Lewis Acid-Directed Reactions of Quinones with Styrenyl Systems: The Case of 2-Methoxy-3-methyl-1,4-benzoquinone

Thomas A. Engler* and Rajesh Iyengar

Department of Chemistry, 2010 Malott, University of Kansas, Lawrence, Kansas 66045

Received October 21, 1997

Reactions of 2-methoxy-3-methyl-1,4-benzoquinone with various (*E*)-1-propenylbenzenes promoted by 1 equiv of Ti(IV), as a 1:1 mixture of $TiCl_4$−Ti(O-*i*-Pr)$_4$, produce *rel*-(1*S*,6*R*,7*R*,8*R*)-8-aryl-4,7-dimethyl-3-methoxybicyclo[4.2.0]oct-3-ene-2,5-diones **3** and *trans*-2-aryl-3,7-dimethyl-6-methoxy-2,3-dihydro-5-benzofuranols **5** as the major products. Reactions promoted by 2 equiv of Ti(IV) as a 1:1 mixture of $TiCl_4$−Ti(O-*i*-Pr)$_4$ or 1 equiv of either $TiCl_4$, $SnCl_4$, or BF_3·OEt_2 give regioisomeric *rel*-(1*R*,6*S*,7*R*,8*R*)-7-aryl-4,8-dimethyl-3-methoxybicyclo[4.2.0]oct-3-ene-2,5-diones (**4**) and/or *trans*-2-aryl-3,6-dimethyl-7-methoxy-2,3-dihydro-5-benzofuranols (**6**). A mechanism involving regioselective coordination of the various Lewis acids to the quinone is used to explain the formation of the products. These reactions demonstrate the effective regiocontrol exerted over the reactions by the nature of the Lewis acid promoters. Cyclobutanes **3** and **4** cleanly undergo rearrangement to the corresponding benzofuranols **5** and **6** on treatment with protic acid. In contrast, reactions of 2-methoxy-1,4-benzoquinone promoted by either BF_3·OEt_2 or Ti(IV), as 1 equiv or excess amounts of $TiCl_4$ or 1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$, all afford the same regioisomeric products, i.e., *rel*-(1*S*,6*R*,7*R*,8*R*)-8-aryl-7-methyl-3-methoxybicyclo[4.2.0]oct-3-ene-2,5-dione **25** and/or *trans*-2-aryl-3-methyl-6-methoxy-2,3-dihydro-5-benzofuranol **27**.

Introduction

Lewis acid-promoted reactions of styrenyl systems with alkoxy-1,4-benzoquinones and mono-/bisimide derivatives regio- and stereoselectively give various products of formal 2 + 2, 3 + 2, and 5 + 2 cycloadditions in good yield.[1] Of particular interest is that the regioselectivity depends on the nature and the number of equiv of Lewis acid used as promoters. For example, $SnCl_4$-promoted reactions of 2-alkoxy-5-alkyl-1,4-benzoquinones give products from apparent activation of the quinone through bidentate binding of the Lewis acid to the C-1 carbonyl and the C-2 alkoxy oxygen, whereas reactions promoted by Ti(IV), as either $TiCl_4$ or mixtures of $TiCl_4$−Ti(O-*i*-Pr)$_4$, could be made to afford products from either bidentate activation or apparent monodentate activation through binding to the C-4 carbonyl group.[1c,2] Similar results were found with 2-alkoxy-4-*N*-(phenylsulfonyl)-1,4-benzoquinone monoimine.[1d]

Previous papers have described studies involving 2-alkoxy-1,4-benzoquinone and its 5- and 6-alkyl derivatives.[1] We now report results of reactions involving 2-methoxy-3-methyl-1,4-benzoquinone,[3] which completes our examination of all of the possible substitution patterns of monoalkyl-substituted alkoxy-1,4-benzoquinones. These studies further demonstrate that the regioselectivity of these reactions can be effectively manipulated by the nature of the Lewis acid.

Results and Discussion

The results of this study are summarized in Scheme 1 and Table 1. Reactions of various propenylbenzenes **1a**−**c** bearing electron-donating groups with quinone **2** promoted by 1 equiv (with respect to the quinone) of Ti(IV), as a 1:1 mixture of $TiCl_4$−Ti(O-*i*-Pr)$_4$, stereoselectively gave cyclobutanes **3** and dihydrobenzofurans **5** as the major products (Table 1, entries 1, 6, and 11). The former were accompanied by small amounts of regioisomeric cyclobutanes **4** in some instances. However, promotion of the same reactions with 1 equiv of $SnCl_4$, BF_3·OEt_2 or $TiCl_4$ or with 2 equiv of Ti(IV) as 1:1 $TiCl_4$:Ti(O-*i*-Pr)$_4$ gave primarily cyclobutanes **4** and dihydrobenzofurans **6** in good yield (Table 1, entries 2−5, 7−10, and 12−15); again, in some cases, minor amounts of cyclobutanes **3** and dihydrobenzofurans **5** were also found. Similarly, the less activated propenylenzenes **1d**/**e** could also be used in the latter reactions and resulted in **4** nearly exclusively. Reactions of **1d**/**e** promoted by mixtures of $TiCl_4$−Ti(O-*i*-Pr)$_4$ required more than 1 equiv

* To whom correspondence should be addressed. Tel.: (785) 864-4670. Fax: (785) 864-5396. E-mail: tengler@caco3.chem.ukans.edu.

(1) (a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931−7933. (b) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567−6587. (c) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588−6599. (d) Engler, T. A.; Chai, W.; LaTessa, K. O. *J. Org. Chem.* **1996**, *61*, 9297−9308. (e) Engler, T. A.; Meduna, S. P.; LaTessa, K. O.; Chai, W. *J. Org. Chem.* **1996**, *61*, 8598−8603. (f) Engler, T. A.; Gfesser, G. A.; Draney, B. W. *J. Org. Chem.* **1995**, *60*, 3700−3706.

