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Radical Addition to 1,4-Benzoquinones: Addition at *O*- versus *C*-Atom

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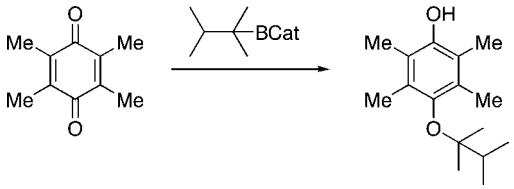
ABSTRACT



Addition of alkyl radicals generated from *B*-alkylcatecholboranes onto 1,4-benzoquinones leads to substituted hydroquinones in good overall yields. Formation of aryl ethers via a unique radical addition to the oxygen atom of the enone system is the main reaction when bulky secondary and tertiary alkyl radicals are used. Less hindered secondary and primary radicals give the expected 1,4-conjugate addition products.

In the last decades, numerous applications of radical chemistry were described in organic synthesis taking advantage of the formation of carbon−carbon bonds under mild reaction conditions.[1] Organoboranes are reactive radical precursors that can be employed for a wide range of radical reactions involving primary, secondary, and tertiary alkyl radicals.[2]

2-Substituted hydroquinones and benzoquinones are common subunits in biologically active secondary metabolites. Incorporation of this framework during the synthesis of natural products remains a challenging problem. In our studies toward the total synthesis of frondosin A and B (Figure 1), we became interested in developing efficient procedures to introduce such aromatic moieties.

Preparative conjugate addition of radicals onto 1,4-benzoquinone derivatives is described in the literature.[3] From a synthetic point of view, addition of radicals generated via decarboxylation of 2-pyridinethione derivatives[4] and from trialkylboranes[5] is the most promising. However, in the trialkylborane approach only one out of the three alkyl groups is transferred. Therefore, the method is restricted to trialkylboranes obtained by hydroboration of easily available and cheap alkenes.

Recently, we have demonstrated that 2-alkylbenzo[*d*]-[1,3,2]dioxaboroles (*B*-alkylcatecholboranes), easily available by hydroboration of alkenes, are excellent radical precursors.[6] For instance, we have reported a modified version of the conjugate addition of organoboranes to enones and enals originally developed by Brown and Negishi.[7] This procedure involves the hydroboration of an alkene with catecholborane followed by addition to an α,β-unsaturated ketone or aldehyde in the presence of oxygen to initiate the radical

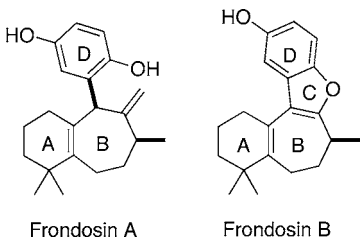


Figure 1. Sesquiterpene hydroquinones frondosin A and B

(1) (a) *Radicals in Organic Synthesis;* Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vols. 1 and 2. (b) Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon−Carbon Bonds*; Pergamon Press: Oxford, UK, 1986. (c) Zard, S. *Advances in Free Radical Chemistry*; Oxford University Press: Oxford, UK, 2003.

(2) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415−3434. Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71−106.

(3) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 5307−5314 and references therein.

10.1021/ol0624629 CCC: $33.50
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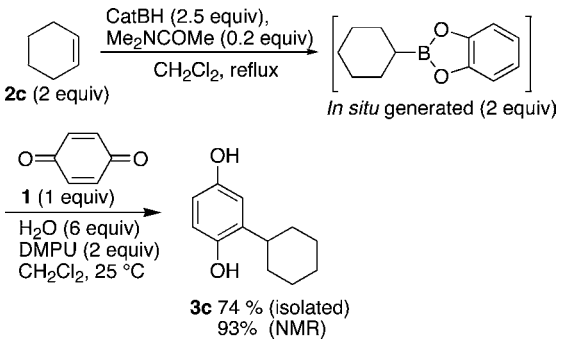
process.[8] Primary, secondary, and tertiary alkyl groups are efficiently added to α,β-unsaturated aldehydes and ketones that are unsubstituted or monosubstituted at the β-position. We describe here our effort to extend this chemistry to 1,4-benzoquinones. An astonishing radical addition to the oxygen atom of 1,4-benzoquinones is reported.

