Asymmetric Reactions of 2-Methoxy-1,4-benzoquinones with Styrenyl Systems: Enantioselective Syntheses of 8-Aryl-3-methoxybicyclo[4.2.0]oct-3-en-2,5-diones, 7-Aryl-3-hydroxybicyclo[3.2.1]oct-3-en-2,8-diones, 2-Aryl-6-methoxy-2,3-dihydrobenzofuran-5-ols, and Pterocarpans

Thomas A. Engler,*,† Michael A. Letavic, Rajesh Iyengar, Kenneth O. LaTessa,‡ and Jayachandra P. Reddy

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

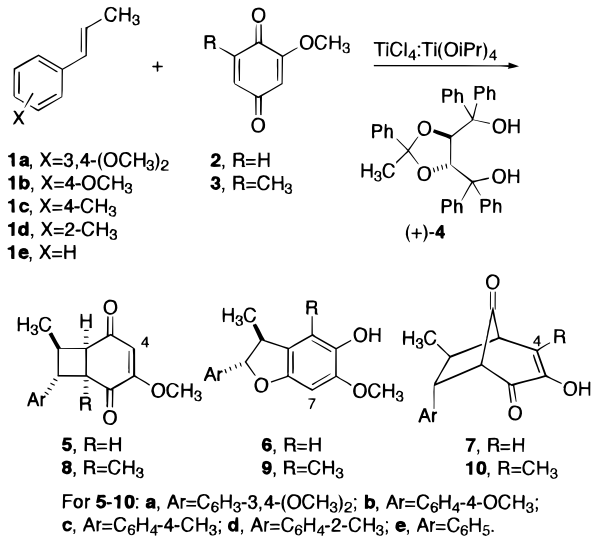
Received October 27, 1998

Reactions of 2-methoxy-1,4-benzoquinones **2** and **3** with (*E*)-propenylbenzenes **1** promoted at −78 °C by Ti(IV)−TADDOLates prepared from diol-(+)-**4** afford (1*R*,6*R*,7*R*,8*R*)-8-aryl-3-methoxy-7-methylbicyclo[4.2.0]oct-3-en-2,5-diones **5**/**8** or (1*R*,5*R*,6*R*,7*R*)-7-aryl-3-hydroxy-6-methylbicyclo[3.2.1]-oct-3-en-2,8-diones **7**/**10** in good yield and high ee. (2*S*,3*S*)-2-Aryl-6-methoxy-3-methyl-2,3-dihydrobenzofuran-5-ols **6**/**9** are also found, but in slightly lower ee. Cyclobutanes **5**/**8** cleanly and efficiently rearrange to the dihydrobenzofurans **6**/**9** without loss of enantiomeric purity upon treatment with the Ti−TADDOLates at higher temperatures. Reactions of (*Z*)-propenylbenzene **17** and of indene with **2** and **3** give products in moderate enantiomeric purity. Products obtained from reactions of 1-anisylcycloalkenes with **2** differ significantly in yield and enantiomeric purity. In the latter reactions, the ee's of the cyclobutane products are consistently much higher than those of the dihydrobenzofuran products. More significantly, products of different absolute configuration result from different cycloalkenes. With 1-anisylcyclopentene or 1-anisylcyclohexene, all of the products are of similar configuration and are obtained in comparable yields and ee's. However, 1-anisylcycloheptene affords products that are diastereomeric with those of the 1-anisylcyclopentene, and in lower ee's. A mechanistic model is proposed. Application of these reactions to the enantioselective synthesis of the pterocarpan class of isoflavonoid natural products is also reported.

Introduction

The effect of molecular chirality on biological activity has generated intense interest in asymmetric synthesis over the last several decades.[1] Much effort has been expended on the development of asymmetric variants of well-established reactions, and upon discovery of a new reaction that creates new stereogenic centers focus often quickly shifts to the development of enantioselective versions using chiral auxiliaries, reagents, or catalysts. We have found recently that reactions of various styrenyl systems **1** with 1,4-benzoquinones **2**/**3** are extraordinarily versatile processes, producing a variety of chiral cycloaddition products.[2] In addition to products of Diels−Alder reaction found under thermal conditions,[3] Lewis acid-promoted reactions give up to three different types of products, **5**−**10** (Scheme 1).[2,4] The latter three types of products significantly extend the synthetic utility of quinone−styrene reactions, which have since been used to access racemic mixtures of a number of chiral biologically active natural products.[2] Products **5**−**10** are obtained in Ti(IV)-promoted reactions of **1** with **2**/**3**, with mixtures of $TiCl_4$ and Ti(O*i*-Pr)$_4$ generally the most effective promoters. For this reason, our interest was drawn to chiral Ti−TADDOLate complexes to potentially generate **5**−**10** in nonracemic form.[5,6] Herein, we describe the full details of these studies.[7]

Scheme 1



† Current address: Lilly Corporate Center, Mail Drop 1523, Eli Lilly and Company, Indianapolis, IN 46285. Phone: (317)433-2885. Fax: (317)277-2035. E-mail: ENGLER_THOMAS@Lilly.com.

‡ Formerly Kenneth O. Lynch, Jr.

(1) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*, Tetrahedron Organic Chemistry Series Vol. 14; Pergamon: Tarrytown, NY, 1996. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(2) (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.; Takusagawa, F. *J. Chem. Soc., Chem. Commun.* **1989** 1573−1576. (c) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D. *J. Org. Chem.* **1990**, *55*, 1248−1254. (d) Engler, T. A.; Letavic, M. A.; Combrink, K. D.; Takusagawa, F. *J. Org. Chem.* **1990** *56*, 5810−5812. (e) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567−6587. (f) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994** *59*, 6588−6599. (g) Engler, T. A.; Gfesser, G. A.; Draney, B. W. *J. Org. Chem.* **1995**, *60*, 3700−06. (h) Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755−69. (i) Engler, T. A.; Iyengar, R. *J. Org. Chem.* **1998**, *63*, 1929−1934.

10.1021/jo982164s CCC: $18.00
Published on Web 03/18/1999

Results

Initial studies employed propenylbenzene **1a** and quinone **2**. Reactions promoted by mixtures of $TiCl_4$ and Ti(O*i*-Pr)$_4$ gave cyclobutane (±)-**5a** and dihydrobenzofuran (±)-**6a**, with the latter usually as the major product. Reactions of **1a** with **2** employing Ti−TADDOLates prepared from chiral diol-(+)-**4**[5,6] by the protocols described by Seebach,[5] Narasaka,[6] and Corey[8a] for Diels−Alder, 2+2 cycloaddition, and allylation reactions, among others,[8b−e] were attempted with little success; either the products were obtained with no enantiomeric enrichment, or the Lewis acid was not an effective promoter.[9] Thus, we surveyed empirically a number of other protocols[5] for preparing a Ti−TADDOLate that would afford the products in high ee. The results summarized in Table 1 revealed 2.5 equiv each with respect to the quinone **2** of $TiCl_4$, Ti(O*i*-Pr)$_4$, and the chiral diol-(+)-**4**, and low reaction temperatures resulted in the formation of the bicyclo[4.2.0]octenedione product (−)-**5a** in high enantiomeric purity (Table 1, entry 4); smaller amounts of the dihydrobenzofuran (−)-**6a** were also produced but in lower ee. The Ti−(+)-**4** complex was prepared by the addition of $TiCl_4$ to a dichloromethane solution of Ti(O*i*-Pr)$_4$ at room temperature followed by the addition of a dichloromethane solution of the diol. The solution of the Ti-complex was then added to a dichloromethane solution of **2** maintained at −78 °C followed by addition of the propenylbenzene. Alternatively, a solution of the quinone could be added to the Ti-complex. After the reactions were judged to be complete by TLC, the mixtures were subjected to a standard aqueous workup. Direct analysis of the crude reaction mixtures by NMR or HPLC was problematic. Thus, the diol and products were separated by flash chromatography prior to determination of enantiomeric purity. The chromatography introduces some uncertainty into the degree of asymmetric induction,[10] but the high yields and ee's of the isolated products impressively demonstrate the preparative value of the reactions. Slowly warming the reaction mixtures produced dihydrobenzofuran (−)-**6a** in good yields, although the enantiomeric excesses were not as high as those found for (−)-**5a** (entries 5 and 6). Longer reaction times at −78 °C had little effect on the ratio of products formed, indicating that rearrangement[2] of the cyclobutane to the dihydrobenzofuran was not occurring to a significant extent at low temperatures.