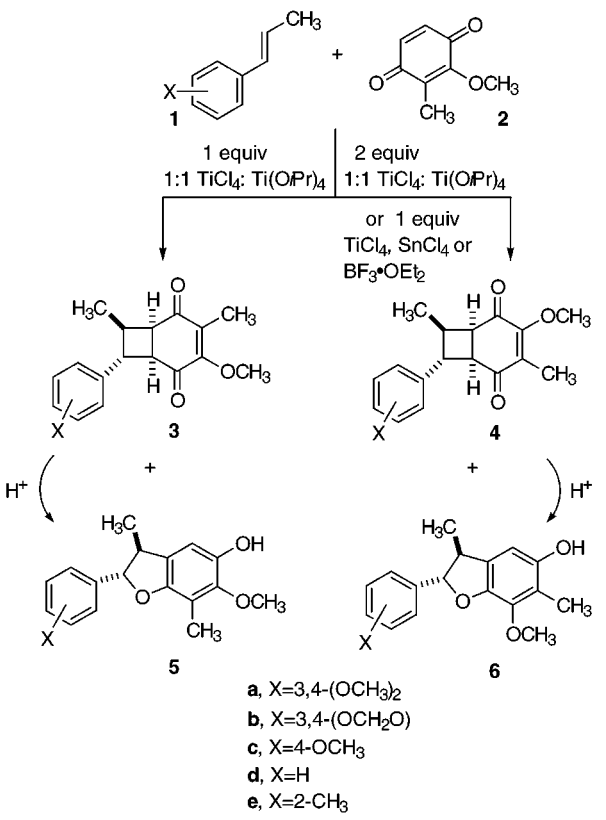
(2) (a) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5012−5014. For seminal studies on the importance of the site of Lewis acid coordination to quinones in Diels−Alder reactions, see: (b) Dickinson, R. A.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1972**, *50*, 2377−2380. (c) Stojanac, Z.; Dickinson, R. A.; Stojanac, N.; Woznow, R. J.; Valenta, Z. *Ibid.* **1975**, *53*, 616−618. (d) Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can J. Chem.* **1979**, *57*, 3308−3319. For studies with other 2-methoxy-1,4-benzoquinones, see: (e) Hendrickson, J. B.; Singh, V. *J. Chem. Soc., Chem. Commun.* **1983**, 837−838. (f) Hendrickson, J. B.; Haestier, A. M.; Stieglitz, S. G.; Foxman, B. M. *New. J. Chem.* **1990**, *14*, 689−693. (g) Engler, T. A.; Letavic, M. A.; Lynch, K. O., Jr.; Takusagawa, F. *J. Org. Chem.* **1994**, *59*, 1179−1183.

(3) Mandell, L.; Roberts, E. C. *J. Heterocycl. Chem.* **1965**, *2*(4), 479−480 and references therein.

(4) (a) Reactions of **1d** with 1 equiv of $TiCl_4$−Ti(O-*i*Pr)$_4$ produced unusual 2:1 propenylbenzene−quinone adducts; see ref 7. (b) The structures of these products also support the 5 + 2 cycloaddition mechanism.

S0022-3263(97)01937-3 CCC: $15.00
Published on Web 02/25/1998

Scheme 1



of Ti(IV) with respect to the quinone, or mixtures enriched in $TiCl_4$, and again gave cyclobutane **4**. The cyclobutanes **3** and **4** rearranged cleanly to dihydrobenzofurans **5** and **6**, respectively, upon treatment with protic acid (Table 2).

The stereochemistry of the cyclobutanes and the dihydrobenzofurans are assigned on the basis of HMQC (one bond C−H correlation)/HMBC (two- and three-bond C−H correlation) NMR (Figures 1 and 3) and $^1H-^1H$ NOE experiments (Figures 2 and 4). For example, in both **3a** and **4a**, the protons attached to C-7 and C-8, respectively, are clearly visible as multiplets at δ 2.95 and 2.99. HMQC experiments then establish the ^{13}C chemical shift of C-7 in **3a** and C-8 in **4a**. In **3a**, the other three methine protons appear as a triplet at δ 3.29 and partially resolved triplets at δ 3.41 and 3.43, and the HMQC spectrum establishes the chemical shifts of the carbons attached to them. Correlations between the C-7 methyl hydrogen signal and two of the latter carbon signals identify them as C-6 and C-8; they are distinguished from one another by an HMBC correlation between the methine hydrogen attached to one of them (C-8) with the aryl ring carbons. The signals for H-1 and C-1 are then assigned by default. Thus, for **3a** the

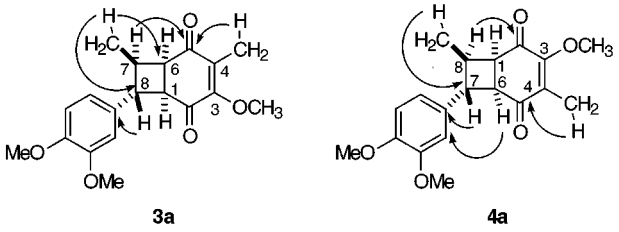


Figure 1. Selected HMBC data collected on **3a** and **4a**.

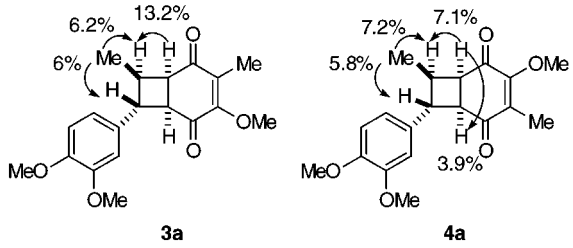


Figure 2. Selected $^1H-^1H$ NOE data collected on **3a** and **4a**.

