

## Reactions of Alkylolithium and Grignard Reagents with Benzoquinone: Evidence for an Electron-Transfer Mechanism

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Quinols have been used as synthons in several synthetic methodologies.<sup>1–3</sup> Preparation of these compounds has been accomplished by addition of alkylolithium or Grignard reagents to quinone monoketals,<sup>4</sup> quinone silylcyanohydrins,<sup>5</sup> and quinones directly, the latter method being complicated by hydroquinone formation. To date, little mechanistic information has been reported on the competitive nature of addition versus reduction for these reactions. In this work we investigate the mechanistic dichotomy of quinone addition versus reduction by organometallic reagents and the factors that influence the product distribution.

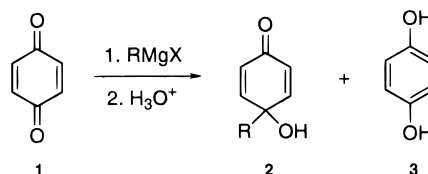
### Results and Discussion

Electron transfer from electron rich donors to electron deficient acceptors is a well-established chemical process producing intermediate radical ion pairs. The subsequent coupling of such radical ion pairs provides an indirect mechanism for bond formation between a donor and an acceptor. This mechanism, usually referred to as the ET or SET (single-electron transfer) mechanism, represents a plausible general alternative to direct, or polar, bond formation.<sup>6</sup>

It is known that carbanion equivalents, such as alkylolithium and Grignard reagents, are susceptible to ET processes as well as conventional polar mechanisms.<sup>7</sup> Consequently, in the presence of a good electron acceptor, carbanion equivalents pose a mechanistic dilemma of polar versus SET processes. Previous reports have indicated that quinones are potential ET acceptors as well as electrophiles in polar additions.<sup>8</sup> This, coupled with our continuing interest in quinone chemistry,<sup>9</sup> prompted our study of the mechanistic nature of alkylolithium and Grignard additions to 1,4-quinones.

The reactions of alkylolithium and Grignard reagents with 1,4-quinones have been the subject of numerous investigations.<sup>10</sup> Previous reports indicate that the re-

Scheme 1



R	2	3
a methyl	95	5
b ethyl	78	22
c propyl	63	37
d <i>n</i> -butyl	60	40
e isopropyl	10	90
f <i>sec</i> -butyl	<5	95
g <i>tert</i> -butyl	<1	99

gioselectivity<sup>11</sup> and stereoselectivity<sup>12</sup> of addition are influenced by quinone substituents, organometallic reagent, and solvent effects. Hydroquinone formation during these reactions has been reported with inference to a SET mechanism;<sup>3,12</sup> however, mechanistic evidence of such a pathway is lacking. Our investigation focuses on the competitive nature of addition and reduction, be it through competing or concerted SET and polar pathways.

We studied the reaction between benzoquinone (**1**) and various Grignard reagents as summarized in Scheme 1. The ratio of addition to reduction products is directly related to the steric effects of R in the organometallic reagent. Addition is most favored in the case of methyl giving 95% **2a**. The amount of addition decreases for primary Grignard reagents (R = ethyl, *n*-propyl, and *n*-butyl) giving 78% **2b**, 63% **2c**, and 60% **2d**, respectively. Reduction products are favored over addition for both secondary (R = isopropyl and *sec*-butyl) and tertiary (R = *tert*-butyl) Grignard reagents giving greater than 90% hydroquinone **3** in all cases as determined by GC–MS and <sup>1</sup>H NMR. It is noteworthy to mention that compounds **2e,f** slowly decompose upon standing for several days at room temperature; thus, combustion analysis proved impossible. Similar observations have been previously reported for compound **2g**.<sup>13</sup>

Since alkylolithiums are better reducing agents than analogous Grignard reagents,<sup>6c,14</sup> one might assume that quinone reduction products would be formed in greater abundance if addition and reduction occurred through competing polar and SET pathways, respectively. As shown in Scheme 2, variation of the metal has no significant effect on product distributions. Methyl, *n*-butyl, *sec*-butyl, and *tert*-butyl alkylolithiums gave similar product ratios upon reacting with **1** as compared to analogous Grignard reagents in Scheme 1. This is a significant observation which is inconsistent with competing polar and SET mechanisms. Consequently, our efforts focused on demonstrating a concerted mechanism with products forming through a common intermediate.