Table 1. Asymmetric Reactions of Propenylbenzene 1a with Quinone 2

entry	promoter: ratio of $TiCl_4$:Ti(O*i*Pr)$_4$:**4**:**2**[b]	temp (°C)	% yield (% ee)[a] (−)-**5a**	% yield (% ee)[a] (−)-**6a**
1	0.5:0.5:0.5:1	−78	63 (60)	36 (6)[c]
2	0.5:0.5:1:1	−78	52 (78)	42 (n.d.)[c,d]
3	1:1:1:1	−78	69 (77)	24 (n.d.)[c,d]
4	2.5:2.5:2.5:1	−78	88 (92)	9 (41)[c]
5	2.5:2.5:2.5:1	−78 to 0		94 (71)[e]
6	2.5:2.5:2.5:1	−78 to rt		95 (82)[f]

[a] Determined by ^{1}H NMR with **11** as a chiral solvating agent (see text). [b] The number of equiv of **1a** used was 1.1−2.6. [c] Only the trans isomer by ^{1}H NMR. [d] n.d. = not determined. [e] trans:cis = 39:1 by NMR. [f] trans:cis = 15:1 by NMR.

Other attempts to prepare effective chiral Ti-complexes for reactions of **1a** with **2** were also examined.[5b,9] The cyclobutane product (−)-**5a** was generally always formed in higher ee than the dihydrobenzofuran (−)-**6a**, and efforts were thus focused on optimizing conditions for generating the former. Deprotonation of diol-(+)-**4** with 2 equiv of *n*-BuLi followed by the addition of $TiCl_4$ afforded a complex that gave (−)-**5a** in good ee (88%), but low yield (29%); **6a** was the major product (54%), but found in poor ee (<5%). A complex prepared from $TiCl_4$/Ti(O*i*-Pr)$_4$/diethyl L-tartrate yielded racemic **6a** as the major product (74%). Systems involving $TiCl_4$ and diol-(+)-**4**, or $TiCl_4$/Ti(O*i*-Pr)$_4$ and racemic binaphthol, were also studied; however, the major products were always **6a** (52−72%), and these reactions were not pursued further.

(3) For leading references: (a) Lora-Tamayo, M. *Tetrahedron* **1958**, *4*, 17. (b) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 563−564. (c) Zhang, Z.-r.; Flachsmann, F.; Moghaddam, F. M.; Rüedi, P. *Tetrahedron Lett.* **1994**, *35*, 2153-2156. (d) Willmore, N. K.; Hoic, D. A.; Katz, T. J. *J. Org. Chem.* **1994**, *59*, 1889−1891. (e) Amatayakul, T.; Cannon, J. R.; Dampawan, P.; Dechatiwongse, T.; Giles, R. G. F.; Huntrakul, C.; Kusamrann, K.; Mokkhasamit, M.; Raston, C. L.; Reutrakul, V.; White, A. H. *Aust. J. Chem.* **1979**, *32*, 71−88. (f) Tanga, M. J.; Reist, E. J. *J. Heterocyclic Chem.* **1991**, *28*, 29−32. (g) Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 3463−3468. (h) Manning, W. B. *Tetrahedron Lett.* **1981**, *22*, 1571−1574. (i) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798−799. (j) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Tamura, O. *Tetrahedron Lett.* **1989**, *30*, 3995−3998. (k) Schlüter, A.-D.; Wegner, G.; Blatter, K. *Macromolecules* **1989**, *22*, 3506.

(4) We, and others, have also extended Lewis acid-promoted reactions of quinones to include other alkenyl systems. For leading references, see: (a) Engler, T. A.; Agrios, K.; Reddy, J. P.; Iyengar, R. *Tetrahedron Lett.* **1996**, *37*, 327−330. (b) Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1987**, 2169−2172. (c) Murphy, W. S.; Neville, D. *Tetrahedron Lett.* **1997**, *38*, 7933−7936. (d) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, 4041−4044. (e) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 2589−2592. (f) Ipaktschi, J.; Heydari, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 313−314. (g) Ipaktschi, J.; Heydari, A. *Chem. Ber.* **1992**, *125*, 1513−1515. (h) Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774−3783. For reviews, see: (i) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series Vol. 9; Pergamon: Oxford, 1992; pp 322−330. (j) Finley, K. T. In *The Chemistry of the Quinonoid Compounds*, Vol. 2; Patai, S., Rappaport, Z., Eds.; Wiley: Chichester, 1988; p 537. (k) Nishigaichi, Y.; Takuwa, A.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395−7426. (l) Cintas, P. *SYNLETT* **1995**, 1087−1109. (m) Fleming, I.; Dunogués, J.; Smithers, R. *Org. React.* **1989** *37*, 57−575. (n) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Org. Synth.* **1992** *71*, 125−131. (o) Naruta, Y.; Maruyama, K. In *The Chemistry of Quinonoid Compounds*, Vol. 2; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: Chichester, 1988; Chapter 8. (p) Mukaiyama, T.; Iwasawa, N.; Yura, T.; Clark, R. S. J. *Tetrahedron* **1987**, *43*, 5003−5017. (q) Nucleophilic additions to quinones bearing electron-withdrawing groups are common; see references cited in the reviews.

(5) (a) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954−974. (b) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788−1799. (c) Seebach, D.; Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710−1740.

(6) (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109−1112. (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345. (c) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869−8885. (d) Narasaka, K.; Iwasawa, N. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Jai Press: London, 1993; Vol. 2, pp 93−112. (e) Narasaka, K. *Synthesis* **1991**, 1−11.

(7) For a preliminary account: Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068−5070.

(8) (a) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289−6292. For recent applications: (b) Yang, H. W.; Romo, D. *Tetrahedron Lett.* **1998**, *39*, 2877−2880. (c) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59−64. (d) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346−355. (e) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687−5691. See also ref 21.

(9) To alleviate concerns about the stoichiometry, we reinvestigated the asymmetric *N*-2-butenoyloxazolidinone/cyclopentadiene Diels−Alder reaction (the "benchmark reaction" for evaluating new chiral Diels−Alder catalysts) and closely reproduced the findings as described in refs 5, 6, and 8. Utilization of these protocols for preparation of Ti−TADDOLates failed for the quinone−propenylbenzene reactions, however, as did our recipe in the Diels−Alder reaction.

(10) Due to clathrate formation or enrichment, see discussion in ref 5b.

Table 2. Asymmetric Reactions of Propenylbenzenes 1 with Quinones 2/3 Promoted by the Ti(IV)−(+)-4-TADDOLate[a]

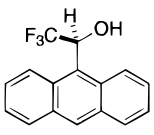
					products[b]					
					(−)-**5**		(−)-**6**[c]		(+)-**7**	
entry	styrene	quinone	time (h)	temp (°C)	% yield	% ee	% yield	% ee	% yield	% ee
1	**1a**	**2**	2	−78	86	92	9	41		
2	**1b**	**2**	2	−94	86	90	11	53		
3	**1b**	**2**	1	−78	69	89	36	78		
4	**1c**	**2**	0.5	−94	71	86				
5	**1d**	**2**	1	−78					64	84
6	**1e**	**2**	5	−78					61	90

					products[b]					
					(−)-**8**		(+)-**9**[c]		(+)-**10**	
entry	styrene	quinone	time (h)	temp (°C)	% yield	% ee	% yield	% ee	% yield	% ee
7	**1a**	**3**	5	−94 → −78	35	88	48	83		
8	**1a**	**3**	3	−78			91	87		
9	**1a**	**3**	2	−78 → −30			81	74		
10	**1b**	**3**	6	−94	61	85				
11	**1b**	**3**	3	−78	72	87	15	78		
12	**1c**	**3**	1.5	−78	<10	70			61	92
13	**1d**	**3**	2	−78					79	96

[a] The Ti−TADDOLate promoter was composed of 2.5 equiv each of $TiCl_4$, $Ti(OiPr)_4$, and **4**, with respect to quinones **2** and **3**. [b] Yields and % ee's of isolated products. [c] t/c ≥ 45:1 by ^1H NMR.

Reactions of other propenylbenzenes **1** with quinones **2** and **3** were then examined employing the "optimized" conditions (Table 1, entry 4). In reactions of **2**, cyclobutanes (−)-**5a**−**c** were formed as the major products with propenylbenzenes **1a**−**c** bearing electron-donating groups on their aromatic rings, whereas bicyclo[3.2.1]-adducts (+)-**7d**,**e** were obtained with propenylbenzenes **1d**,**e** (Table 2). Both types of products were isolated in high ee. Reactions of quinone **3** at low reaction temperatures also gave cyclobutanes (−)-**8**, but at higher reaction temperatures, greater amounts of dihydrobenzofurans (+)-**9** were found. The latter reactions suggested an in situ rearrangement of **8** to **9** under the reaction conditions (vide infra and ref 2). Similar to reactions of **2**, reactions of **3** with the more neutral propenylbenzenes **1c**,**d** gave bicyclo[3.2.1]-adducts (+)-**10c**,**d**. All reactions were routinely subjected to flash chromatography to separate the excess diol[5b] prior to measurement of ee. Thus, the degree of asymmetric induction implied by the enantiomeric purity of the isolated products should be viewed cautiously.[5b] Nevertheless, the reactions are effective for accessing highly enantiomerically enriched products in reasonably good yields.

