propenyl)cyclohexanone oxime, 59239-07-5; 4-(2-hydroxyethyl)-benzaldehyde oxime, 102494-22-4; 2-(4-hydroxybutyl)cyclohexanone oxime, 102494-23-5; cyclohexanone (2,4-dinitrophenyl)hydrazone, 1589-62-4; diphenylmethanone (2,4-dinitrophenyl)hydrazone, 1733-62-6; benzaldehyde (2,4-dinitrophenyl)hydrazone, 1157-84-2; 1,2,3,4-tetrahydronaphthalen-1-one (2,4-dinitrophenyl)hydrazone, 853-95-2; 1,2-diphenylethanone (2,4-dinitrophenyl)hydrazone, 5637-51-4; 1-[4-(2-hydroxyethyl)-phenyl]ethanone (2,4-dinitrophenyl)hydrazone, 102494-24-6; 2-(3-propenyl)cyclohexanone (2,4-dinitrophenyl)hydrazone, 1044-31-1; 2-cyclohexenone (1,2-dinitrophenyl)hydrazone, 1459-31-0; 2-(2,3-dihydroxypropyl)cyclohexanone (2,4-dinitrophenyl)-hydrazone, 102494-26-8.

Communications

A General, Regiospecific Synthesis of Highly Substituted Quinones

Summary: A general route to a wide variety of substituted quinones (furyl, indolo, pyrrolo, quinolino, naphtho, and anthra) has been developed via the thermolysis (160 °C, xylene) and subsequent oxidation (air or Ce^{4+}) of 4-hydroxy-4-substituted-cyclobutenones (eq 1) and 2-hydroxy-2-substituted-benzocyclobutenones which were formed by the regioselective addition of an appropriate aryl or heteroaryl (etc.) lithium reagent to the corresponding cyclobutenedione.

Sir: As a result of our long-standing interest in transition-metal complexes of cyclobutenediones and benzocyclobutenediones,[2] we began probing the reaction of derivatives of these very interesting organic molecules with low-valent metal species. In an attempt to prepare a new metallacycle, 4-hydroxy-4-phenyl-2,3-dimethylcyclobutenone (prepared by addition of PhLi to 3,4-dimethylcyclobutenedione in 44% yield) was heated with η^5-CpCo(CO)$_2$ at 160 °C in xylene for 5 min, when an exceptionally clean thermal transformation of the organic substrate occurred to give 2,3-dimethylnaphthohydroquinone. After exposure to air, 2,3-dimethylnaphthoquinone was isolated in 87% yield. A control reaction in the absence of η^5-CpCo(CO)$_2$ gave the same results. This unexpected reaction was particularily intriguing because thermal rearrangements of 4-vinylcyclobutenones have provided a significant synthetic route to highly substituted phenols,[3] but cyclobutenediones and benzocyclobutenediones (which can be readily prepared from simple starting materials[4]) have not been investigated in any detail as starting materials for a similar synthesis of highly functionalized quinones by thermal rearrangement of 4-hydroxy-4-vinyl(or aryl or hetero)cyclobutenones.[5]

Scheme I

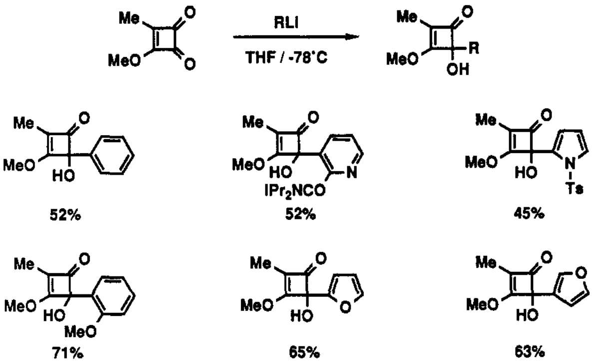
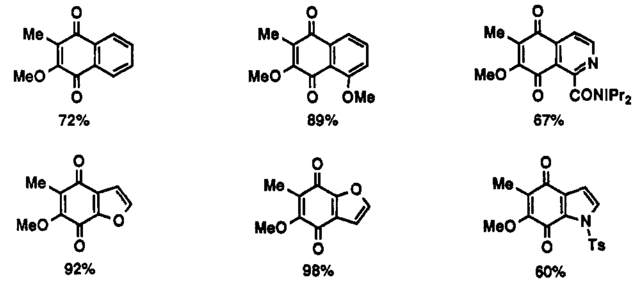
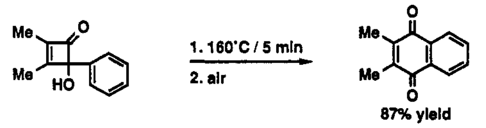