Table 1. Lewis Acid-Promoted Cycloadditions of Propenylbenzenes with 2-Methoxy-3-methyl-1,4-benzoquinone[a]

entry	styrene (X)	Lewis acid (total equiv of Ti(IV)with respect to **2**)	*T* (°C)	time (h)	yield[b] (%) **3/4** (ratio)[c]	**5**	**6**
1	3,4-$(OCH_3)_2$	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78	8	41 (4:1)	59	
2	3,4-$(OCH_3)_2$	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (2)	−78	5	55 (1:3.3)		14
3	3,4-$(OCH_3)_2$	$TiCl_4$ (1)	−78	0.5	16 (1:3)	14	32
4	3,4-$(OCH_3)_2$	BF_3·OEt_2 (1)	−78	2.5	4 (0:1)		56
5	3,4-$(OCH_3)_2$	$SnCl_4$ (1)	−78	8	15 (0:1)		24
6	3,4-(OCH_2O)	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78	8	36 (1:0)	30	
7	3,4-(OCH_2O)	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (2)	−78	5	39 (0:1)		30
8	3,4-(OCH_2O)	$TiCl_4$ (1)	−78	0.5	4 (0:1)	3	32
9	3,4-(OCH_2O)	BF_3·OEt_2 (1)	−78	2.5	16 (0:1)		65
10	3,4-(OCH_2O)	$SnCl_4$ (1)	−78	8	43 (1:5)		15
11	4-OCH_3	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78	3	31 (2:1)	31	8
12	4-OCH_3	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (2)	−78	0.75	48 (0:1)		48.5
13	4-OCH_3	$TiCl_4$ (1)	−78	1.5	8 (0:1)	5	35
14	4-OCH_3	BF_3·OEt_2 (1)	−78	2	16 (0:1)		70
15	4-OCH_3	$SnCl_4$ (1)	−78	1.5	5 (0:1)	11	31.5
16	H	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78 → 10	18	*d*		
17	H	2:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78 → 0	20	30 (0:1)[d]		
18	H	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (2)	−78	6	51 (1:16)		
19	H	$TiCl_4$ (1)	−78	16	76 (0:1)		
20	H	BF_3·OEt_2 (1)	−78	10	42 (0:1)		
21	H	$SnCl_4$ (1)	−78	11	29 (0:1)		
22	2-CH_3	2:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78 → −5	18	see text		
23	2-CH_3	4:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (1)	−78 → 10	12	20 (0:1)		
24	2-CH_3	1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$ (2)	−78	7	45 (0:1)		

[a] All reactions were performed in CH_2Cl_2 at −78 °C. [b] Isolated yields. [c] When **3** and **4** were both formed, they were obtained as a mixture after chromatography. The ratio of the two was determined by ^1H NMR. Simple recrystallization of these mixtures generally afforded the major isomer in pure form. [d] See ref 4.

Table 2. Rearrangement of Cyclobutanes 3/4 to Dihydrobenzofurans 5/6[a]

compd	time (h)	product	yield (%)
3a	1.5	**5a**	80
4a	1.5	**6a**	78
3b	1	**5b**	78
4b	2	**6b**	74
4c	2.5	**6c**	65
4d	72	**6d**	76
4e	96	**6e**	80

[a] All reactions conducted in CH_2Cl_2 at room temperature with catalytic amounts of *p*-TsOH.

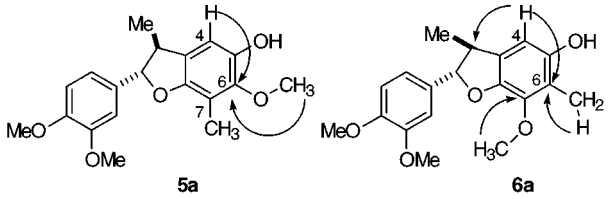


Figure 3. Selected HMBC data collected on **5a** and **6a**.

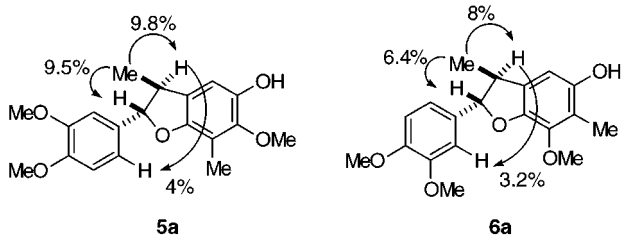


Figure 4. Selected $^1H-^1H$ NOE data collected on **5a** and **6a**.

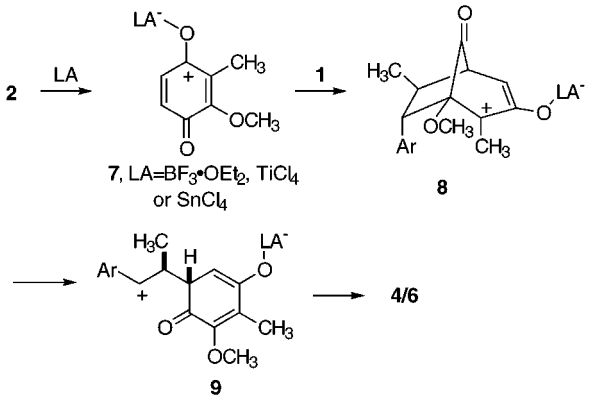
chemical shifts (ppm) are H-1, 3.41; H-6, 3.43; H-7, 2.95; H-8, 3.29; C-1, 47.8; C-6, 43.9; C-7, 38.5; and C-8, 52.3.

In **4a**, all of the methine signals are well resolved and appear as triplets at δ 3.23, 3.35, and 3.44. Once again, the signals of the C-7 carbon (δ 52.6) and the proton attached to it (H-7, δ 3.23) are assigned as described above. The most downfield methine signal correlates (HMBC) with an aryl ring carbon (i.e., that attached to C-7) and must be from H-6; C-6 (δ 47.6) is in turn assigned by HMQC correlation to this proton. This leaves the other methine proton as H-1. With assignments of H-1 and H-6 through H-8 established, $^1H-^1H$ NOE experiments (Figure 2) then clearly indicate the relative stereochemistry about the four-membered ring in both **3a** and **4a**. The stereochemistry of the other cyclobutane products are assigned by spectral comparison with **3a** and **4a**.

The substitution pattern on the enedione moiety of **3a** is assigned by an HMBC correlation between the C-4 methyl hydrogens (Figure 1) with one of the carbonyl signals (δ 197.3) that is in turn correlated with H-7. In **4a**, the C-4 methyl hydrogens are again correlated with one of the carbonyl signals (δ 198.0), but it is the other (δ 193.4) that is correlated to H-8.