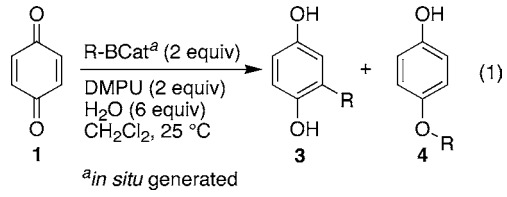
B-Alkylcatecholboranes are easily obtained by hydroboration of olefins with commercially available catecholborane.[9] The reaction conditions were optimized by using cyclohexene **2c** (Scheme 1). Using 2 equiv of *B*-alkylcatecholborane

Scheme 1. Hydroboration and Subsequent in Situ Radical Addition to 1,4-Benzoquinone



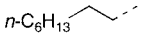
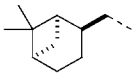
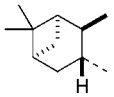
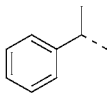
generated in situ by *N*,*N*-dimethylacetamide catalyzed hydroboration and 1 equiv of 1,4-benzoquinone turned out to be the best conditions for this transformation. Under these reaction conditions, oxidation of the 2-cyclohexyl-1,4-hydroquinone **3c** to the corresponding substituted 1,4-quinone derivative could be prevented.[10] The desired 2-cyclohexyl-1,4-hydroquinone **3c** was produced in 93% yield (NMR yield, separation of the product from catechol was not attempted at this stage, see Table 1 entry 3 for the isolated yield). The reactions were run under nitrogen and no extra addition of oxygen was necessary to initiate the reaction (Scheme 1).

Reactions with several alkenes according to eq 1 were



investigated next. The results are summarized in Table 1. The addition of primary radicals derived from 1-octene **2a** and β-pinene **2b** (entries 1 and 2) onto 1,4-benzoquinone affords the expected 2-alkylated 1,4-hydroquinones **3a** and **3b** in 72% and 95% yield, respectively. Reaction with

Table 1. Addition of *B*-Alkylcatecholborane to 1,4-Benzoquinone According to Eq 1

entry	R	3 yield[a]	4 yield[a]
1[b]		**3a** 72%	
2[b]		**3b** 95%	
3[b]		**3c** 74 %	
4[b]		**3d** 36%	**4d** 39%
5[c]		**3e** 9%	**4e** 61%
6[b]		**3f** 16%	**4f** 60%

[a] Isolated yields. [b] Hydroboration catalyzed by Me_2NCOMe. [c] Hydroboration catalyzed by $(Ph_3P)_3RhCl$.

cyclohexene (entry 3) results in the formation 2-cyclohexyl-1,4-hydroquinone **3c** in 74% yield (entry 3). The reaction with α-pinene gives the expected hydroquinone **3d** in 36% accompanied by the aryl ether **4d** in 39% yield (entry 4). A similar result is obtained with styrene when the hydroboration is catalyzed by the Wilkinson's catalyst (entry 5). The aryl ether **4e** is the major product (61%) and the conjugate addition product **3e** is only formed in 9% yield. The tertiary thexyl radical generated from 2,3-dimethylbut-2-ene **2f** (entry 6) affords the aryl ether **4f** (60% yield) together with **3f** (16%).

The reaction was also tested with duroquinone (= 2,3,5,6-tetramethylbenzoquinone) (Scheme 2). Reaction with *B*-cyclohexylcatecholborane does not afford any identified addition product. Interestingly, *B*-thexylcatecholborane (= thexyl = 2,3-dimethylbut-2-yl = 1,1,2,2-tetramethylethyl) gives the *O*-addition product in 80% yield as the only identified product.

A radical mechanism is expected for the formation of the *C*-addition product in analogy to the work of Brown on conjugate addition of trialkylboranes to enones[2,11] as well

(4) See ref 3 and: (a) Barton, D. H. R.; Sas, W. *Tetrahedron* **1990**, *46*, 3419−3430. (b) Ling, T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2002**, *124*, 12261−12267. (c) Ling, T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3089−3091. (d) Yamago, S.; Hashidume, M.; Yoshida, J.-i. *Tetrahedron* **2002**, *58*, 6805−6813.