Table I. Quinones by Thermolysis of 4-Aryl(or hetero)-4-hydroxycyclobutenones





A further investigation of the thermal reaction of 4-(aryl or heteroaryl)-4-hydroxy-2,3-disubstituted-cyclobutenones

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(1) Fellow of the Alfred P. Sloan Foundation, 1983–1987; Camille and Henry Dreyfus Teacher Scholar, 1986–1991.

(2) Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Blount, J. F. *J. Organomet. Chem.* **1980**, *202*, C73. Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397. Baysdon, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771. South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 4181. Liebeskind, L. S.; Baysdon, S. L.; Chidambaram, R.; Goedken, V. L. *Organometallics*, in press. Liebeskind, L. S.; Leeds, J. P.; Baysdon, S. L.; Iyer, S. I. *J. Am. Chem. Soc.* **1984**, *106*, 6451. Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S. I.; Leeds, J. P. *Tetrahedron, Symp.* **1985**, *41*, 5839. Liebeskind, L. S.; Jewell, C. F., Jr. *J. Organomet. Chem.* **1985**, *285*, 305. Jewell, C. F., Jr.; Liebeskind, L. S.; Williamson, M. *J. Am. Chem. Soc.* **1985**, *107*, 6715.

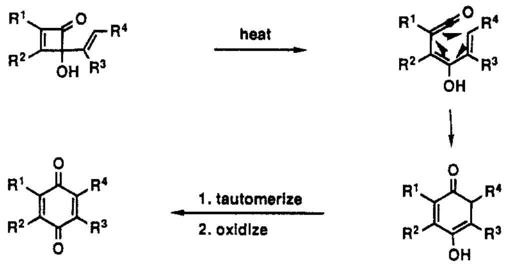
(3) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1674. For earlier work on thermal rearrangements of cyclobutenones, see footnote 8 in this reference.

(4) Benzocyclobutenediones: South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815 and references therein. Cyclobutenediones: Liebeskind, L. S., Baysdon, S. L. *Tetrahedron Lett.* **1984**, *25*, 1747 and references therein.

(5) A novel variant of this chemistry using 4-alkynyl-2,3-dimethoxy-4-(trimethylsiloxy)cyclobutenones has been described recently by Moore: Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.