The enantiomeric purities of the cycloadducts were determined by ^1H NMR utilizing (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**11**) as a chiral solvating agent[11]



11

and/or by HPLC (Chiralcel OJ). Racemic samples were used as standards in both assays. In general, the signals for the C-4 vinyl proton of the racemic cyclobutanes **5**/**8**, the C-7 aromatic proton of the racemic dihydrobenzofurans **6**/**9**, and the C-4 hydrogen of the bicyclo[3.2.1]-octenediones **7** were resolved in the presence of the solvating agent (representative examples of spectra can be found in the Supporting Information accompanying our preliminary communication[7]). For **10**, the ee's were determined using the HPLC method.

Table 3. Rearrangements of Cyclobutanes 5/8 to Dihydrobenzofurans 6/9[a]

entry	cyclobutane, % ee	temp (°C)	product, t/c	% yield[b]	% ee[b]
1	(−)-**5a**, 100[c]	−78 to −10	(−)-**6a**, 93:1	94	100[c]
2	(−)-**5b**, 90	−78 to 0	(−)-**6b**, 15:1	79	93
3	(−)-**5c**, 86	−78 to 0	(−)-**6c**, 17:1	93	82
4	(−)-**8a**, 100[c]	−78 to −30	(+)-**9a**, 99:1[d]	100	100[c]
5	(−)-**8b**, 100[c]	−78 to −30	(+)-**9b**, 17:1	83	100[c]

[a] The Ti−TADDOLate promoter was composed of 0.6−0.8 equiv each of $TiCl_4$, $Ti(OiPr)_4$, and **4**, with respect to the cyclobutanes. [b] Yield or ee of isolated product. [c] Only one enantiomer observed in the NMR/HPLC assays described in the text. [d] Only trans by NMR.

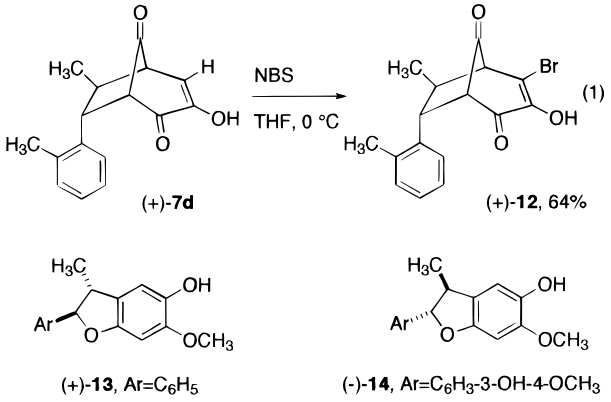
Enantiomerically pure (within the limits of the NMR/HPLC assays) cyclobutanes **5a**/**8a**,**b** and bicyclo[3.2.1]-adducts **7d**,**e** were obtained by simple recrystallization of enantiomerically enriched material. Resubjecting the enantiomerically enriched, or pure, cyclobutanes at −78 °C to the chiral Ti-diol complex prepared from 0.63−0.78 equiv each of $TiCl_4$/$Ti(O\textit{i}\text{-}Pr)_4$/diol-(+)-**4**, followed by warming the mixtures to −30 or 0 °C effected rearrangement to the dihydrobenzofurans **6**/**9** with little, if any, loss in enantiomeric purity (Table 3). Similar rearrangements of **5**/**8** to **6**/**9** can be carried out with protic acids;[2] however, the trans:cis ratio of the dihydrobenzofuran products are lower (∼6−10:1) than those found with the Ti(IV)−Lewis acid promoter.[12] In reactions of enantiomerically enriched **5b**,**c**, recrystallization of the products **6b/c** afforded enantiomerically pure material. The stepwise formation of the dihydrobenzofurans by first isolating the cyclobutanes and then effecting their rearrangement offers a significant advantage over the direct formation via allowing the cycloaddition reactions to warm. The cyclobutanes readily recrystallize to enantiomerically pure material, and their rearrangement to the dihydrobenzofurans occurs without loss of enantiomeric purity.

(11) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.

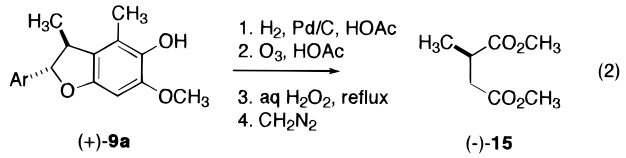
(12) The difference in ratios of cis:trans **6** is significant insofar as their specific rotations are vastly different and of opposite sign (see Experimental Section). Thus, attempts to monitor enantiomeric purity of these mixtures by optical rotation can be very misleading.

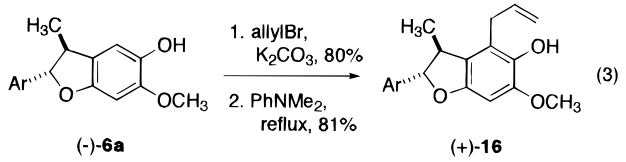
It should be noted that the Ti−TADDOLate promoter gave ratios of cyclobutane to dihydrobenzofuran products considerably different from those found with simple mixtures of $TiCl_4$/Ti(O*i*-Pr)$_4$. With the former, the cyclobutane products were generally found as the major products with electron-rich styrenes at low reaction temperatures, whereas with $TiCl_4$/Ti(O*i*-Pr)$_4$, the dihydrobenzofuran products were usually obtained as the major products.[2] With the more neutral styrenes **1c**−**e**, the bicyclo[3.2.1]-products **7**/**10** were found as major products with the Ti−TADDOLate promoter, whereas with $TiCl_4$/Ti(O*i*-Pr)$_4$, these products were found only in minor amounts. These results suggest that the TADDOLate Lewis acid varies considerably in Lewis acid strength from simple mixtures of $TiCl_4$/Ti(O*i*-Pr)$_4$.[13]

The structure and absolute configuration of the bicyclo[3.2.1]-adduct **7d** was determined by conversion to heavy atom derivative (+)-**12** (eq 1) followed by single-crystal X-ray analysis using the anomalous scattering of the bromine atom (Bijvoet method).[14] The absolute configurations of the other bicyclo[3.2.1]-adducts were then assigned by analogy.

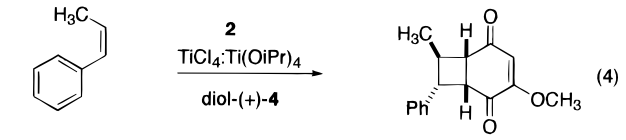


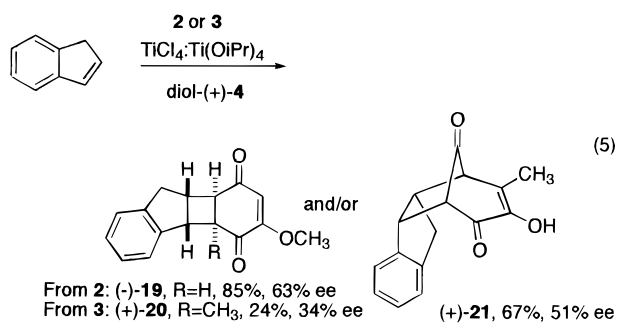
The absolute configurations of the dihydrobenzofuran products (−)-**6** were assigned by comparison of [α] and/or ORD data with those of the natural products (2*R*,3*R*)-(+)-obtusafuran,[15] **13**, and (2*S*,3*S*)-(−)-melanoxin, **14**,[16] of known configuration. The fact that the sign of the optical rotations of dihydrobenzofurans (−)-**6** and (+)-**9** were opposite was of initial concern. However, degradation of (+)-**9a** to dimethyl (*R*)-(+)-2-methyl succinate (**15**),[17] by methods described for similar degradations of **13** and **14** (eq 2),[15,16] confirmed the (2*S*,3*S*) configuration. Furthermore, to verify that introduction of a 4-alkyl group on the dihydrobenzofuran core of (−)-**6a** changed its sign of optical rotation, it was converted to an allyl ether followed by Claisen rearrangement to give (+)-**16** (eq 3) with dextrorotatory rotation. The relative configurations of **5**/**8** were established previously, and their absolute configuration is assigned on the basis of their conversions to **6** and **9**, respectively.





Reactions of (*Z*)-propenylbenzene **17** and of styrenyl systems imbedded in ring systems were also studied. In our original work on Lewis acid-promoted quinone−styrene reactions, we observed that reactions of (*Z*)-propenylbenzenes were in general slower and not as clean as those of the corresponding (*E*)-isomers.[2e] Similarly, reaction of **17** with the Ti-(+)-**4**-TADDOLate prepared as described above afforded the cyclobutane product (−)-**18** in modest yield, but reasonably good ee (eq 4). Indene reacted with quinones **2** and **3** to give products (−)-**19** and (+)-**20**/**21**, respectively, in good yields, but modest ee's (eq 5). The enantiomeric purities of **18**−**21** were again established via ^{1}H NMR using **11** and/or HPLC (Chiralcel OJ) with racemic mixtures as standards. Recrystallization of **18** gave enantiomerically homogeneous material, but no attempts were made to obtain **19**−**21** in higher enantiomeric enrichment. The absolute configurations of the products are assigned tentatively from mechanistic considerations (vide infra).