(5) (a) Hawthorne, M. F.; Reintjes, M. *J. Am. Chem. Soc.* **1964**, *86*, 951. (b) Hawthorne, M. F.; Reintjes, M. *J. Am. Chem. Soc.* **1965**, *87*, 4585−4587. (c) Kabalka, G. W. *J. Organomet. Chem.* **1971**, *33*, C25−C28. (d) Bieber, L. W.; Rolim Neto, P. J.; Generino, R. M. *Tetrahedron Lett.* **1999**, *40*, 4473−4476.

(6) Schaffner, A.-P.; Renaud, P. *Eur. J. Org. Chem.* **2004**, 2291−2298.

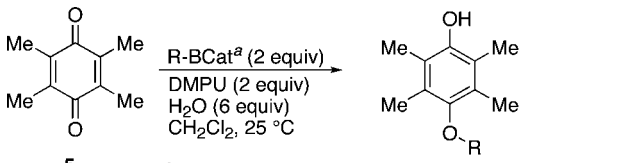
(7) Brown, H. C.; Negishi, E.-I. *J. Am. Chem. Soc.* **1971**, *93*, 3777−3779.

(8) Ollivier, C.; Renaud, P. *Chem. Eur. J.* **1999**, *5*, 1468−1473.

(9) Catalysis by Me_2NCOMe: Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 3224−3225. Catalysis with Wilkinson's catalyst: Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* **1991**, *56*, 1670−1672.

(10) 1,4-Benzoquinone oxidizes substituted 1,4-hydroquinone derivatives. This oxidation occurs due to a lower oxidation potential of the substituted quinones compared to the one of their nonsubstituted counterparts. For reviews on this topic see: (a) *The Chemistry of the Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vols. 1 and 2. (b) *Naturally Occurring Quinones IV*: *Recent Advances*, 4th ed.; Thomson, R. H., Ed.; Blackie Academic & Professional: London, UK, 1997.

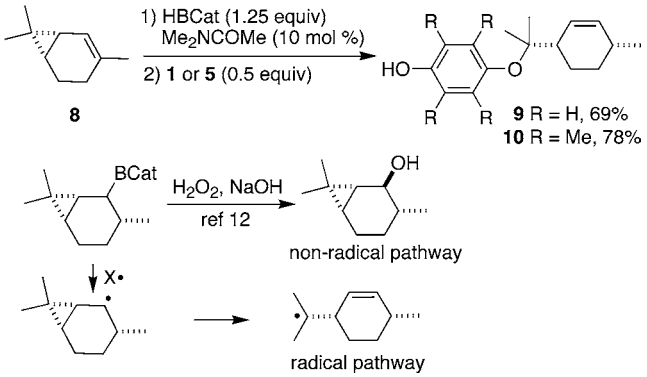
Scheme 2. Addition of *B*-Alkylcatecholboranes to Duroquinone



as our related work starting with *B*-alkylcatechoboranes.[6] In both reactions, no addition of initiator such as oxygen was necessary when an efficient radical trap such as a vinyl ketone was used. Traces of oxygen coming presumably from the solvent were sufficient to initiate the reaction. Since 1,4-benzoquinone is a particularly reactive radical trap, we expected the same phenomenon to occur since no extra oxygen was added for the reaction described in eq 1 (Table 1). Several attempts to run the reaction starting from α-pinene **2d** under oxygen free conditions with carefully degassed solvents and reagents in a glove box afforded the reaction products **3d** and **4d** in similar yield and ratio as the ones reported in Table 1 (entry 4). This indicates that either the reaction does not involve a radical intermediate or that a minute amount of oxygen is sufficient to initiate a particularly efficient radical chain process. Another type of radical initiation involving for example a single electron-transfer process cannot be excluded at the moment. The radical nature of the mechanism was further investigated by running a reaction with (+)-2-carene **8**, a well-established radical probe for reactions involving *B*-alkylcatecholborane derivatives.[12] Hydroboration of (+)-2-carene **8** followed by addition to 1,4-benzoquinone **1** and duroquinone **5** under our standard reaction conditions affords the aryl ethers **9** and **10** as exclusive product in 69% and 78% yield, respectively (Scheme 3). Compounds **9** and **10** result from a ring opening of the cyclopropyl ring demonstrating the presence of radical intermediates. The ring-opening process does not occur under non-radical conditions such as for instance the oxidative treatment with alkaline hydrogen peroxide.[12]