0022-3263/86/1951-3065$01.50/0

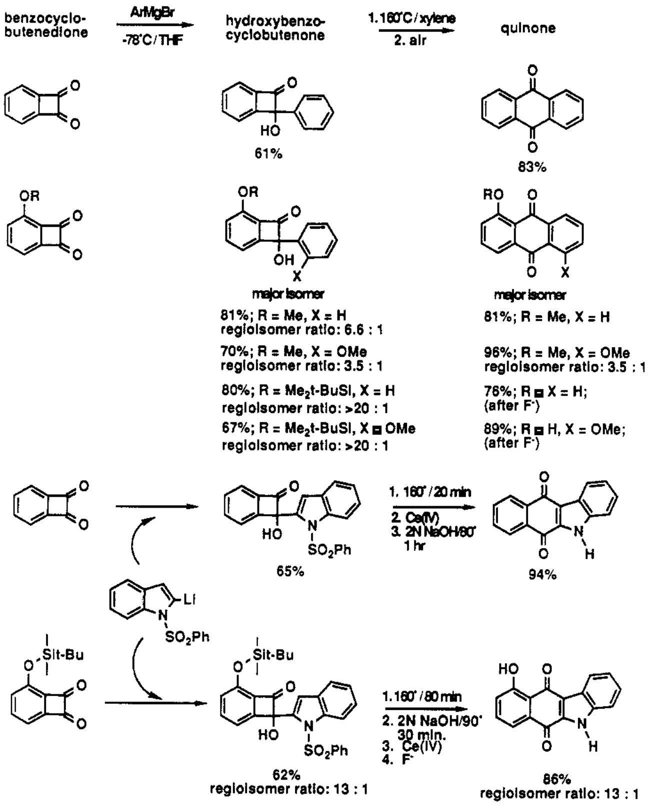
Scheme II



demonstrated that the unexpected reaction of eq 1 was only one example of a very general process for the regiospecific synthesis of highly substituted quinones.[6] For example, 3-methoxy-4-methylcyclobutenedione[7] reacted with high regioselectivity with PhLi, 2-lithioanisole, 2-lithiofuran, 3-lithiofuran, 2-lithio-*N*-(*p*-toluenesulfonyl)pyrrole, and 3-lithio-2-(*N*,*N*-diisopropylamino)pyridine to provide the adducts shown in Scheme I. On heating a xylene solution of these molecules in an oil bath maintained at 160 °C, clean transformation of each substrate occurred within 20 min to 4 h to produce the corresponding quinones after exposure to $FeCl_3$ (Table I). Regioselective reaction at the more electrophilic carbonyl group adjacent to the methoxy substituent was established for the adduct from 2-lithioanisole by subsequent conversion to the known quinone, 5-methoxy-3-hydroxy-2-methyl-1,4-naphthoquinone (droserone 5-methyl ether).[8] The regioselectivity of the other reactions was presumed to follow analogously.

This chemistry was also extended to the reaction of benzocyclobutenediones.[4] Swenton has developed an elegant route to anthraquinones based on the addition of vinyllithium reagents to benzocyclobutenedione *monoketals*;[9] he reported an attempted reaction of an organolithium reagent with benzocyclobutenedione that failed.[10] We suspected that the difficulties with the addition of an organometallic to benzocyclobutenedione might be alleviated by quenching the reaction at low temperature, and our expectations were fully realized. Both benzocyclobutenedione and 3-methoxybenzocyclobutenedione[11] reacted with a variety of nucleophiles to produce good yields of the corresponding adducts. Although 3-methoxybenzocyclobutenedione showed only moderate regioselectivity in its reactions with the nucleophiles used in this study, very high selectivity could be achieved through the use of 3-(*tert*-butyldimethylsiloxy)benzocyclobutenedione[12] (Table II). Proof of the regiochemistry of the nucleophilic addition is based on the formation of 1-hydroxy-5-methoxyanthraquinone[13] from the adduct of anisole-2-MgBr with 3-(*tert*-butyldimethylsiloxy)benzocyclobutenedione (Table II). Simple thermolysis of the benzocyclobutenone substrates provided high yields of quinones after oxidation by exposure to air or ceric ammonium nitrate.

Table II. Anthraquinones by Thermolysis of 2-Aryl-2-hydroxybenzocyclobutenones



By analogy with other work on the thermolysis of cyclobutenones,[3,5] the unprecedented formation of quinones as described in this manuscript probably follows the vinyl ketene route shown in Scheme II, and it is significant in that the ring opening of the cyclobutenone must selectively occur to rotate the OH group away from the ketene functionality. In a recent publication,[14] Houk has addressed the issue of inward vs. outward rotation of 3- and 3,4-substituted cyclobutenes and noted that outward rotation increased as the p-donor nature of the substituent increased. Specifically, outward rotation of an alkoxy substituent was 14 kcal/mol easier than inward rotation. Additionally, evidence was presented supporting the postulate that steric effects were of secondary importance in controlling the direction of rotation. The synthetic ramifications of this observation are obvious—it is not necessary to protect the alcohol functional group to achieve excellent yields of quinones.

In conclusion, we have developed a truly general synthesis of highly substituted quinones. The method relies on the availability of cyclobutenediones and benzocyclobutenediones as starting materials, and numerous methods are known for the preparation of these compounds. To a chemist inexperienced in the synthesis and handling of these molecules, they may seem fraught with synthetic

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(6) Similar results have been independently observed by H. Moore and co-workers: Perri, S. P.; Foland, L. D.; Decker, O. H. W.; Moore, H. *J. Org. Chem.*, following communication in this issue.

(7) Numerous syntheses of this material have been described: Chickos, J. S. *J. Am. Chem. Soc.* **1970**, *92*, 5749. Bellus, D.; Fischer, H.; Greuter, H.; Martin, P. *Helv. Chim. Acta* **1978**, *61*, 1784. Brady, W. T.; Watts, R. D. *J. Org. Chem.* **1980**, *45*, 3525. Dehmlow, E. V.; Schell, H. G. *Chem. Ber.* **1980**, *113*, 1. Bellus, D.; Martin, P.; Sauter, H.; Winkler, T. *Helv. Chim. Acta* **1980**, *63*, 1130.