Reactions of 1-anisylcycloalkenes with quinone **2** were far more complex. As with styrenes **1**, reactions of **22**/**23**

(13) The strength of the Lewis acid promoter in reactions of styrenyl systems with 2-alkoxy- and 2-alkoxy-6-methyl-1,4-benzoquinones has a significant influence on the ratio of the dihydrobenzofuran versus the cyclobutane products. In general, with the strong Lewis acid $TiCl_4$, mainly dihydrobenzofurans are found, whereas with mixtures of $TiCl_4$/Ti(O*i*-Pr)$_4$ more of the cyclobutanes are produced, in many cases as the major products. A further consideration in the Ti−TADDOLate-promoted reactions is the large amount of Ti(IV) employed. Some of the excess Ti(IV) may coordinate to the carbonyl group in **36**, slowing C−O bond formation to **6**/**9**, but having a relatively much lesser effect (if any) on C−C bond formation leading to **5**/**8**. This stoichiometry may also play a role in the difference in ee found between the cyclobutane and dihydrobenzofuran products from reactions of **1** with **2**/**3**. Coordination of a second Ti(IV) to **36** may allow a deprotonation−reprotonation sequence to compete (see eq 11), resulting in lower ee for **6**/**9**. The rearrangements of **5**/**8** to **6**/**9**, however, employ only 1 equiv or less of Ti(IV), where **36**−(Ti)$_2$ complexes are not likely, and proceed without loss of enantiomeric purity.

(14) See ref 1b, pp 25 and 113, and Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502−510.

(15) Gregson, M.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Dietrichs, H. H.; Gottlieb, O. R. *Phytochemistry* **1978**, *17*, 1395−1400.

(16) Donnelly, B. J.; Donnelly, D. M. X.; O'Sullivan, A. M.; Prendergast, J. P. *Tetrahedron* **1969**, *25*, 4409−4414.

(17) Hayashi, T.; Yamamoto, A.: Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723−727.

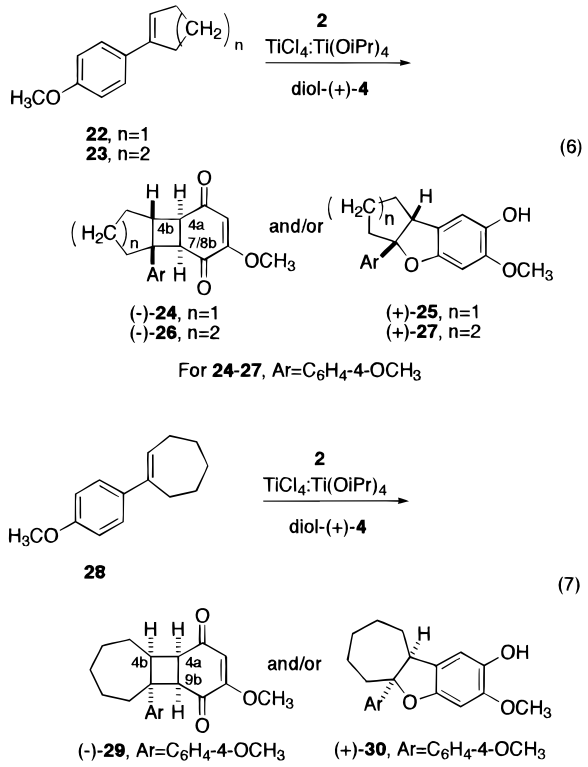
Table 4. Asymmetric Reactions of 1-Anisylcycloalkenes with Quinone 2 Promoted by Ti(IV)−TADDOLates

Entry	Alkene	Promoter: ratio of $TiCl_4$:$Ti(OiPr)_4$:(+)-**4**:**2**[a]	Temp (°C)	Time (min)	Products (-)-**24** % Yield[b]	(-)-**24** % ee[c]	(+)-**25** % Yield[b]	(+)-**25** % ee[c]
1	**22**	2.5:2.5:2.5:1	-95	180	41	89	30	20
2	**22**	2.5:2.5:2.5:1	-78	20	48	96	42	20
3	**22**	2.5:2.5:2.5:1	-78	45	32	89	51	22
4	**22**	2.5:2.5:2.5:1	-78	60	39	90	43	20
5	**22**	2.5:2.5:2.5:1	-78	120	42	86	52	10
6	**22**	1.2:1.2:1.2:1	-94	60	28	89	50	20
7	**22**	1.2:1.2:1.2:1	-78	20	31	88	39	10
8	**22**	1.2:1.2:1.2:1	-78	180	15	88	72	22
		$TiCl_4$:$Ti(OiPr)_4$:(-)-**4**:**2**[a]			ent-(+)-**24**		ent-(-)-**25**	
9	**22**	2.5:2.5:2.5:1	-78	20	31	87	48	15
		$TiCl_4$:$Ti(OiPr)_4$:(+)-**4**:**2**[a]			(-)-**26**		(+)-**27**	
10	**23**	2.5:2.5:2.5:1	-78	60	20	92	40	20
		$TiCl_4$:$Ti(OiPr)_4$:(-)-**4**:**2**[a]			ent-(+)-**26**		ent-(-)-**27**	
11	**23**	2.5:2.5:2.5:1	-78	60	21	>90[d]	54	n.d.[e]
		$TiCl_4$:$Ti(OiPr)_4$:(+)-**4**:**2**[a]			(-)-**29**		(+)-**30**	
12	**28**	2.5:2.5:2.5:1	-78	45	25	57	59	20
13	**28**	2.5:2.5:2.5:1	-78	150	14	52	62	32
14	**28**	1.2:1.2:1.2:1	-90	60	24	42	59	20

[a] The number of equiv of alkene used was 1.0−1.1. [b] Isolated yields. [c] Determined by NMR and/or HPLC on isolated samples. [d] Estimated from optical rotation. [e] Not determined.

afforded cyclobutanes (−)-**24**/**26** in high ee accompanied by dihydrobenzofurans (+)-**25**/**27** in considerably lower ee (Table 4). Contrary to reactions of the styrenes, however, was that the dihydrobenzofuran products **25**/**27** were often found in quantities greater than the cyclobutanes, even at low reaction temperatures. Reactions of **22** with **2** were conducted under a variety of conditions in efforts to optimize the formation of (−)-**24**, with some improvement. In addition, reactions of the cycloheptene derivative **28** gave a cyclobutane product (−)-**29** in moderate yield but with ee significantly lower than those found for analogous products **24**/**26**; dihydrobenzofuran (+)-**30** was also found in moderate yield and low ee (eq 7). More importantly, initial structural analysis (^{1}H NMR, ^{1}H−^{1}H NOE) suggested that cyclobutane (−)-**29** possessed a different relative stereochemistry than products **24**/**26**. As a result, the absolute stereochemistries of all of the products were in question; rearrangements of cyclobutanes with the relative stereochemistries of **24**/**26** and **29** would give dihydrobenzofurans with opposite absolute configuration.

Detailed structural analyses of the products and further examination of reaction conditions for their formation were undertaken. The relative cis−anti−cis stereochemistry for cyclobutanes **24**/**26** and the cis−syn−cis stereochemistry around the cyclobutane ring in (−)-**29** were assigned from ^{1}H−^{1}H NOE data (summarized in the Experimental Section). The enantiomeric excesses of (−)-**24**/**26** were determined by ^{1}H NMR analysis in the presence of **11**, in which signals at 5.94 and 5.88 ppm (H-3) for (−)-**24** and (−)-**26**, respectively, split into pairs of well-resolved singlets. To verify the accuracy of these NMR experiments, considerable effort was expended in obtaining racemic samples of **24**, a previously unknown compound.[2e] Careful analysis of reactions of **22** with **2** promoted by various mixtures of $TiCl_4$/$Ti(OiPr)_4$ at low



(6)

(7)

temperature revealed that cyclobutane *rac*-**24** was produced in low, but serviceable yield; as in our previous studies, dihydrobenzofuran *rac*-**25** was usually found as the major product (Table 5).[2e] Attempts to isolate cyclobutane *rac*-**26** from similar reactions of **23** with **2** were not successful. However, promotion of reactions of both **22** and **23** with **2** using a Ti−TADDOLate formed from diol ent-(−)-**4** gave cyclobutane products *ent*-(+)-**24**/**26** (Table 4, entry 11), whose NMR spectra in the presence