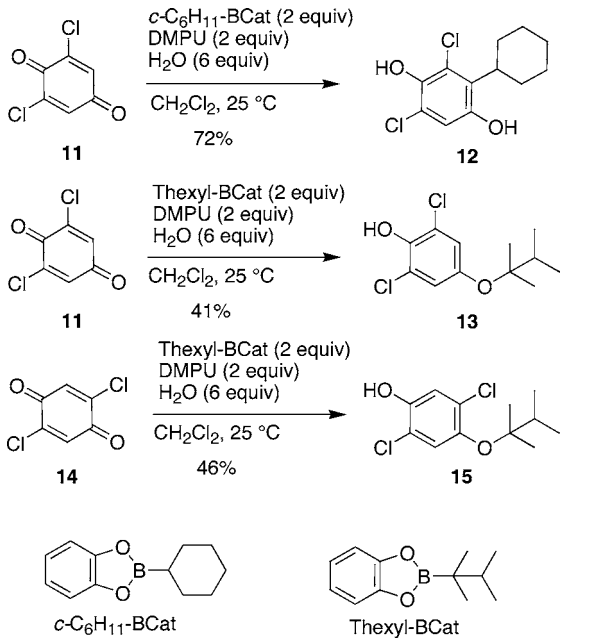
The reaction proceeds similarly with substituted 1,4-benzoquinone derivatives. By adding the cyclohexyl radical onto 2,6-dichloro-1,4-benzoquinone **11**, a clean addition at the carbon atom could be observed that gives the hydroquinone **12** in 72% yield (Scheme 4). Reaction of **11** with *B*-thexylcatecholborane affords the *O*-addition product **13** in 41% yield as the major and only isolated product. The regioselectivity of this reaction, i.e., addition at the less substituted C4-carbonyl group, supports a radical mechanism where no activation of 1,4-benzoquinone by complexation of the carbonyl group by the organoborane is occurring since

Scheme 3. Reaction of the Radical Probe 2-Carene **8** with 1,4-Benzoquinone **1** and Duroquinone **5**



such an activation should favor the addition at the more hindered C1 carbonyl group.[13] However, reversible complexation of both carbonyl group cannot be excluded.[14]

Scheme 4. Addition of *B*-Alkylcatecholboranes to Bischlorinated Quinones



Addition of *B*-thexylcatecholborane to 2,5-dichloro-1,4-benzoquinone **14** gives the *O*-addition product **15** in 46% yield. The similarity of product distribution between the reaction of benzoquinone **1** and dichlorobenzoquinones **11** and **14** supports further a radical mechanism for the formation of *O*- and *C*-addition products. Indeed, a plausible electron-

(11) Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed.* **1972**, *11*, 692−700.

(12) We have established that its hydroboration followed by an oxidative treatment with alkaline hydrogen peroxide leads to the corresponding alcohols without opening of the cyclopropane ring: Cadot, C.; Dalko, P. I.; Cossy, J.; Ollivier, C.; Chuard, R.; Renaud, P. *J. Org. Chem.* **2002**, *67*, 7193−7202.

(13) Reaction of alkylaluminum dichlorides with 1,4-quinones gives aryl ethers via a radical−radical coupling process. Complexation of the carbonyl oxygen atom by aluminum is occurring in this particular case: Florjanczyk, Z.; Szymanska-Zachara, E. *J. Organomet. Chem.* **1983**, *259*, 127−137.