To invoke a concerted polar mechanism leading to **3**, the quinol **2** would have to degrade to **3** through dealky-

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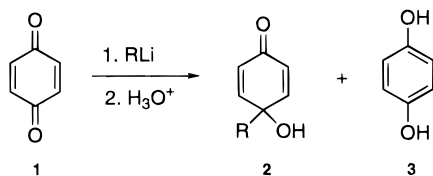
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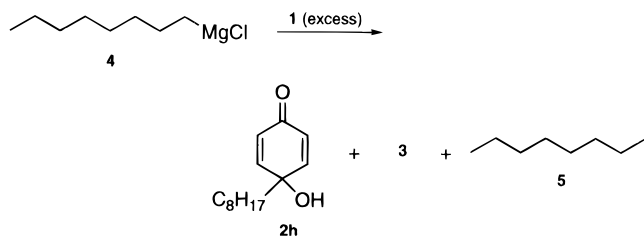
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Scheme 2



R	2	3
a methyl	89	11
d <i>n</i> -butyl	61	39
f <i>sec</i> -butyl	<4	96
g <i>tert</i> -butyl	<1	99

Scheme 3



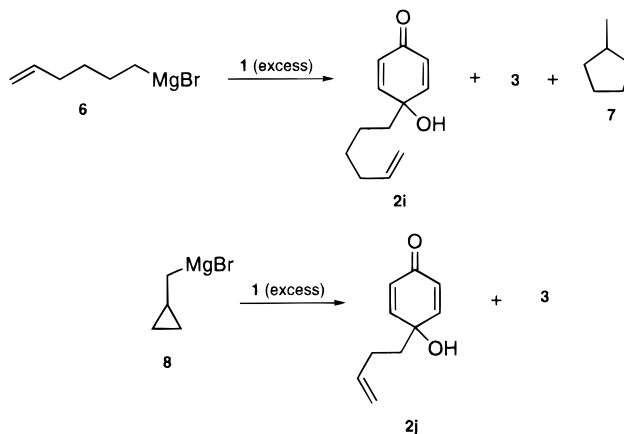
Solvent	Quench	5 (%D)
THF	H <sub>3</sub> O <sup>+</sup>	0
THF	D <sub>3</sub> O <sup>+</sup>	<2
THF- <i>d</i> <sub>6</sub>	H <sub>3</sub> O <sup>+</sup>	89

lation. Similar dealkylation reactions which lead to rearomatization have been observed in dienone–phenol rearrangements.<sup>15,16</sup> To determine the feasibility of this pathway, we studied the stability of quinol analogs under our reaction conditions. Compounds **2a,d** were stirred in THF in the presence of aqueous acid for 24 h. Formation of **3** was not observed in any case. On the basis of the data reported in Schemes 1 and 2 and the absence of **3** resulting from quinol degradation, it is suggested that SET is involved in the reaction of alkyl-lithium and Grignard reagents with quinones.

In order to provide evidence for the presence of alkyl radical intermediates formed through a SET mechanism, several experiments were conducted using octylmagnesium chloride (**4**), deuterium labeling in the solvent, and aqueous quench. The choice of **4** was based on the ease of detecting the scavenging products of the octyl radical. As shown in Scheme 3, addition of **4** to excess **1** gave 60% **2h** and 40% **3**, a distribution analogous to that of primary Grignard reagents shown in Scheme 1. In addition to **2h** and **3**, octane **5** was produced in similar quantities to **3** (ratio of **5/3** = 0.91) as determined by GC–MS. To eliminate the possibility of **5** forming due to protonation of unreacted Grignard, we conducted a parallel experiment utilizing a D<sub>3</sub>O<sup>+</sup> quench. In this case, no significant deuterium incorporation was observed in **5**. Based on these results, it was determined that **5** was produced prior to quenching the reaction, possibly through hydrogen atom abstraction by the octyl radical.

A common source of hydrogen atoms in a reaction involving radicals is the solvent.<sup>17</sup> To test the hypothesis that THF is a hydrogen atom donor to the octyl radical,

Scheme 4



**4** was allowed to react with **1** in THF-*d*<sub>6</sub>. In this experiment, the deuterium content of **5** rose to 89%. These results indicate the intermediacy of radical intermediates and that THF serves as a hydrogen atom donor to alkyl radicals.

To determine whether addition products formed through a SET pathway, we employed organometallic based radical probes, which have been used extensively to elucidate mechanisms where radical intermediates are suspected.<sup>6c</sup> The 5-hexenyl Grignard is typical of these probes and served as our initial study. Intermediacy of the 5-hexenyl radical is easily detected by a well-precedented rearrangement to the methylcyclopentyl radical, provided that coupling of the radical pair is slower than the rate of cyclization (10<sup>5</sup> s<sup>-1</sup>).<sup>18</sup> As shown in Scheme 4, the reaction of 5-hexenylmagnesium bromide (**6**) with **1** gave 47% **3** and 52% **2i** as the only observed addition product. Methylcyclopentane (**7**) was also produced in similar quantities to **3** (ratio of **7/3** = 0.88) as determined by GC–MS. Although the presence of **7** provides evidence for radical intermediates, the lack of cyclization of R in **2i** does not rule out that addition occurs through a competitive direct carbanion addition or that coupling of the radical pair is faster than cyclization of the 5-hexenyl radical.