Table 5. Ti(IV)-Promoted Reactions of 1-Anisylcyclopentene 22 with Quinone 2

entry	$TiCl_4$:$Ti(OiPr)_4$ (equiv)[b]	temp (°C)	time (min)	% yield[a] *rac*-**24**	% yield[a] *rac*-**25**
1	1:1 (0.5)	−78	120	8	64
2	2:1 (0.5)	−78	30	7	65
3	1:1 (1.0)	−85	120	33[c]	62[c]
4	2:1 (1.0)	−90	15	12	68
5	1:1 (2.5)	−78	30	6	33

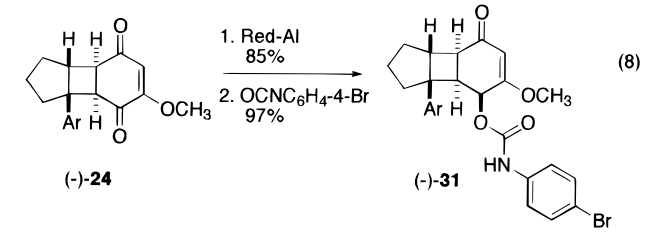
[a] Isolated yields. [b] Equiv of Ti/quinone. [c] Based on recovered **22** (54%).

of **11** and [α] identified them as enantiomers of (−)-**24**/**26**. *rac*-**24** and *ent*-**24**/**26** were then used as standards to validate the NMR assay developed to measure ee, as well as to develop an HPLC method in which a Chiralcel OD column worked well.

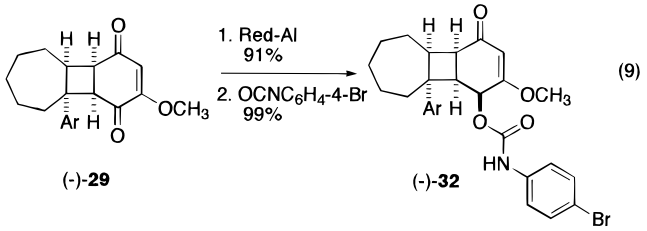
Cyclobutane (−)-**29** was also analyzed by both the ^1H NMR method with **11** and by chiral HPLC (Chiralcel OD column). The NMR experiment showed that a signal at 6.12 ppm split into a pair of well-resolved singlets upon addition of the chiral solvating agent, and the ratio of these signals was consistent with the ratio of two signals observed in the chiral HPLC experiment.

Again, simple recrystallization of enantiomerically enriched samples of both (−)-**24**/**26** gave enantiomerically pure material, within the limits of the NMR/HPLC assays described above. Similarly, recrystallization of (−)-**29** gave a sample that was homogeneous in these assays and was thus taken to be enantiomerically pure. In all cases, the only peaks observed in the analyses of the recrystallized samples were those corresponding to the major isomers from the cycloaddition reactions.

To confirm their structures, enantiomerically homogeneous cyclobutanes (−)-**24** and (−)-**29** were selectively reduced with Red-Al and the alcohol products converted to carbamates (−)-**31** and (−)-**32**, respectively (eqs 8 and 9), which were subjected to single-crystal X-ray analyses.



(8)



(9)

The structures revealed and the absolute configurations indicated by the anomalous scattering[14] were consistent with the original assignments of (−)-**24** and (−)-**29**. The absolute configuration of (−)-**26** was then assigned due to the similarity of $^1H-^1H$ NOE data collected from it and from (−)-**24** (Figure 1).

Enantiomerically homogeneous cyclobutanes (−)-**24**/**26**/**29** underwent protic acid-catalyzed rearrangement to enantiomerically homogeneous dihydrobenzofurans (+)-**25**, (+)-**27**, and (+)-**30** in good yields (>94%) and with no apparent loss of enantiomeric purity. As before, the enantiomeric purities were determined by the NMR and HPLC analyses described above utilizing racemic samples[2e] as standards. In the ^1H NMR experiments, singlets at 6.44, 6.49, and 6.48 ppm for (+)-**25**, (+)-**27**, and (+)-**30**, respectively, all split into well-resolved signals upon addition of (−)-**11**. $^1H-^1H$ NOE experiments[18] ruled out the possibility of trans-fused diastereomers. Furthermore, to double-check the assignment of absolute stereochemistry, dihydrobenzofuranol (+)-**25** was converted to a *p*-bromobenzoate (eq 10), the structure of which was

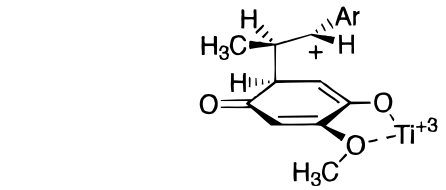
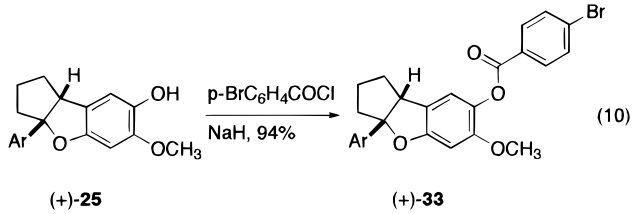


Figure 1. Alignment for four-membered ring closure.



(10)

confirmed by single-crystal X-ray analysis.[14] The absolute stereochemistries of (+)-**27** and (+)-**30** were then assigned from the mechanism likely operative in their formation from (−)-**26**/**29**. That the diastereomeric cyclobutanes **24**/**26** and **29** from the cycloaddition reactions with the Ti−(+)-**4** TADDOLate all have the same sign of optical rotation as do the diastereomeric dihydrobenzofurans **25**/**27** and **30** is apparently fortuitous.

Discussion

We have suggested that the mechanism for the quinone−propenylbenzene reactions involves bidentate coordination of Ti(IV) to the quinone followed by a 5+2 ($4\pi+2\pi$) cycloaddition of the pentadienyl carbocation moiety of complex **34**[19] with the propenylbenzene to

(18) $^1H-^1H$ NOE data for (±)-**25** and (±)-**27** can be found in ref 2e. Similar $^1H-^1H$ NOEs are also found in (±)-**30**.

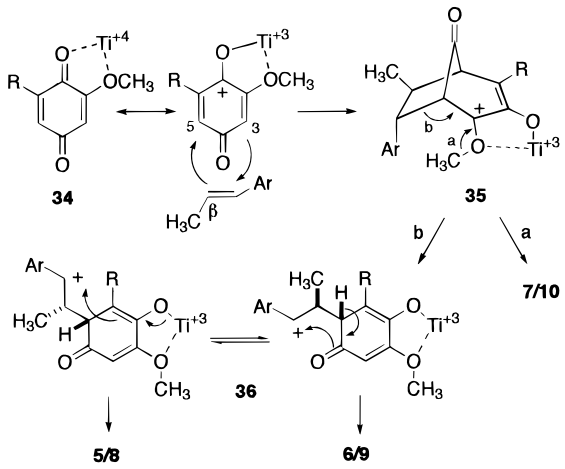
(19) Similar 5+2 cycloadditions are observed in carbocations formed in solvolysis of quinone monoketals or oxidation of phenols, see: (a) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073−8075. (b) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717−3719. (c) Mak, C.-P.; Büchi, G. *J. Org. Chem.* **1981**, *46*, 1−3. (d) Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2305−2307. (e) Angle, S. R.; Turnbull, K. D. *J. Org. Chem.* **1993,** *58*, 5360−5369. (f) Gates, B. D.; Dalidowicz, P.; Tebben. A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135−2143. (g) Yamamura, S.; Shizuri, Y.; Shigemori, H.; Okuno, Y.; Ohkubo, M. *Tetrahedron* **1991**, *47*, 635−644. (h) Takakura, H.; Yamamura, S. *Tetrahedron Lett.* **1998**, *39*, 3717−3720. (i) Shizuri, Y.; Shigemori, H.; Suyama, K.; Nakamura, K.; Okuno, Y.; Ohkubo, M.; Yamamura, S. In *Studies in Natrural Product Chemistry*, Vol. 8; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; pp 159−173. (j) Grieco, P. A.; Walker, J. K. *Tetrahedron* **1997**, *53*, 8975−8996. (k) Collins, J. L.; Grieco, P. A., Walker, J. K. *Tetrahedron Lett.* **1997**, *38*, 1321−1324. An analogous process is the perezone to pipitzol rearrangement, see: (l) Joseph-Nathan, P.; Santillan, R. L. In *Studies in Natrural Product Chemistry*, Vol. 5; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam; 1989; pp 763−813. Intramolecular carbocation activation of quinones to intermolecular 5+2 cycloaddition with styrene has been reported; see: (m) Mamont, P. *Bull. Soc. Chim. Fr.* **1970**, 1557−1564.