(8) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic Press: New York, 1971; p 236.

(9) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. Anderson, D. K.; Coburn, C. E.; Haag, A. A.; Swenton, J. S. *Tetrahedron Lett.* **1983**, *24*, 1329. Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1801.

(10) Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182.

(11) We have developed a convenient new preparation of 3-methoxybenzocyclobutenedione by utilizing the simple synthesis of 6-methoxybenzocyclobutenone reported by Stevens (Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 3293) followed by double benzylic bromination with NBS and acid hydrolysis to the dione exactly following the procedure used by us to prepare the parent benzocyclobutenedione.[4] For experimental details refer to the supplementary material.

(12) Preparation: 3-methoxybenzocyclobutenedione prepared as described in footnote 12 was demethylated with excess $AlCl_3$ in CH_2Cl_2 at reflux and then silylated according to standard procedures.

(13) Klemore, K.; Gehrke, G. German Patent 117441, 1964; *Chem. Abstr.* **1964**, *61P*, 16027f.

(14) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.

difficulties. To the contrary, it has been our experience over the last 6 years that these molecules can be readily synthesized and are easy to handle. And with the generality of the quinone synthesis described herein, it is anticipated that newer, even simpler methods of cyclobutenedione synthesis will be explored in the near future. By combining the chemistry described in this manuscript with the numerous procedures known for directed metalation of aryl and heterocyclic systems,[15] a powerful procedure is at hand for the synthesis of quinone based biologically active molecules.

Acknowledgment. This investigation was supported by PHS Grant CA 40157 awarded by the National Cancer Institute, DHHS. We are grateful to Professor Harold Moore of U.C. Irvine for communicating his results to us prior to publication and to Dr. Romanworq Ferede and Mr. Charles McSwain for their efforts on the project.

Supplementary Material Available: Complete experimental details for the synthesis of the compounds described in this manuscript (13 pages). Ordering information is given on any current masthead page.

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[15] Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. For the two most recent articles in this area see: Shankaran, K.; Soan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997 and Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. *J. Am. Chem. Soc.* **1985**, *107*, 6312.

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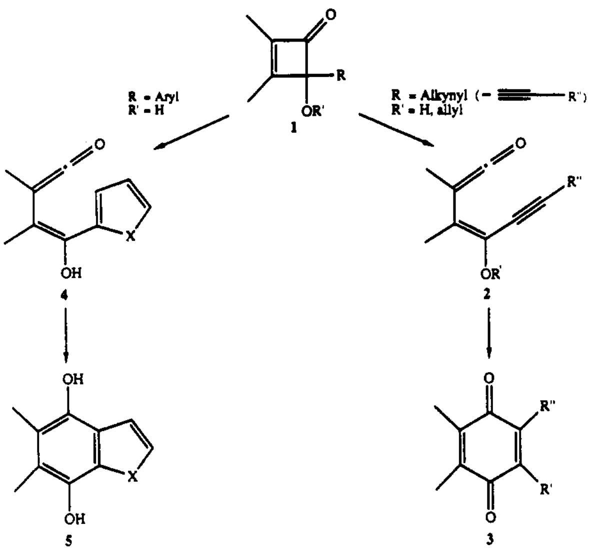
Synthesis of Benzoquinones and Annulated Derivatives from Conjugated Ketenes

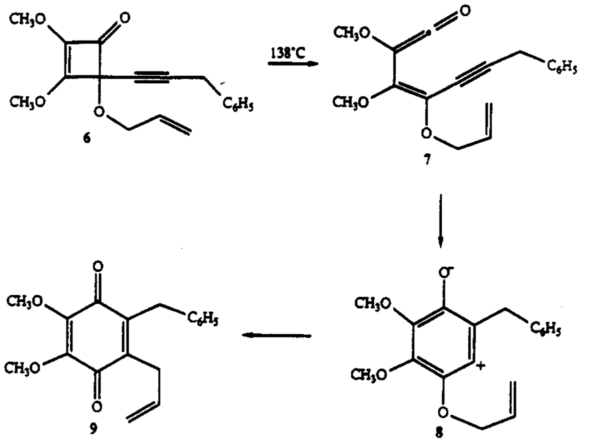
Summary: A new convergent general synthesis of annelated quinones and highly substituted benzoquinones from in situ generated conjugated ketenes is presented.