In order to answer this question, we examined the reaction of (cyclopropylmethyl)magnesium bromide (**8**) with **1**. At low temperatures, **8** has been shown to be efficiently trapped by electrophiles without rearrangement.<sup>19</sup> This trapping, coupled with the observation that the cyclopropylmethyl radical ring opens to the 3-butenyl radical with a rate constant of 10<sup>8</sup> s<sup>-1</sup>, makes **8** a valid probe for our system.<sup>20</sup> As shown in Scheme 4, addition of **8** to **1** at –78 °C resulted in formation of 37% **3** and 52% **2j** as the only addition product. Clearly, the intermediacy of the cyclopropylmethyl radical in quinol formation is demonstrated by the acyclic nature of R in **2j**. These observations taken as a whole demonstrate the operability of the SET mechanism in quinol and hydroquinone formation.

In summary, the mechanism of alkyl-lithium and Grignard reagents can be represented by the concerted SET pathway in Scheme 5. Initial reduction of the quinone by the organometallic reagent results in the alkyl radical **9** and the quinone radical anion **10**, the precursor

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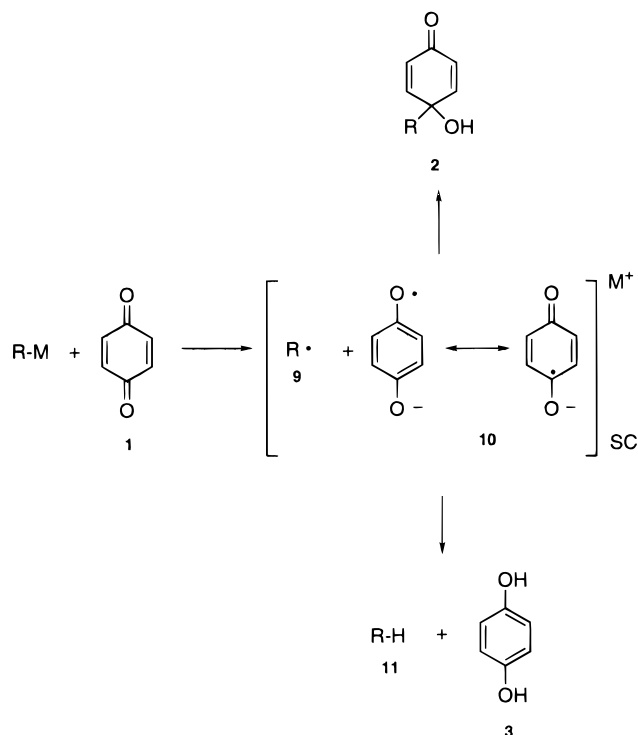
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## Scheme 5



to all quinone-derived products. Radical coupling of **9** and **10** followed by protonation results in the observed addition product **2**. Increased steric hindrance of **9** disfavors radical coupling. Thus, the radical pair diffuses out of the solvent cage, resulting in formation of **3** and the alkane **11**, formed through scavenging processes followed by protonation.

## Experimental Section

**General Methods.**  $^1\text{H}$  (250 MHz) and  $^{13}\text{C}$  (62.9 MHz) NMR spectra were determined in  $\text{CDCl}_3$  unless otherwise specified. Chemical shifts are reported in ppm downfield from internal TMS ( $\delta$ ). Mass spectra were determined at an ionizing voltage of 70 eV. Tetrahydrofuran was distilled under nitrogen from  $\text{LiAlH}_4$ . Compounds **6** and **8** were synthesized according to the literature.<sup>19,21</sup> All other materials were obtained from commercial suppliers.

**General Procedure for Addition of Organometallics to Benzoquinone.** In a 250-mL round-bottom flask were placed benzoquinone (**1**) (5.0 mmol) and THF (100 mL) under nitrogen. The solution was cooled to  $-78^\circ\text{C}$  and maintained throughout

the reaction. Added to the quinone solution was a THF solution of the organometallic (5.0 mmol). The resulting mixture was stirred for 30 min. The reaction mixture was then poured through 5% aqueous ammonium chloride (150 mL) to quench the reaction and extracted with dichloromethane ( $2 \times 40$  mL). The organic phase was washed with water ( $3 \times 60$  mL) and dried over anhydrous  $\text{MgSO}_4$ . The solvent was removed under reduced pressure. Product distribution of the reaction mixtures was determined by GC-MS and  $^1\text{H}$  NMR for compounds **2a,d,g** and **3**, which were identified by comparison to previously reported spectral data or authentic samples.<sup>13</sup> The crude products for **2b,c,e,f,h-j** were purified by flash chromatography (base-washed silica gel, 30% acetone/hexane)<sup>13</sup> which gave yellow oils having the following properties.