afford bicyclo[3.2.1]octenyl carbocation **35** (Scheme 2; for clarity, the other ligands on Ti are not shown). In this cycloaddition, the stereoselectivity is a result of a preference for the aryl group of the propenylbenzene to occupy an endo orientation with respect to the carbocation moiety. The regioselectivity is directed by bond formation between the more nucleophilic C-β of the propenylbenzene and the electrophilic C-5 atom of the Ti−quinone complex. From **35**, dealkylation (a) affords the bicyclo-[3.2.1]-adducts **7**/**10**. Alternatively, C-1/C-7 bond cleavage (b) gives stabilized benzylic carbocation **36**, and C−C bond formation between the carbocation center and the Ti−enolate produces **5**/**8**, whereas C−O bond formation with loss of H^+ yields **6**/**9**. In the latter processes, collapse to **5**/**8** is best described as the product of kinetic control; that is, yields of **5**/**8** relative to **6**/**9** are highest at low reaction temperature. Formation of **6**/**9** is thermodynamically preferred, as evidenced by its exclusive formation at higher cycloaddition temperatures and by rearrangement of the cyclobutanes **5**/**8** to **6**/**9** under either Ti(IV)- or H^+-promoted processes. The kinetic preference for **5**/**8** is likely stereoelectronic in origin. The carbocation center can approach the enolate from a direction close to the preferred perpendicular alignment with little distortion (Figure 1); however, considerable twisting is required for the carbocation to be placed in a position to bond to an electron lone pair on the carbonyl oxygen.[13]

The effects of substituents, on either the quinone or the propenylbenzene, on the relative yields of the various products are readily explained by this mechanism. Reactions of propenylbenzenes **1** bearing electron-donating OCH_3 substitutents produce no 5+2 products, suggesting that the rate of dealkylation is slow relative to collapse to stabilized benzylic carbocation **36**. That the neutral propenylbenzene **1e** gives only the 5+2 products indicates that the dealkylation competes effectively in this case with collapse to **36**. Reaction of **1d** is particularly instructive; only the 5+2 product is found, which indicates again that collapse of **35** to **36** is slow compared to the dealkylation, probably due to steric inhibition of resonance stabilization of the developing benzylic carbocation by the *o*-methyl group. The higher yields of dihydrobenzofurans relative to the cyclobutanes in reactions of **3**, compared to reactions of **2**, are likely due either to slower formation of the latter from intermediate **36** or to faster rearrangement of the cyclobutane to the dihydrobenzofuran. Either can be attributed to steric interaction between the methyl group-R and the aryl ring.

The cycloaddition model proposed in Scheme 2 is useful for rationalizing the enantioselectivities found in the products from reactions of the quinones with propenylbenzenes **1**. Although it may appear that the chiral ligands of the Ti−TADDOLate−quinone complex would be far from the center of action, the reactions do provide products in high ee; thus the ligands obviously have considerable influence. Seebach[5] and DiMare[20] have suggested a model[21] for the Ti−TADDOLate-promoted

Scheme 2



reactions. Applying this model to the quinone−propenylbenzene reactions, the observed attack on the C-3 *si*/C-5 *re* face[22] is represented as **A** in Figure 2. In this model, one of the quasiaxial phenyl rings of the TADDOL ligand blocks the C-3 *re*/C-5 *si* face of the quinone. The alternative binding mode **B** places the carbonyl group to be activated in an unfavorable position cis rather than trans to a Cl ligand.[20] In addition, upon approach of a propenylbenzene with the aryl group in an endo position, a steric interaction develops between the aryl group and Cl* in **B** (see arrow) that is not found in **A**. The more sluggish reactions and lower ee's found with (*Z*)-propenylbenzene **17** and with indene reflect the higher steric expense in placing both the aryl and methyl groups in an endo orientation.

Caution is recommended, however, in relying strongly on this preliminary model. The experimental "recipes" used for preparation of Ti−TADDOLate promoter(s) vary

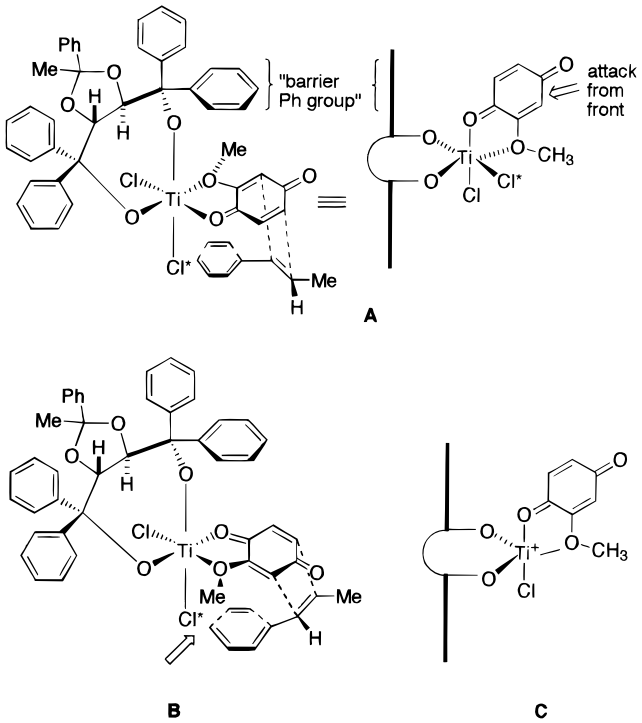


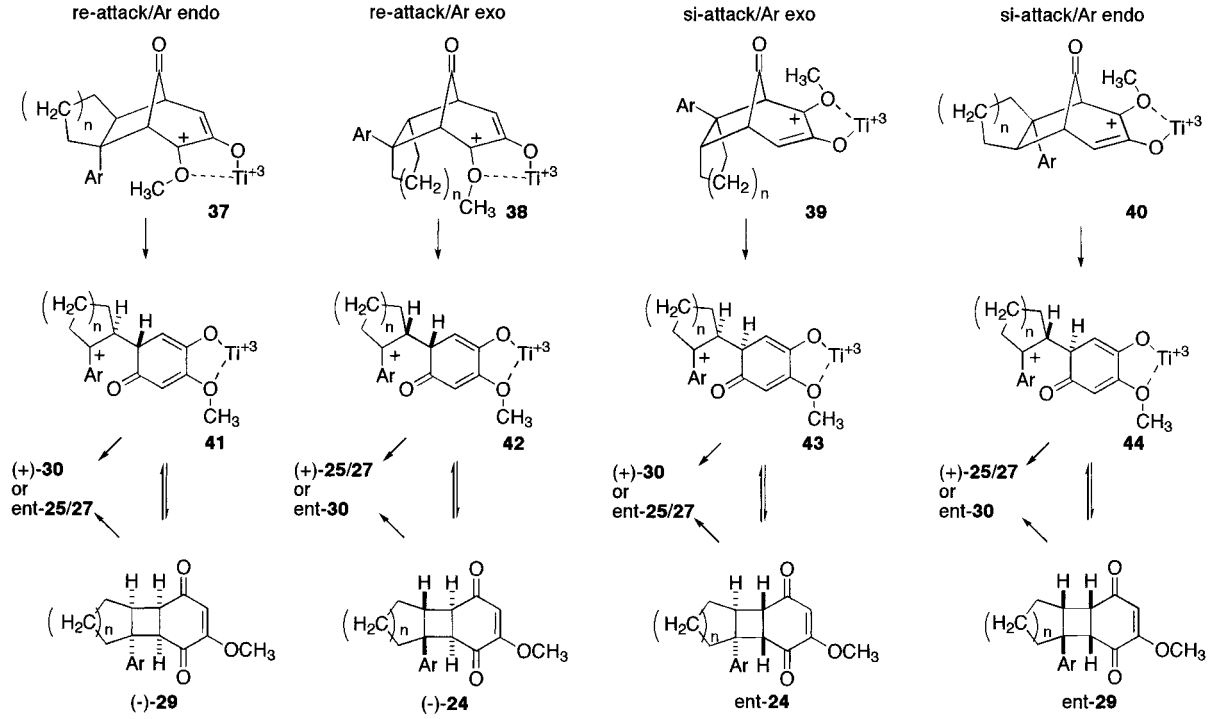
Figure 2. Possible transition states for Ti−TADDOLate-promoted reactions of **1** with **2** based on models[5,20,21] proposed by Seebach and DiMare.

(20) (a) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777−1787. (b) This model is further supported by quantum chemical calculations, see: García, J. I.; Martínez-Merino, V.; Mayoral, J. A. *J. Org. Chem.* **1998**, *63*, 2321−2324.

(21) For other models, see ref 8 and Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 6847−6851.

(22) The same facial selectivity is also found in Diels−Alder reactions of quinones promoted by Ti−TADDOLates: Engler, T. A.; Letavic, M. A.; Lynch, K. O., Jr.; Takusagawa, F. *J. Org. Chem.* **1994** *59*, 1179−1183.