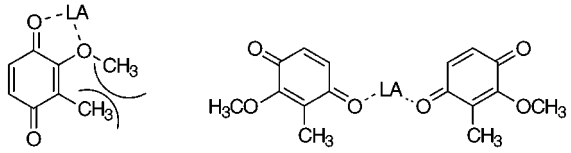
In the case of **5a/6a**, the regiochemistry is assigned on the basis of the relative position of H-4 with respect to the $-OCH_3$ or the $-CH_3$ groups on the aromatic system of the dihydrobenzofuran. In **5a**, H-4 is a singlet at δ 6.61 and shows an HMBC correlation to the C-6 signal that is established by an HMBC correlation with the $-OCH_3$ group attached to it. In **6a**, the H-4 (δ 6.37) correlates to C-6, which in this case shows a correlation with the protons of the CH_3 group attached to it. In addition, H-4 in **6a** shows a correlation with C-3, the signal of which is easily assigned by HMQC data. Finally, the signals for H-2, H-3, and the C-3 CH_3 are assigned by inspection, and $^1H-^1H$ NOE data firmly secure the trans stereochemistry in both **5a** and **6a** (Figure 4). As above, the structures of the other dihydrobenzofurans are assigned by spectral comparison to **5a** and **6a**.

Scheme 2



The regioselectivity of reactions promoted by the monodentate Lewis acid $BF_3{\cdot}OEt_2$ is consistent with selective activation of the quinone through coordination with the more basic ester-like C-4 carbonyl oxygen. The resultant complex **7** undergoes a 5 + 2 ($4\pi + 2\pi$) cycloaddition with the propenylbenzene affording bicyclic carbocation **8**, which proceeds on to **4** and **6** via **9** as described previously (Scheme 2).[1] The stereochemistry of the reactions results from the preference for the aryl group of the propenylbenzene to adopt an endo orientation with respect to the pentadienyl carbocation moiety of **7** in the cycloaddition.

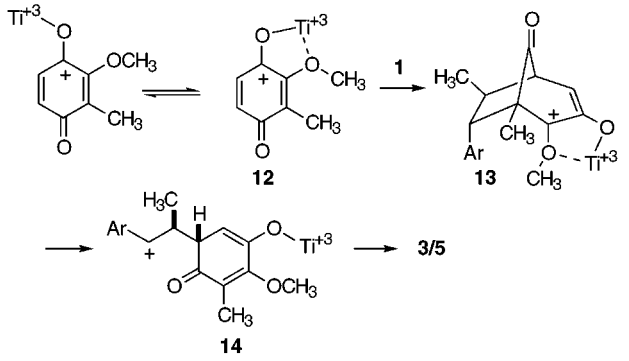
Reactions promoted by $TiCl_4$ or $SnCl_4$ apparently also proceed via **7**. With these Lewis acids, the expected bidentate complexation may be overridden by steric effects; on bidentate binding, the C-2 methoxy group is forced into a conformation **10**, incorporating a significant CH_3-CH_3 $A^{1,3}$ strain. To adopt the expected octahedral coordination for Ti(IV)/Sn(IV), 2:1 quinone−Lewis acid complexes **11** or dimeric complexes might be involved.[5]



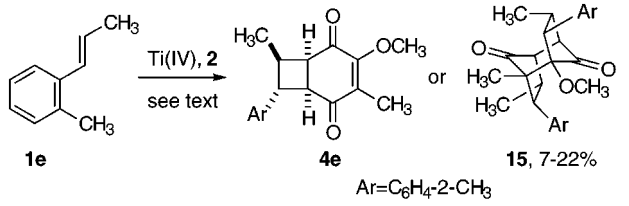
Reactions promoted by a 1:1 mixture of $TiCl_4-Ti(O\text{-}i\text{-}Pr)_4$ are more complex, and intriguing. The results show that the regioselectivity is dependent upon the Ti(IV)−quinone stoichiometry; **3**/**5** are formed with a 1:1 ratio,

(5) (a) Turin, E.; Nielson, R. M.; Merbach, A. E. *Inorg. Chim. Acta* **1987**, *134*, 79−85, 67−78. (b) Bachand, B.; Wuest, J. D. *Organometallics* **1991**, *10*, 2015−2025. (c) Denmark, S. E.; Almstead, N. G. *Tetrahedron* **1992**, *48*, 5565−5578. (d) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133−3139. (e) Springer, J. B.; DeBoard, J.; Corcoran, R. C. *Tetrahedron Lett.* **1995** *36*, 8733−8736. For reviews, see: (f) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256−272. (g) Shambayati, S.; Schreiber, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, p 283.

Scheme 3



Scheme 4

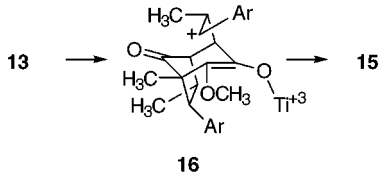


whereas **4**/**6** are formed with a 2:1 ratio. This Lewis acid is likely weaker than the others, and an equilibrium between coordination to the C-1/C-2 oxygens and the C-4 carbonyl may be involved. In this scenario, Curtin−Hammett conditions may prevail and the preferred site of coordination may be unimportant. The regioselectivity may depend solely on the relative rates of the cycloaddition of the two complexes with the propenylbenzene, and if so, the relative stabilities of the bicyclic cationic cycloadducts may be a determining factor. Thus, we rationalize that reactions promoted with 1 equiv of Ti(IV), as $TiCl_4$−Ti(O-*i*-Pr)$_4$, proceed through the thermodynamically more stable oxygen-stabilized carbocationic cycloadduct **13** (Scheme 3), which may or may not involve bidentate coordination. The more powerful Lewis acids $TiCl_4$, $SnCl_4$, and BF_3·OEt_2, or mixtures of $TiCl_4$−Ti(O-*i*-Pr)$_4$ enriched in $TiCl_4$, sufficiently activate the quinone to react via the less stable carbocationic cycloadduct **8**. With 2 equiv of Ti(IV) as $TiCl_4$−Ti(O-*i*-Pr)$_4$, a 1:2 quinone−Ti(IV) complex[6] of some undetermined structure may be involved that is again reactive enough to access an intermediate similar to **8**.

