (33% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **6** (25% NMR yield).

General procedure B was employed using 2-methylnaphthoquinone (34 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **6** (17% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **6** (15% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **6** (<2% NMR yield). The data matches those previously reported.[18]

3,5-Dichloro-2-isopropylcyclohexa-2,5-diene-1,4-dione (7) and 2,6-Dichloro-3,5-diisopropylcyclohexa-2,5-diene-1,4-dione (7-Bis)

General procedure A was employed using 2,6-dichloro-1,4-benzoquinone (35 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **7** (36% NMR yield) and **7-Bis** (22% NMR yield); trace amounts of a product corresponding to a mass of **7-Bis**, minus chlorine, were observed (ESI-TOF: *m*/*z* calcd 269.1302; found: 269.1351). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **7** (40% NMR yield) and **7-Bis** (20% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **7** (32% NMR yield).

General procedure B was employed using 2,6-dichloro-1,4-benzoquinone (35 mg, 0.2 mmol) and isobutyric acid (37 µL, 0.4 mmol). The reaction afforded **7** (52% NMR yield). When isobutyraldehyde (36 µL, 0.4 mmol) was used, the reaction afforded **7** (12% NMR yield). When valine (47 mg, 0.4 mmol) was used, the reaction afforded **7** (<2% NMR yield).

Previously isolated NMR data were used as a reference to calculate NMR yields.

Compound 7

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (s, 1 H), 3.55–3.45 (m, 1 H), 1.33 (d, *J* = 7.1 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 177.3, 149.7, 144.9, 140.6, 132.3, 30.9, 19.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_9H_{10}Cl_2O_2^+$: 218.9974; found: 218.9949.

7-Bis

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51–3.40 (m, 2 H), 1.32 (d, *J* = 7.1 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 148.6, 140.8, 30.7, 19.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}Cl_2O_2^+$: 261.0444; found: 261.0422.

[1,1′-Bi(cyclohexane)]-3,6-diene-2,5-dione (8), [1,1′:4′,1″-Tercyclohexane]-3′,6′-diene-2′,5′-dione (8-Bis-C2,C5) and [1,1′:3′,1″-Tercyclohexane]-3′,6′-diene-2′,5′-dione (8-Bis-C2,C6)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and cyclohexanoic acid (51 mg, 0.4 mmol). The reaction afforded **8** (17.6 mg, 46%) as a yellow after separation by silica gel chromatography (5% EtOAc in hexanes). The data matches those previously reported.[2] The same reaction also afforded a mixture of **8-Bis-C2,C5** and **8-Bis-C2,C6** (1:1) (14 mg, 24%) as a yellow oil.

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and cyclohexanoic acid (51 mg, 0.4 mmol). The reaction afforded **8** (17.9 mg, 47%) as a yellow oil separated by silica gel chromatography (5% EtOAc in hexanes). The data matches those previously reported.[10b]

8-Bis-C2,C5 and 8-Bis-C2,C6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (d, *J* = 1.0 Hz, 2 H), 6.42 (s, 2 H), 2.75–2.63 (m, 4 H), 1.86–1.71 (m, 20 H), 1.47–1.30 (m, 10 H), 1.27–1.08 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.0, 188.2, 187.0, 154.5, 153.4, 131.4, 130.3, 36.8, 36.2, 32.3, 32.2, 27.2, 26.5, 26.5, 26.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}O_2^+$: 273.1849; found: 273.1837 and 273.1842, respectively.

2-Pentylcyclohexa-2,5-diene-1,4-dione (9)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and *n*-hexanoic acid (50 µL, 0.4 mmol). The reaction afforded **9** (7.7 mg, 22%) as a yellow oil separated by silica gel chromatography (5% EtOAc in hexanes).

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and *n*-hexanoic acid (50 µL, 0.4 mmol). The reaction afforded **9** (4.5 mg, 13%) as a yellow oil separated by silica gel chromatography (5% EtOAc in hexanes). The data matches those previously reported.[10b]

2-(*tert*-Butyl)cyclohexa-2,5-diene-1,4-dione (10)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and pivalic acid (41 mg, 0.4 mmol). The reaction afforded **10** (16.7 mg, 51%) as a yellow oil separated by silica gel chromatography (5% EtOAc in hexanes).

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and pivalic acid (41 mg, 0.4 mmol). The reaction afforded **10** (8.8 mg, 27%) as a yellow oil separated by silica gel chromatography (5% EtOAc in hexanes). The data matches those previously reported.[19]

4′,4′-Difluoro-[1,1′-bi(cyclohexane)]-3,6-diene-2,5-dione (11)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 4,4-difluorocyclohexane-1-carboxylic acid (66 mg, 0.4 mmol). The reaction afforded **11** (32.9 mg, 73%) as a yellow oil separated by silica gel chromatography (10% EtOAc in hexanes).