Scheme 3



significantly for different applications,[5b] and structural data on the complexes are lacking for most.[20,21] The reactions described herein are a case in point. The stoichiometry required to generate an effective promoter, devised empirically after substantial effort, differs considerably from those used by Seebach,[5] Narasaka,[6] and Corey[8] for *N*-2-butenoyloxazolidinone/cyclopentadiene Diels–Alder reactions and other applications; that is, best results were found with a complex prepared from a 2.5:2.5:2.5:1 combination of $TiCl_4$/Ti(O*i*-Pr)$_4$/diol-**4**/quinone (i.e., 2 equiv of Ti/diol and 5 equiv of Ti/quinone). Recently, Seebach[5c] suggested that Ti–TADDOLate-catalyzed reactions may proceed via cationic trigonal-bipyramidal complexes such as **C** (Figure 2), formed by abstraction of Cl^- from complex **A** by a second Ti(IV) entity. This suggestion may account for the stoichiometry required in the quinone–propenylbenzene reactions.

Of obvious concern are the significant differences in ee's found for the cyclobutane products in comparison to the dihydrobenzofurans from the same reactions. This concern is heightened in reactions of the arylcycloalkenes in which the major products are usually the dihydrobenzofurans, formed in low ee, whereas the minor cyclobutane products are found in high ee. In the latter reactions, bicyclo[3.2.1]-adducts are not found;[23] thus the involvement of bicyclic cationic intermediates is questionable. However, it is not necessary to distinguish between the direct formation of benzylic carbocations **41**–**44** (Scheme 3) from their formation via the cycloaddition mechanism wherein bicyclo[3.2.1]carbocations **37**–**40** are formed initially followed by fragmentation as shown. Both mechanisms can lead to cyclobutane products. In principle, the arylcycloalkene can approach the C-5 carbon of the quinone–Ti complex from the *si* or *re* face and in orientations with the aryl group endo or exo with respect to the pentadienyl moiety (i.e., face selectivity with respect to the alkene; the exo or endo terms are used for convenience and need not imply a cycloaddition mechanism). After complexation and either cycloaddition or alkylation, four bicyclic carbocations **37**–**40** or benzylic cations **41**–**44** are possible, which then lead to products. Since the ring fusions in the 2+2 adducts are cis in all cases (trans fused systems are apparently prohibitively strained), each of the carbocations **37**–**40**, or **41**-**44**, gives rise to a cyclobutane of unique diastereochemistry and chirality. This is not the case with the dihydrobenzofuran products; either of two of the carbocationic intermediates, or cyclobutanes, can produce the same enantiomeric dihydrobenzofuran. Thus, the stereochemistry of the cyclobutane products provides the most information regarding the quinone facial selectivity and orientation of the approaching arylcycloalkene.

The structures of (–)-**24**/**26** from reactions promoted by the Ti–(+)-**4** complex suggest a pathway leading via intermediates **38** or **42**, i.e., C-5 *re* attack, aryl group exo (Scheme 3). On the other hand, the structure of the arylcycloheptene 2+2 adduct, (–)-**29,** indicates a route via **37** or **41**, i.e., C-5 *re* attack, aryl group endo. These results again establish *re* face selectivity with respect to the C-5 carbon of the quinone.[22] Reasons for the apparent switch from an endo-aryl orientation in reactions of the propenylbenzenes **1** and arylcycloheptene **28** to an exo orientation in reactions with arylcyclopentene **22** and arylcyclohexene **23** are not apparent. In the absence of structural information for the chiral Ti-promoter or its complex with the quinone, explanations for this change in orientation would be highly speculative. The routes to the dihydrobenzofuran enantiomers (+)-**25**/**27** and (+)-**30** each could involve two different cations in the series **37**–**40** or **41**–**44**. They could also result from rearrangement of two different cyclobutane products.

As previously mentioned, the difference in enantiomeric purities of the cyclobutanes versus the dihydroben-

(23) Bicyclo[3.2.1]-adducts have however been found in reactions of arylcycloalkenes with quinones promoted by simple mixtures of $TiCl_4$/Ti(O*i*-Pr)$_4$; see ref 2e.

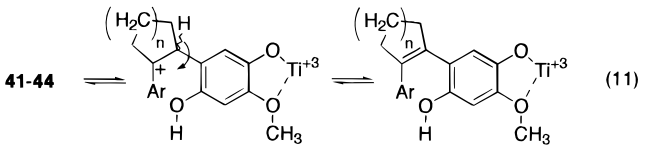
Table 6. Rearrangement of (−)-24[a] to (+)-25 Promoted by Ti−TADDOLates

entry	reactants: ratio of $TiCl_4$:Ti(O*i*-Pr)$_4$:(+)-**4**:**24**	quench temp (°C)[b]	time (min)	(−)-**24** % consumption[c]	(+)-**25** % ee[d]
1	2.5:2.5:2.5:1	−78	7	91	100
2	1.6:1.6:1.6:1	−75	10	16	100
3	1.6:1.6:1.6:1	−60	20	32	100
4	1.6:1.6:1.6:1	−40	30	68	100
5	1.6:1.6:1.6:1	−20	40	87	100
6	1.6:1.6:1.6:1	−5	50	98	100
7	1.6:1.6:1.6:1	10	60	>99	100[e]
entry	reactants: ratio of $TiCl_4$:Ti(OiPr)$_4$:(−)-**4**:**24**	quench temp (°C)[b]	time (min)	(−)-**24** % consumption[c]	(+)-**25** % ee[d]
8	2.5:2.5:2.5:1	−78	10	98	100
9	1.6:1.6:1.6:1	−75	10	92	100
10	1.6:1.6:1.6:1	−60	20	>99	100[e]

[a] Enantiomerically pure. [b] Reactants were combined at −78 °C and allowed to warm to this temperature over the time indicated. [c] Based on disappearance of (−)-**24** by HPLC. [d] By HPLC; 100 indicates that only one enantiomer was observed. [e] By HPLC and NMR (see text) after workup and flash chromatography.

zofurans from the same reaction mixtures raises questions about a common mechanism for their formation. Possible explanations include (1) entirely different mechanisms for formation of the two types of products, (2) formation of cationic intermediates **37**−**40** or **41**−**44**, in some unknown proportion, followed by a kinetic partitioning in their collapse to the products, or (3) racemization during rearrangement of one or more of the cyclobutanes to the dihydrobenzofurans. With respect to the possibility of entirely different mechanisms, there is no evidence for other intermediates. Thus, this possibility remains open, but will not be discussed further. An explanation based on kinetic partitioning involves a complex set of kinetic expressions, and information required for a complete analysis is lacking. To explain the amount of any one product requires knowing something about the relative rates of formation of each intermediate **37**−**40** and/or **41**−**44** and the relative rates of their respective collapse to two different products. The possibility that some of the individual steps in this scheme may be reversible (see below) further complicates matters.

Racemization during conversion of the cyclobutanes to dihydrobenzofurans seems unlikely on initial consideration, since enantiomerically pure cyclobutanes (−)-**24**/**26**/**29** undergo protic acid-catalyzed rearrangement to dihydrobenzofurans (+)-**25**/**27**/**30** without loss of enantiomeric purity. However, these rearrangements are done at room temperature using protic acid (*p*-TsOH) while the cycloaddition experiments involve a Ti(IV)−Lewis acid at −78 °C. Thus, a rearrangement under the cycloaddition reaction conditions must occur at low temperatures and likely involve the chiral Lewis acid. In the latter event, it is possible that the rearrangement process is slowed enough for a racemization via a deprotonation−protonation sequence on the carbocationic intermediates (eq 11) to compete with dihydrobenzofuran formation.



(11)

To study the possibility of an in situ cyclobutane to dihydrobenzofuran rearrangement, attempts were made to resubject enantiomerically pure cyclobutane (−)-**24** to the reaction conditions, with interesting results. Cyclobutane (−)-**24** was chosen because (a) it could be readily prepared in sufficient quantities and in high enantiomeric excess from the cycloaddition reaction, (b) a single recrystallization then afforded enantiomerically pure material, and (c) its ee and that of (+)-**25** from the same cycloaddition reaction were dramatically different. These experiments were carried out with Ti−TADDOLates prepared from both (+)-**4** and ent-(−)-**4**. Thus, (−)-**24** was treated with 1:1:1 mixtures of $TiCl_4$/Ti(O*i*-Pr)$_4$/(+)- or (−)-diols **4**, 2.5 equiv of each with respect to the cyclobutane, and the reactions were monitored by chiral HPLC. After complete disappearance of the cyclobutane, the reactions were worked up and chromatographed to isolate (+)-**25**. The relative rates of disappearance of (−)-**24** with both enantiomeric Ti(IV)−TADDOLates were very high even at low temperature (Table 6, entries 1 and 8). To explain the sizable amounts of the cyclobutanes isolated from the original cycloaddition reactions, it was postulated that the number of equivalents of the free chiral Lewis acid with respect to the cyclobutane in the original reaction mixture was lower than that in the rearrangement experiments now described. Some of the Lewis acid was likely bound to other species present in the reaction mixtures (the dihydrobenzofuran, the quinone, and/or the alkene).