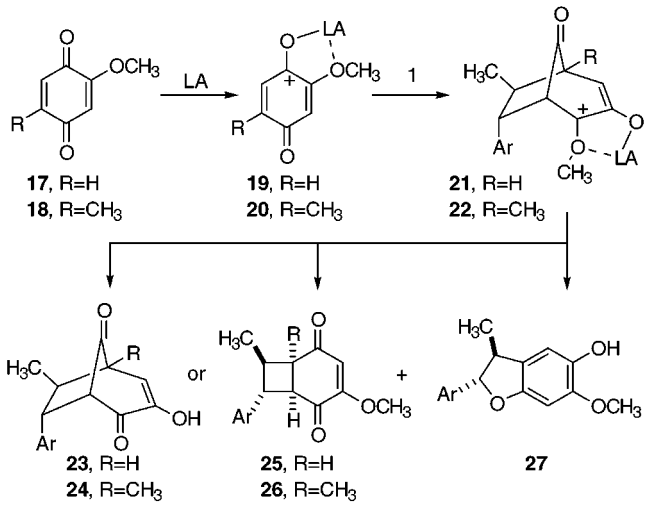
Evidence supporting the 5 + 2 cycloaddition process was found in reactions of (*E*)-2-methyl-1-propenylbenzene (**1e**). Reactions promoted by 2 equiv of Ti(IV), again as a 1:1 mixture of $TiCl_4$−Ti(O-*i*-Pr)$_4$, gave cyclobutane **4e** as expected, but those promoted by 1 equiv of a 2:1 mixture produced the unusual tricyclic system **15** in 7−22% yield (Scheme 4).[4b] The latter reactions were quite sluggish and required the slightly stronger Lewis acid. With a considerably more powerful 4:1 mixture of $TiCl_4$−Ti(O-*i*-Pr)$_4$, cyclobutane **4e** was again found. In all of these reactions, considerable amounts of the propenylbenzene were recovered; however, the quinone was lost presumably due to decomposition.

Of particular interest is that the tricyclic product **15** is found as a single stereoisomer; its structure was determined by single-crystal X-ray analysis.[7] We ratio-

Scheme 5



Scheme 6



nalize that it results from alkylation of bicyclic cation **13** (Scheme 5), generated stereoselectively as discussed above, with a second equivalent of the propenylbenzene to afford **16** followed by carbon−carbon bond formation between the cationic center and the titanium enolate. Indeed, the highest yields of **15** resulted from use of excess amounts of **1e**. The stereochemistry in the formation of **16** from **13** is a result of approach of the propenylbenzene from the sterically more accessible exo direction.

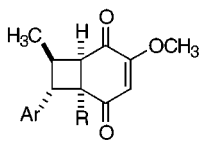
The regioselectivity of the BF_3·OEt_2-promoted reactions of **2** and previous reports of regioselective Lewis acid-activation of quinones in Diels−Alder reactions[2] led us to reexamine the BF_3·OEt_2-promoted reactions of 2-methoxy-1,4-benzoquinone (**17**) and 2-methoxy-5-methyl-1,4-benzoquinone (**18**). We have previously reported that Sn(IV)-promoted reactions of **17**/**18** with propenylbenzene **1a** afforded bicyclo[3.2.1]adducts **23**/**24**, cyclobutanes **25**/**26**, and/or dihydrobenzofurans **27** (Scheme 6), apparently via complexes **19**/**20**, respectively.[1a−c] Careful examination of BF_3·OEt_2-promoted reactions of **17** with propenylbenzene **1a** again revealed that only **27** was formed in 63% yield; no evidence for other products (i.e., **23**, **25**, or **28**) or dihydrobenzofuran regioisomer **30** was found. Similarly, reactions of **18** with **1a** gave only cyclobutane **26** in 23% yield with no evidence for regioisomer **29** or dihydrobenzofuran **31**. Apparently, the regioselectivity of these reactions is determined by the greater stability of presumed intermediates **21**/**22**, compared to **32**/**33**, and not on the expected site of coordination of the monodentate BF_3·OEt_2 to the quinone.

Finally, reactions of quinone **17** promoted by excess amounts of Ti(IV) have also been examined. Previous studies on reactions of **18** and those of **2** reported herein have demonstrated that different regioisomeric products are obtained depending upon the quantities of Ti(IV) used as promoter. However, reactions of **17** with propenylbenzene **1a** promoted by 2 equiv of $TiCl_4$, 2−5 equiv of

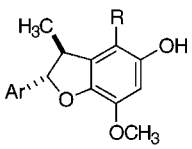
(6) For discussions of carbonyl−(Lewis acid)$_2$ complexes as potential intermediates, see refs 5g and 1c and references therein.

(7) Engler, T. A.; Scheibe, C.; Iyengar, R. *J. Org. Chem.* **1997**, *62*, 8274−8275.

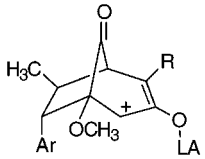
1:1 $TiCl_4$−Ti(O-*i*-Pr)$_4$, or 1 equiv each of $TiCl_4$ and $SnCl_4$ afforded only cyclobutane **25** (in 14, 50−56, 0% yields, respectively) and/or dihydrobenzofuran **27** (69, 35−43, 53% yields, respectively). Again, no evidence for isomers **28** or **30** was found.



28, R=H
29, R=CH_3



30, R=H
31, R=CH_3



32, R=H
33, R=CH_3

Conclusions

Lewis acid-promoted reactions of 2-methoxy-3-methyl-1,4-benzoquinone (**2**) and 2-methoxy-5-methyl-1,4-benzoquinone (**18**) with various propenylbenzenes selectively give regioisomeric 8-arylbicyclo[4.2.0]oct-3-ene-2,5-diones and/or 2-aryl-2,3-dihydrobenzofurans depending upon the nature and the number of equivalents of Lewis acid promoters employed. The results demonstrate that substituent electronic and steric effects on these quinones play a key role in the site of Lewis acid activation as evidenced by a "regiochemical switch" in the products obtained from reaction with different Lewis acids. On the other hand, reactions of 2-methoxy-1,4-benzoquinone (**17**) seem to be controlled more by the stability of the cationic 5 + 2 cycloaddition intermediate.