Sir: Reported here are two related general synthetic routes to highly substituted benzoquinones and annulated derivatives (Scheme I). First, 4-alkynyl-4-hydroxy- and 4-alkynyl-4-(allyloxy)cyclobutenones **1** (R = alkynyl) were found to undergo an interesting rearrangement (138 °C, *p*-xylene) to the quinones **3** in which R′ is a proton or an allyl group, respectively.[1] Second, 4-aryl-4-hydroxycyclobutenones **1** (R = aryl) were found to rearrange to the hydroquinones **5** (X = S, O, $-CH=CH-$) when subjected to the same conditions.[2,3] These transformations are suggested to be dictated by a favored conrotatory ring opening of the cyclobutenones **1** such that the electron-donating substituents (OR′) rotate outward.[4] Thus, the configuration of the resulting ketenes **2** and **4** is such that their electrophilic site can directly interact with the proximal alkyne or aryl group.

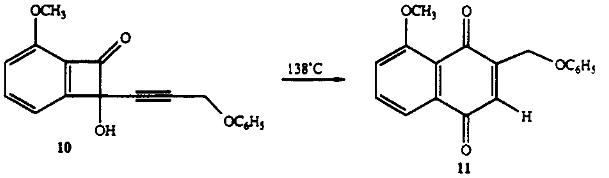
Scheme I



Scheme II



Scheme III



A particularly interesting example is that involving the allyl group migration (Scheme II). Here, the starting cyclobutenone **6** was prepared from 2,3-dimethoxycyclobutenedione via initial alkynylation ($LiC\equiv CCH_2C_6H_5$, THF, −78 °C; 5% NH_4Cl; 65%) followed by allylation of the resulting alcohol ($ICH_2CH=CH_2$, Ag_2O, K_2CO_3, dioxane, 25 °C; 74%).[5] Thermolysis of **6** for 1 h in refluxing *p*-xylene gave the benzoquinone **9** (76%). This rear-

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[1] In a related report, 4-alkynyl-4-(trimethylsiloxy)cyclobutenones were shown to rearrange to trimethylsilyl-substituted benzoquinones. See: Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.

[2] This reaction has been independently discovered. See: Liebeskind, L. S.; Iyer, S.; Jewell, C. F. Jr. *J. Org. Chem.*, previous communication in this issue.

[3] This is analogous to the ring expansion of other 4-arylcyclobutenones lacking the 4-OR group to phenols. See: Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1939**, *61*, 2619. Smith, L. I.; Hoehn, H. H. *Ibid.* **1941**, *63*, 1181. Nieuwenhuis, J.; Arens, J. F. *Rec. Trav. Chim. Pays-Bas* **1958**, *77*, 1153. Wittmann, H.; Illi, V.; Sterk, H.; Ziegler, E. *Monatsh. Chem.* **1968**, *99*, 1982. Zubovics, Z.; Wittmann, H. *Liebigs Ann. Chem.* **1972**, *765*, 15. Kipping, C.; Schiefer, H.; Schonfelder, K. *J. Prakt. Chem.* **1973**, *315*, 887. Neuse, E. W.; Green, B. R. *Liebigs Ann. Chem.* **1974**, *9*, 1534. Mayr, H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 500. Huisgen, R.; Mayr, H. *J. Chem. Soc., Chem. Commun.* **1976**, 55. Huisgen, R.; Mayr, H. *Ibid.* **1976**, 57. Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1674.

[4] A theoretical evaluation of this conrotatory mode which is in agreement with this prediction has been reported for the electrocyclic ring openings of cyclobutenes. See: Houk, K. N.; Randan, N. G. *J. Am. Chem. Soc.* **1985**, *107*, 2099. For an experimental analogy in the cyclobutenone series, see: Baldwin, J. E.; McDaniel, M. C. *Ibid.* **1968**, *90*, 611.

[5] All new compounds gave satisfactory C,H analyses or high resolution mass spectroscopy data. Their assigned structures are consistent with spectral data.