**4-Hydroxy-4-ethylcyclohexa-2,5-dien-1-one (2b):**  $^1\text{H}$  NMR  $\delta$  6.74 (d,  $J = 10.2$  Hz, 2H), 6.08 (d,  $J = 10.2$  Hz, 2H), 3.97 (s, 1H), 1.71 (q,  $J = 7.5$  Hz, 2H), 0.75 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR  $\delta$  186.23, 152.08, 127.95, 70.23, 32.61, 11.78. Anal. Calcd for  $\text{C}_8\text{H}_{10}\text{O}_2$ : C, 69.55; H, 7.29. Found: C, 69.37; H, 7.38.

**4-Hydroxy-4-propylcyclohexa-2,5-dien-1-one (2c):**  $^1\text{H}$  NMR  $\delta$  6.83 (d,  $J = 10.0$  Hz, 2H), 6.15 (d,  $J = 10.0$  Hz, 2H), 3.26 (s, 1H), 1.73 (t,  $J = 8.16$  Hz, 2H), 1.24 (m, 2H), 0.91 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR  $\delta$  186.09, 152.05, 127.95, 69.912, 42.041, 17.00, 14.27. Anal. Calcd for  $\text{C}_9\text{H}_{12}\text{O}_2$ : C, 71.03; H, 7.95. Found: C, 71.42; H, 8.22.

**4-Hydroxy-4-isopropylcyclohexa-2,5-dien-1-one (2e):**  $^1\text{H}$  NMR  $\delta$  7.26 (d,  $J = 10.2$  Hz, 2H), 6.61 (d,  $J = 10.2$  Hz, 2H), 3.65 (s, 1H), 1.65–1.51 (m, 1H), 1.60 (d,  $J = 6.9$  Hz, 3H), 1.36 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR  $\delta$  186.69, 151.51, 128.36, 71.48, 30.73, 22.42, 21.94.

**4-Hydroxy-4-sec-butylcyclohexa-2,5-dien-1-one (2f):**  $^1\text{H}$  NMR  $\delta$  6.81 (d,  $J = 10.3$  Hz, 2H), 6.18 (d,  $J = 10.3$  Hz, 2H), 3.73 (s, 1H), 1.22–1.08 (m, 3H), 0.91–0.79 (m, 6H);  $^{13}\text{C}$  NMR  $\delta$  188.22, 158.53, 132.61, 70.64, 44.14, 23.79, 13.63, 12.58.

**4-Hydroxy-4-octylcyclohexa-2,5-dien-1-one (2h):**  $^1\text{H}$  NMR  $\delta$  6.78 (d,  $J = 10.0$  Hz, 2H), 6.09 (d,  $J = 10.0$  Hz, 2H), 3.69 (s, 1H), 1.88–1.19 (m, 14H), 0.82 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR  $\delta$  185.97, 152.09, 127.91, 69.84, 39.89, 31.85, 29.69, 29.22, 29.07, 25.67, 22.57, 13.98. Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$ : C, 75.63; H, 9.97. Found: C, 75.31; H, 9.88.

**4-Hydroxy-4-(5-hexenyl)cyclohexa-2,5-dien-1-one (2i):**  $^1\text{H}$  NMR  $\delta$  6.83 (d,  $J = 10.0$  Hz, 2H), 6.18 (d,  $J = 10.0$  Hz, 2H), 5.84–5.68 (m, 1H), 5.05–4.92 (m, 2H), 2.53 (s, 1H), 2.04–1.44 (m, 4H), 1.36–1.25 (m, 4H);  $^{13}\text{C}$  NMR  $\delta$  185.72, 151.38, 138.35, 128.27, 114.77, 69.97, 39.67, 35.25, 28.94, 23.01. Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_2$ : C, 74.97; H, 8.39. Found: C, 75.19; H, 8.58.

**4-Hydroxy-4-(3-butenyl)cyclohexa-2,5-dien-1-one (2j):**  $^1\text{H}$  NMR  $\delta$  6.82 (d,  $J = 10.1$  Hz, 2H), 6.13 (d,  $J = 10.1$  Hz, 2H), 5.80–5.66 (m, 1H), 5.02–4.92 (m, 2H), 3.19 (s, 1H), 2.02–1.77 (m, 4H);  $^{13}\text{C}$  NMR  $\delta$  185.77, 151.45, 137.14, 128.08, 115.27, 69.62, 38.82, 27.74. Anal. Calcd for  $\text{C}_{10}\text{H}_{12}\text{O}_2$ : C, 73.15; H, 7.37. Found: C, 73.38; H, 7.39.

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