Experimental Section

General Methods. All compounds were prepared as racemic mixtures. Melting points were determined on a capillary melting point apparatus and are uncorrected. All reactions were run under an inert atmosphere of nitrogen or argon in flame-dried glassware and stirred magnetically. Solvents and Lewis acids were distilled under nitrogen from appropriate drying agents just before use. Propenylbenzenes were used as received from Aldrich Chemical Co. (**1a**, trans−cis = 23:1; **1b**, trans−cis = 7:1) or prepared using known procedures (**1e**, trans−cis = 25:1). 2-Methoxy-3-methyl-1,4-benzoquinone was prepared using known methods.[8,9] Brine refers to saturated aqueous sodium chloride. Reactions were monitored by thin-layer chromatography (TLC) on precoated 0.25 mm silica gel plates (Merck Kieselgel 60 F254) with fluorescent indicator, and visualization was effected by viewing under a UV lamp and/or by staining with *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid. R_f's reported are from TLC using the eluents indicated. Flash chromatography was performed on silica gel (EM-Kieselgel 60, 0.04−0.063 mm mesh) with the eluent indicated. NMR spectra were recorded on samples dissolved in $CDCl_3$, unless otherwise noted, and chemical shifts are reported in δ (ppm) relative to internal TMS or residual $CHCl_3$. Coupling constants (J) are reported in Hz.

2-Methoxy-3-methyl-1,4-benzoquinone (2).[8,9] NaH (1.29 g, 60% suspension in mineral oil, 32 mmol) was washed with hexanes (3 × 5 mL), dried under a stream of argon, and suspended in dry THF (25 mL). A solution of 2-methyl resorcinol (4.0 g, 32 mmol) in THF (25 mL) was added, and the mixture was stirred for 15 min at room temperature. After being cooled to −10 °C, the mixture was treated with MeI (5.0 mL, 81 mmol). The temperature was allowed to increase to 20 °C over 20 h and the reaction then quenched with 3 N HCl (ca. pH 4), extracted with Et_2O, dried (Na_2SO_4), and concentrated to a red oil. Flash chromatography (20% EtOAc−hexanes) yielded 3-methoxy-2-methylphenol (2.4 g, 55%) as a yellow oil: R_f 0.54 (30% EtOAc−hexanes); ^{1}H NMR (300 MHz) 6.96 (t, J = 5, 1H), 6.45 (d, J = 5, 1H), 6.40 (t, J = 5, 1H), 4.78 (br s, 1H), 3.82 (s, 3H), 2.11 (s, 3H).

To a solution of this phenol (1.0 g, 7.2 mmol) in acetone (200 mL) was added a solution of Fremy's salt (6.69 g, 25.0 mmol) in buffered water (2.31 g of KH_2PO_4 in 300 mL). The reaction mixture was stirred at room temperature for 1.5 h and extracted with Et_2O, and the extracts were dried (Na_2SO_4) and concentrated to a yellow oil. Flash chromatography (10% EtOAc−hexanes) yielded **2** (979 mg, 89%) as a yellow oil that solidified in refrigerator: mp 21−28 °C (lit.[3] mp 19−30 °C); R_f 0.42 (30% EtOAc−hexanes); ^{1}H NMR (300 MHz) 6.69 (d, J = 10, 1H), 6.61 (d, J = 10, 1H), 4.02 (s, 3H), 1.95 (s, 3H).

Representative Procedures for Reactions of Propenylbenzenes with 2-Methoxy-3-methyl-1,4-benzoquinone (2): Reactions of 1a. I. Promotion by $TiCl_4$−Ti(O-*i*-Pr)$_4$. (A) $TiCl_4$ (20 μL, 0.18 mmol) was added to a solution of Ti(O-*i*-Pr)$_4$ (53 μL, 0.18 mmol) in CH_2Cl_2 (2−4 mL). After being stirred for 20 min at room temperature, the mixture was cooled to −78 °C and a solution of quinone **2** (50 mg, 0.33 mmol) in CH_2Cl_2 (3−4 mL) added followed by propenylbenzene **1a** (61 μL, 0.36 mmol), either neat or as a solution in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 8 h and then quenched by the sequential addition of solid sodium bicarbonate (~1 g) and *i*-PrOH (~3 mL). The resulting mixture was filtered through a pad of wet (H_2O) Celite, the Celite rinsed with CH_2Cl_2, and the combined filtrate and rinse extracted with CH_2Cl_2. The extracts were combined, washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography with 20% acetone/hexanes as eluent gave a 3.6:1 mixture of **3a**/**4a** as a colorless oil (45 mg, 41%) and **5a** (64 mg, 59%) as a white solid. Crystallization (EtOAc−hexanes) of the mixture of **3a**/**4a** gave pure **3a**. Physical and spectral data for **3a**: mp 131−133 °C (EtOAc−hexanes); R_f 0.21 (20% acetone−hexanes); ^{1}H NMR (500 MHz) 6.80−6.77 (m, 3H), 4.03 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.43 (apparent t, J = 9.5, 1H), 3.41 (apparent t, J = 9.5, 1H), 3.29 (apparent t, J = 9.5, 1H), 2.95 (m, 1H), 1.98 (s, 3H), 1.13 (d, J = 7.0, 3H); ^{13}C NMR (125 MHz) 197.3, 193.6, 160.0, 149.1, 148.1, 135.3, 134.0, 118.3, 111.3, 109.7, 60.0, 56.0, 55.9, 52.3, 47.8, 43.9, 38.5, 17.4, 9.5. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.08; H, 6.71. Found: C, 69.20; H, 6.50. Physical and spectral data for **5a**: mp 149−151 °C (EtOAc−hexanes); R_f 0.17 (20% acetone−hexanes); ^{1}H NMR (500 MHz) 6.96 (m, 2H), 6.86 (d, J = 8.1, 1H), 6.61 (s, 1H), 5.36 (br s, 1H), 5.0 (d, J = 9.4, 1H), 3.88 (s, 6H), 3.79 (s, 3H), 3.38 (dq, J = 9.4, 6.5, 1H), 2.21 (s, 3H), 1.33 (d, J = 6.5, 3H); ^{13}C NMR (125 MHz) 151.2, 149.1, 149.0, 145.0, 143.0, 133.0, 126.6, 119.0, 113.0, 110.9, 109.3, 107.2, 92.5, 60.9, 55.9, 55.8, 45.7, 17.4, 9.4. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.08; H, 6.71. Found: C, 69.00; H, 7.00.