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 4,4-difluorocyclohexane-1-carboxylic acid (66 mg, 0.4 mmol). The reaction afforded **11** (20.2 mg, 45%) as a yellow oil separated by silica gel chromatography (10% EtOAc in hexanes). The data matches those previously reported.[10b]

2-(Tetrahydro-2*H*-pyran-4-yl)cyclohexa-2,5-diene-1,4-dione (12), 2,5-Bis(tetrahydro-2*H*-pyran-4-yl)cyclohexa-2,5-diene-1,4-dione (12-Bis-C2,C5) and 2,6-Bis(tetrahydro-2*H*-pyran-4-yl)cyclohexa-2,5-diene-1,4-dione (12-Bis-C2-C6)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and tetrahydro-2*H*-pyran-4-carboxylic acid (56 mg, 0.4 mmol). The reaction afforded **12** (14.4 mg, 38%) as a yellow solid separated by silica gel chromatography (10% EtOAc in hexanes). The same reaction also afforded a mixture of **12-Bis-C2,C5** and **12-Bis-C2,C6** (1:1) (9.5 mg, 17%) as a yellow oil.

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and tetrahydro-2*H*-pyran-4-carboxylic acid (56 mg, 0.4 mmol). The reaction afforded **12** (8.1 mg, 21%) as a yellow solid separated by silica gel chromatography (10% EtOAc in hexanes).

Compound 12

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79–6.70 (m, 2 H), 6.52 (dd, *J* = 2.3, 1.2 Hz, 1 H), 4.05 (dd, *J* = 11.6, 4.4 Hz, 2 H), 3.53 (td, *J* = 11.8, 2.1 Hz, 2 H), 3.01–2.90 (m, 1 H), 1.72–1.64 (m, 2 H), 1.56 (ddd, *J* = 25.1, 12.5, 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.9, 187.0, 152.0, 137.1, 136.2, 131.3, 67.9, 34.0, 31.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}O_3^+$: 193.0859; found: 193.0857.

12-Bis-C2,C5 and 12-Bis-C2,C6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (s, 2 H), 6.48 (s, 2 H), 4.09–4.01 (m, 8 H), 3.56–3.53 (m, 8 H), 3.00–2.95 (m, 4 H), 1.69–1.66 (m, 8 H), 1.62–1.50 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2, 187.5, 186.5, 152.3, 151.6, 131.7, 130.9, 68.0, 66.0, 34.3, 33.8, 31.7, 31.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}O_4^+$: 277.1434; found: 277.1419 and 277.1422, respectively.

2-Benzylcyclohexa-2,5-diene-1,4-dione (13), 2,5-Dibenzylcyclohexa-2,5-diene-1,4-dione (13-Bis-C2,C5), 2,6-Dibenzylcyclohexa-2,5-diene-1,4-dione (13-Bis-C2,C6) and 2,3-Dibenzylcyclohexa-2,5-diene-1,4-dione (13-Bis-C2,C3)

General procedure A was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and 2-phenylacetic acid (54 mg, 0.4 mmol). The reaction afforded **13** (20.5 mg, 52%) as a yellow oil separated by silica gel chromatography (5% EtOAc in hexanes). The data matches those previously reported.[15] The same reaction also afforded a mixture of **13-Bis-C2,C3**, **13-Bis-C2,C5** and **13-Bis-C2,C6** (1:2:4) (7 mg, 12%) as a yellow oil.

General procedure B was employed using 1,4-benzoquinone (22 mg, 0.2 mmol) and benzoic acid (54 mg, 0.4 mmol). The reaction afforded **13** (12.3 mg, 31%) as a yellow solid separated by silica gel chromatography (10% EtOAc in hexanes).

13-Bis-C2,C3

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 4H), 7.29–7.22 (m, 4H), 7.13–7.10 (m, 2H),6.78 (s, 2H), 3.93 (s, 4H)

^{13}C NMR (100 MHz, $CDCl_3$), mixture of all three isomers: δ = 188.0, 187.8, 187.7, 187.3, 148.9, 148.7, 143.9, 137.8, 136.7, 136.6, 136.5, 133.5, 133.3, 129.5, 128.98, 128.97, 128.8, 128.7, 127.13, 127.11, 126.7, 35.6, 35.0, 32.0.

HRMS (ESI-TOF): calcd for $C_{20}H_{17}O_2^+$ [M+H]$^+$ 289.1223 found 289.1256

13-Bis-C2,C5

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 4H), 7.29–7.22 (m, 4H), 7.21–7.15 (m, 2H), 6.29 (s, 2H), 3.75 (s, 4H)

^{13}C NMR (100 MHz, $CDCl_3$), mixture of all three isomers: δ = 188.0, 187.8, 187.7, 187.3, 148.9, 148.7, 143.9, 137.8, 136.7, 136.6, 136.5, 133.5, 133.3, 129.5, 128.98, 128.97, 128.8, 128.7, 127.13, 127.11, 126.7, 35.6, 35.0, 32.0.