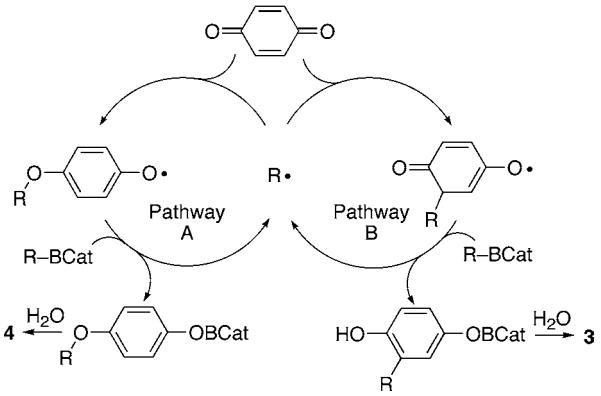
(14) Such a complexation during the addition of trialklyboranes to enones has been proposed: Beraud, V.; Gnanou, Y.; Walton, J. C.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195−1198.

transfer mechanism leading to the aryl ether and involving formation of a carbenium ion should have been favored with the bischlorinated quinones since they are better oxidants than non-chlorinated quinones.

Since the conversion of **11** to **13** suggests that the reaction is a simple radical addition to the noncomplexed 1,4-benzoquinone, we decided to investigate the reaction of the Barton ester derived from pivalic acid with 1,4-benzoquinone **1** (see the Supporting Information for experimental details). Under our reaction conditions (excess of the Barton ester relative to the quinone), no product of *C*-addition was isolated and only 4-*tert*-butoxyphenol resulting from the addition at the oxygen atom was obtained in low yield (24%). This observation supports our assumption that complexation of the quinone by the organoboron compound is not required for the addition at the oxygen atom of a quinone. The low yield of the Barton ester reaction results presumably from the lack of an efficient propagation step. The mechanistic details of this low-yielding transformation have not been further examined.

On the basis of these results, a possible reaction mechanism rationalizing the formation of *C*- and *O*-addition products during the addition of *B*-alkylcatecholboranes to quinones is depicted in Scheme 5. The quinone reacts with an alkyl radical via either *O*-addition (Pathway A, 1,6-addition) or *C*-addition (Pathway B, 1,4-addition).[15,16] The radical adducts react rapidly with R-BCat to produce a boronphenolate and the alkyl radical R•. Hydrolysis of the boronphenolates affords the hydroquinone **3** and the aryl ether **4**.

Scheme 5. Proposed Mechanism for the Addition of *B*-Alkylcatecholborane to 1,4-Benzoquinone



In conclusion, addition of alkyl radicals generated from *B*-alkylcatecholboranes onto 1,4-benzoquinones leads to substituted hydroquinone derivatives in good overall yield. Formation of aryl ethers via a unique radical addition to the oxygen atom of the enone system is the main reaction when bulky secondary and tertiary alkyl radicals are used. Less hindered secondary and primary residues give the normal 1,4-conjugate addition products. The unexpected C−O bond-forming reaction represents an interesting and unique procedure for the conversion of organoboranes to aryl ethers.

Acknowledgment. We thank the Swiss National Science Foundation (Project 20-103627) for financial support and BASF Corporation for the gift of catecholborane.

Supporting Information Available: Experimental procedures and product characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Addition of acyl radicals to carbonyl oxygen atom is reported in the literature: (a) Urry, W. H.; Nishihara, A.; Niu, J. H. Y. *J. Org. Chem.* **1967**, *32*, 347−352. (b) Kuivila, H. G.; Walsh, E. J., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 571−576. (c) Kuivila, H. G.; Walsh, E. J., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 576−581. (d) Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 1833−1834.

(16) See ref 13 and: Ferreira, V. F.; Schmitz, F. J. *J. Organomet. Chem.* **1998**, *571*, 1−6. Addition of the 2-cyano-2-propyl radical generated by thermal decomposition of AIBN to 1,4-benzoquinone has been described and formation of aryl ethers via either *C*-addition followed by a rearrangement or via direct *O*-addition has been postulated: Giorgini, E.; Tommasi, G.; Stipa, P.; Tosi, G.; Littarru, G.; Greci, L. *Free Radical Res.* **2001**, *35*, 63−72. See also: Buckley, R. P.; Rembaum, A.; Swarc, M. *J. Chem. Soc.* **1958**, 3442. Simandi, T. L.; Rockenbauer, A.; Simandi, L. *Eur. Polym. J.* **1995**, *31*, 555−558.