(B) In a similar experiment according to procedure I, a mixture of $TiCl_4$ (40 μL, 0.36 mmol) and Ti(O-*i*-Pr)$_4$ (107 μL, 0.36 mmol) was used to promote a reaction of quinone **2** (50 mg, 0.33 mmol) with propenylbenzene **1a** (61 μL, 0.36 mmol). Workup and chromatography gave a 1:3.3 mixture of **3a**/**4a** as a colorless oil (60 mg, 55%) and **6a** (15 mg, 14%) as a white solid. Crystallization (EtOAc−hexanes) of the mixture of **3a**/**4a** gave pure **4a**. Physical and spectral data for **4a**: mp 113−114 °C (EtOAc−hexanes); R_f 0.21 (20% acetone−hexanes); ^{1}H NMR (500 MHz) 6.79 (m, 3H), 4.04 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.43 (apparent t, J = 9.0, 1H), 3.35 (apparent t, J = 9.0, 1H), 3.23 (apparent t, J = 9.0, 1H), 2.99 (m, 1H), 1.97 (s, 3H), 1.19 (d, J = 7.0, 3H); ^{13}C NMR (125 MHz) 198.0, 193.4, 160.9, 149.0, 148.0, 134.4, 134.2, 118.1, 111.2, 109.8, 60.3, 55.9, 55.8, 52.6, 47.6, 43.1, 38.8, 17.5, 9.7. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.08; H, 6.71. Found: C, 69.00; H, 6.52. Physical and spectral data for **6a**: mp 132−133 °C (EtOAc−hexanes); R_f 0.15 (20% acetone−hexanes); ^{1}H NMR (500 MHz) 6.97 (m, 2H), 6.85 (d, J = 8.1, 1H), 6.37 (s, 1H), 5.05 (d, J = 9.3, 1H), 4.71 (br s, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.35 (dq, J = 9.3, 6.7, 1H), 2.15 (s, 3H), 1.35 (d, J = 6.7, 3H);

(8) Cavitt, S. B.; Sarrafizadeh, R. H.; Gardner, P. D. *J. Org. Chem.* **1962**, *27*, 1211−1216.
(9) This preparation followed the procedure of Ishii, H.; Ohtake, R.; Ohida, H.; Mitsui, H.; Ikeda, N. *J. Pharm. Soc. Jpn.* **1970**, *90*, 1283−1289.

^{13}C NMR (125 MHz) 149.1, 149.0, 148.4, 143.9, 142.1, 133.2, 131.0, 118.8, 115.6, 110.9, 109.2, 104.8, 92.8, 60.0, 55.9, 55.8, 45.7, 17.5, 8.8. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.08; H, 6.71. Found: C, 68.90; H, 6.93.

II. Promotion by $TiCl_4$, $SnCl_4$, or $BF_3{\cdot}OEt_2$. A solution of the Lewis acid in CH_2Cl_2 (2−4 mL) was cooled to −78 °C, and a solution of the quinone (0.39−0.82 mmol) in CH_2Cl_2 (3−4 mL) was added followed by the propenylbenzene (0.39−0.82 mmol), either neat or as a solution in CH_2Cl_2 (3 mL). The reaction mixture was stirred for the times indicated in Table 1 and worked up as described above.

(C) According to procedure II, a $TiCl_4$-promoted (43 μL, 0.39 mmol) reaction of quinone **2** (60 mg, 0.39 mmol) with propenylbenzene **1a** (67 μL, 0.39 mmol) gave a 1:3 mixture of **3a**/**4a** as a colorless oil (20 mg, 15.5%), **5a** (18 mg, 14%) as a white solid, and **6a** (41 mg, 32%) as a white solid.

(D) According to procedure II, a $SnCl_4$-promoted (96 μL, 0.82 mmol) reaction of quinone **2** (125 mg, 0.82 mmol) with propenylbenzene **1a** (139 μL, 0.82 mmol) gave **4a** (40 mg, 15%) as a colorless oil and **6a** (65 mg, 24%) as a white solid.

(E) According to procedure II, a $BF_3{\cdot}OEt_2$-promoted (90 μL, 0.71 mmol) reaction of quinone **2** (108 mg, 0.71 mmol) with propenylbenzene **1a** (120 μL, 0.71 mmol) gave **4a** (10 mg, 4%) as a colorless oil and **6a** (130 mg, 56%) as a white solid.

Reaction of 1e with 2. (A) According to procedure I, a mixture of $TiCl_4$ (48 μL, 0.44 mmol) and Ti(O-*i*-Pr)$_4$ (65 μL, 0.22 mmol) in CH_2Cl_2 (2 mL) was used to promote a reaction of quinone **2** (100 mg, 0.66 mmol) with propenylbenzene **1e** (288 μL, 1.98 mmol). The reaction temperature increased to −5 °C over 18 h, and workup and chromatography gave **15** (60 mg, 22%) as a pale yellow solid: mp 166−167 °C (CH_2Cl_2−hexanes); R_f 0.48 (25% acetone−hexanes); ^{1}H NMR (400 MHz) 7.70 (d, J = 8.0, 1H), 7.17−7.27 (m, 6H), 6.98 (d, J = 7, 1H), 3.29 (d, J = 8.0, 1H), 2.85 (d, J = 9.8, 1H), 2.74−2.78 (m, 2H), 2.67 (s, 3H), 2.46 (d, J = 6.4, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.24 (s, 3H), 1.16 (d, J = 7.1, 3H), 0.98 (d, J = 6.4, 3H), 0.86 (m, 1H); ^{13}C NMR (100 MHz) 213.8, 211.1, 139.5, 138.0, 136.2, 135.7, 130.6, 130.4, 129.8, 128.9, 127.2, 126.4, 126.3, 126.2, 85.0, 66.9, 55.6, 54.1, 52.6, 51.8, 48.0, 41.7, 37.7, 21.2, 21.1, 20.5, 14.7, 13.0; HRMS m/z 416.2326 (M^+, calcd for $C_{28}H_{32}O_3$, 416.2352).