HRMS (ESI-TOF): calcd for $C_{20}H_{17}O_2^+$ [M+H]$^+$ 289.1223 found 289.1226

13-Bis-C2,C6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 4H), 7.29–7.22 (m, 4H), 7.21–7.15 (m, 2H), 6.35 (t, *J* = 1.6 Hz, 2H), 3.71 (d, *J* = 1.2 Hz, 4H)

^{13}C NMR (100 MHz, $CDCl_3$), mixture of all three isomers: δ = 188.0, 187.8, 187.7, 187.3, 148.9, 148.7, 143.9, 137.8, 136.7, 136.6, 136.5, 133.5, 133.3, 129.5, 128.98, 128.97, 128.8, 128.7, 127.13, 127.11, 126.7, 35.6, 35.0, 32.0.

HRMS (ESI-TOF): calcd for $C_{20}H_{17}O_2^+$ [M+H]$^+$ 289.1223 found 289.1247

General Kinetic Procedures

To a vial containing a stir bar was added benzoquinone (44 mg, 0.4 mmol, 1 equiv), the radical precursor (0.8 mmol, 2 equiv) and the oxidant (0.8 mmol, 2 equiv) followed by dichloroethane (2 mL) and H_2O (1.8 mL). Tetrabutylbenzene (31 µL, 0.2 mmol) was then added as the internal standard. The reaction mixture was stirred for 1 min without catalyst. A 10 µL aliquot was then taken using a glass syringe and transferred into a GC vial. The vial was then filled with EtOAc and placed into the GCMS (Agilent Technologies 5975 Series MSD GCMS) for analysis. A solution of $AgNO_3$ (0.2 mL of a 0.4 M solution in H_2O, 0.04 mmol) was added to the reaction in one portion. Aliquots (10 µL) were taken for GCMS analysis every 20 min for the first hour, then after 30 min for the second hour followed by one one-hour sample (3 hours), two two-hour samples (5 h and 7 h), a four-hour sample (11 h) and finally a twenty-four-hour sample. A previously prepared calibration curve with benzoquinone and *tert*-butylbenzene as the standard along with their corresponding GC peak areas from each sample produced the kinetic data in Scheme 3.

Parvaquone

2-Cyclohexylnaphthoquinone

To a vial containing a stir bar was added 1,4-naphthoquinone (316 mg, 2.0 mmol, 1 equiv), cyclohexanecarboxylic acid (512 mg, 4 mmol, 2 equiv) and $(NH_4)_2S_2O_8$ (912 mg, 4 mmol, 2 equiv) followed by dichloroethane (10 mL) and H_2O (10 mL). $AgNO_3$ (68 mg, 0.4 mmol, 20 mol%) was added in one portion. The reaction was capped with a screw cap and stirred at room temperature for 24 h. Upon completion, the reaction mixture was transferred into a separatory funnel containing saturated $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated in vacuo. The reaction afforded 2-cyclohexylnaphthoquinone (364 mg, 75% yield) as a yellow solid separated by silica gel chromatography (5% EtOAc in hexanes). The data matches those previously reported.[15]

1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione

EtOH (3.8 mL) was added to a vial containing 2-cyclohexylnaphthoquinone (364 mg, 1.5 mmol) and the vial was heated at 80 °C until all the solid had dissolved. Next, 30% H_2O_2 (600 µL) and Na_2CO_3 (950 µL of a 1.1 M solution in H_2O, 1.0 mmol) was added in one portion and the resulting pink reaction mixture was stirred for 1 h. Upon completion, the resulting white solution was added to a test tube containing H_2O (3 mL). The aqueous phase was extracted with Et_2O (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated in vacuo. The reaction afforded 2-cyclohexyl-(2,3)-oxirane-1,4-naphthoquinone (361 mg, 93% yield) as a pale yellow oil. The data matches those previously reported.[15]

Parvaquone

Concentrated H_2SO_4 (2.5 mL) was added to a vial containing 2-cyclohexyl-(2,3)-oxirane-1,4-naphthoquinone (361 mg, 1.4 mmol). The resulting blood-red solution was then stirred in an ice bath for 1 h. Upon completion, the reaction was transferred to a separatory funnel. A solution of NaOH (4 M) was added until the pH tested approximately 7. The reaction mixture was then extracted multiple times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated in vacuo. The reaction afforded parvaquone (220 mg, 57%) as a yellow solid separated by silica gel chromatography (10% Et_2O in hexanes). The data matches those previously reported.[15]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610005.

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