(B) According to procedure I, a mixture of $TiCl_4$ (54 μL, 0.5 mmol) and Ti(O-*i*-Pr)$_4$ (148 μL, 0.5 mmol) was used to promote a reaction of quinone **2** (75 mg, 0.49 mmol) with propenylbenzene **1e** (72 μL, 0.49 mmol). Workup and chromatography gave **4e** (62 mg, 45%) as a pale yellow solid: mp 88−90 °C (EtOAc−hexanes); R_f 0.41 (25% acetone−hexanes); ^{1}H NMR (400 MHz) 7.37 (d, J = 7.0, 1H), 7.22 (m, 1H), 7.13 (m, 2H), 4.06 (s, 3H), 3.52 (apparent t, J = 8.6, 1H), 3.39 (apparent t, J = 8.6, 1H), 3.43 (apparent t, J = 8.6, 1H), 3.01−3.11 (m, 1H), 2.22 (s, 3H), 1.99 (s, 3H), 1.14 (d, J = 7.0, 3H); ^{13}C NMR (100 MHz) 198.2, 193.6, 160.8, 139.0, 136.1, 134.5, 130.4, 126.9, 126.4, 125.2, 60.3, 49.5, 48.0, 42.9, 38.9, 19.8, 17.3, 9.8. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.68; H, 7.30.

Reaction of 1a with 17. According to procedure II, a $BF_3{\cdot}OEt_2$-promoted (58 μL, 0.46 mmol) reaction of quinone **17** (64 mg, 0.46 mmol) with propenylbenzene **1a** (78 μL, 0.46 mmol) for 5 min gave after workup and chromatography (10% EtOAc/hexanes) **27** (91 mg, 63%) as a white solid. Spectral data matched that previously reported.[1a]

Reaction of 1a with 18. $BF_3{\cdot}OEt_2$ (79 μL, 0.65 mmol) was added to a solution of **18** (100 mg, 0.65 mmol) in CH_2Cl_2 (15 mL) maintained at −78 °C followed after 20 min by **1a** (220 μL, 1.30 mmol). After being stirred for 48 h, the reaction was worked up according to procedure II and chromatography (20% EtOAc−hexanes) gave **26** (170 mg, 23%) as a white solid. Spectral data matched that previously reported.[1c]

General Procedure for Protic Acid-Catalyzed Rearrangement of Cyclobutanes 3/4 to Dihydrobenzofurans 5/6. *p*-Toluenesulfonic acid (*p*-TsOH, 2−10 mg) was added to a solution of the cyclobutane (15−33 mg) in CH_2Cl_2 (1−5 mL) at room temperature. The reaction was monitored by TLC and stirred for the times indicated in Table 2, after which it was quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was extracted with CH_2Cl_2, and the extracts were dried ($MgSO_4$) and concentrated. Chromatography with 10% acetone/hexanes as eluent afforded the dihydrobenzofurans in the yields indicated in Table 2.

Physical and spectral data for **6d**: a colorless oil; R_f 0.28 (25% acetone−hexanes); ^{1}H NMR (400 MHz) 7.24−7.42 (m, 5H), 6.35 (s, 1H), 5.12 (d, J = 8.8, 1H), 4.59 (br s, 1H), 3.94 (s, 3H), 3.33 (dq, J = 8.8, 6.8, 1H), 2.15 (s, 3H), 1.35 (d, J = 6.8, 3H); ^{13}C NMR (100 MHz) 148.4, 144.0, 142.0, 141.0, 130.8, 128.5, 128.1, 126.0, 115.6, 104.8, 92.6, 60.0, 46.0, 17.9, 8.8; HRMS m/z 270.1279 (M^+, calcd for $C_{17}H_{18}O_3$ 270.1256).

Physical and spectral data for **6e**: colorless oil as a 10:1 mixture of trans−cis isomers; R_f 0.36 (25% acetone−hexanes); ^{1}H NMR (400 MHz) 7.36 (d, J = 6.9, 2H), 7.20 (m, 3H), 6.37 (s, 1H), 5.40 (d, J = 8.0, 1H), 4.40 (br s, 1H), 3.94 (s, 3H), 3.40 (dq, J = 8.0, 6.8, 1H), 2.40 (s, 3H), 2.15 (s, 3H), 1.38 (d, J = 6.8, 3H); ^{13}C NMR (100 MHz) 148.3, 143.9, 142.1, 138.8, 135.5, 130.9, 130.7, 127.8, 126.4, 126.1, 115.6, 104.9, 90.2, 60.0, 45.1, 19.6, 18.2, 8.8; HRMS m/z 284.1399 (M^+, calcd for $C_{18}H_{20}O_3$ 284.1412).

Acknowledgment. We thank Mr. Pankaj Desai for results of experiments with **18**, Dr. Martha Morton for help with the HMQC/HMBC and NOE experiments, and Professor Jeffrey Aubé's group for use of an HPLC. This work was supported financially by the National Science Foundation (OSR-955223) and the KU General Research Fund.

Supporting Information Available: Experimental details for preparation of, and physical and spectral for, **3b**/**c**, **4b**−**d**, **5b**/**c**, **6b**−**d**; IR and mass spectral data for all new compounds; copies of ^{1}H and ^{13}C NMR spectra for all compounds with HRMS (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971937U