Efforts were then made to modify the conditions to slow the rearrangement and perhaps to more accurately mimic the cycloaddition conditions. Thus, rearrangements of cyclobutane (−)-**24** to (+)-**25** promoted by complexes formed from 1.6 equiv of each $TiCl_4$/Ti(O*i*-Pr)$_4$/TADDOLs-**4** were studied (Table 6). The results clearly demonstrated that the rearrangement of (−)-**24** promoted by Ti−(+)-**4** proceeded more slowly than with Ti−ent-(−)-**4**. For example, at −60 °C the rearrangement of (−)-**24** with Ti−ent-(−)-**4** was almost complete in 20 min (>99% consumption of the cyclobutane), while the rearrangement with Ti−(+)-**4** stood at 32% conversion (Table 6, entries 10 and 3) and was at 87% conversion only after 40 min at −20 °C (entry 5). The faster reaction with Ti−ent-(−)-**4** was clean and free of ent-(−)-**25** by HPLC analysis. The slower reaction promoted by Ti−(+)-**4** was not as clean, and although at longer reaction times the major product was clearly (+)-**25**, sizable peaks with retention times similar to ent-(−)-**25** were apparent in the crude reaction mixture. A co-inject with authentic *rac*-**25** did not discount the presence of small amounts of ent-(−)-**25**. However, in both reactions the dihydrobenzofuran product (+)-**25** was isolated chromatographically

and found to be a single enantiomer (~80% yields) by the chiral HPLC and NMR assays.

This study established that (1) Ti−TADDOLate mixtures do promote the rearrangement of the cyclobutanes to the dihydrobenzofurans apparently with little or no loss of enantiomeric purity, and (2) the rearrangement proceeds at significantly different rates with the enantiomeric Ti−TADDOLate's, i.e., Ti−(+)-**4** versus Ti−ent-(−)-**4**.

Taken as a whole, the data indicate that the facial or exo/endo selectivities in the formation of **37**−**40** or **41**−**44** (Scheme 3) are probably not in fact as high as implied by the ee's of the isolated cyclobutane products. For example, in reactions involving the Ti−(+)-**4** TADDOLate, if one assumes that (1) both enantiomers of cyclobutane **24** are formed, with (−)-**24** major as a result of some facial selectivity and complete exo or endo selectivity, (2) under the reaction conditions the minor isomer ent-(+)-**24** rearranges faster than (−)-**24**, and (3) these processes are occurring exclusively, then the dihydrobenzofuran product isolated should be enriched in ent-(−)-**25**. But this is not the case. The yield of the isolated product (+)-**25** coupled with what is known about the rearrangement of (−)-**24** to (+)-**25** with Ti−(+)-**4** (slow) as compared to that of ent-(+)-**24** to ent-(−)-**25** with Ti−(+)-**4** [fast, i.e., the same as (−)-**24** with Ti−ent-(−)-**4**] indicates that dihydrobenzofuran (+)-**25** must be formed by some mechanism other than rearrangement of (−)-**24**. If this alternate route gives mainly (+)-**25**, such a process occurring simultaneously with rearrangement of the minor cyclobutane isomer ent-(+)-**24** results in enrichment of isolated (−)-**24** and low ee of (+)-**25**. A similar argument can be made assuming complete facial selectivity and some exo/endo selectivity.

Thus, some type of kinetic partitioning from intermediates **37**−**40** or **41**−**44** (Scheme 3) likely explains the formation of cyclobutanes **24**/**26** and dihydrobenzofurans **25**/**27** in different ee's. It is not clear whether a similar argument can be made to explain the difference in the ee's found in products (−)-**29** and (+)-**30** from reactions of arylcylcoheptene **28** with quinone **2**. The low yields and modest ee's found for (−)-**29** (diastereomeric with **24**/**26**) coupled with a lack of a supply of ent-**29** discouraged the exploration of relative rates of rearrangement of these cyclobutanes with the enantiomeric Ti−TADDOLates.

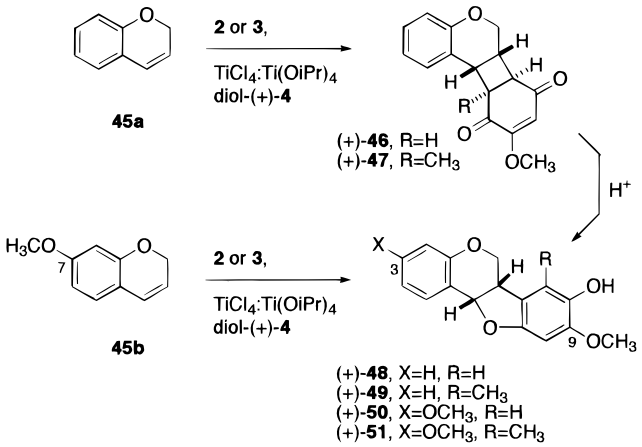
The cyclobutane to dihydrobenzofuran rearrangements mediated by the chiral Ti−TADDOLates described above establish that the rates of these processes are considerably different for isomeric cyclobutanes. Different rearrangement rates are not unexpected for diastereomeric cyclobutanes, and the case of **24** versus ent-**24** represents a kinetic resolution.[1] To explore the latter, *rac*-**24** was treated with the chiral Ti−TADDOLate mixtures under various conditions (0.25−2.5 equiv of the Ti−TADDOLate, −85 to −10 °C, 15−60% conversion), after which the reactions were worked up and recovered starting material and products isolated and analyzed for enantiomeric enrichment. There was little evidence of kinetic resolution (% ee of product **25** < 6%; % ee of recovered **24** < 5%). There are, however, significant differences in the conditions of these experiments and those of the original cycloaddition of **22** and **2**. The latter reactions likely contain, in addition to the Ti−TADDOLate and chiral products **24**/**25**, unreacted quinone and arylcycloalkene, which could alter the nature of the Lewis acid. A second, perhaps more significant issue is that the rearrangements are not catalytic in Ti(IV) since a Ti(IV)−phenoxide results with loss of H^+. The protic acid generated could alter the nature of the Ti−TADDOLate or effect the rearrangement of each enantiomer of **24** to the respective enantiomers of **25** in an enantiospecific manner, thus leading to racemic product. These potential kinetic resolutions were not explored further due to the limited availability of *rac*-**24**.

Applications

The 2-aryl-2,3-dihydrobenzofuran framework is imbedded in the structure of the pterocarpan family of natural products. Pterocarpans and related isoflavonoids exhibit a variety of biological activities, particularly as antifungal and antibacterial agents.[24] Some pterocarpans also show significant anti-HIV activity, as HIV-1 reverse transcriptase inhibitors,[2h] and represent a unique and underexplored class of such agents. Because of these biological activities, there has been considerable interest recently in asymmetric syntheses of pterocarpans.[25]

In the present study, reactions of 2*H*-chromenes **45a**/**b** with quinones **2** and **3** were developed as efficient and expedient asymmetric syntheses of pterocarpans (Scheme 4 and Table 7), particularly those with oxygen substit-

Scheme 4



uents at C-3 and C-9.[26] As observed in the reactions promoted by simple mixtures of $TiCl_4$/Ti(O*i*-Pr)$_4$,[2c] reactions of **45b**, bearing a C-7 methoxy substituent, provided the pterocarpan products (+)-**50**/**51**, whereas reactions of **45a** at low temperatures yielded the cyclobutane

(24) See references cited in ref 2c,h and (a) van Aardt, T. G.; van Heerden, P. S.; Ferreira, D. *Tetrahedron Lett.* **1998**, *39*, 3881−3884. For reviews, see: (b) Dean, F. M. In *Total Synthesis of Natural Products*, Vol 1; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973; pp 467−562. (c) Jain, A.C; Tuli, D. K. *J. Sci. Ind. Res.* **1978**, *37*, 287−304. (d) Ingham, J. L. In *Progress in the Chemistry of Organic Natural Products*, Vol. 43; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: Wien, 1983; pp 1−266. (e) Dewick, P. M. In *The Flavonoids, Advances in Research Since 1986*; Harborne, J. B., Ed.; Chapman & Hall: London, 1994; Chapter 5. (f) Boland, G. M.; Donnelly, D. M. X. *Nat. Prod. Rep.* **1998**, *15*, 241−260, and previous reviews in these series.

(25) For recent examples, see: (a) Versteeg, M.; Bezuidenhoudt, B. C. B.; Ferreira, D.; Swart, K. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1317−1318. (b) Pinard, E.; Gaudry, M.; Hénot, F.; Thellend, A. *Tetrahedron Lett.* **1998**, *39*, 2739−2742. (c) Mori, K.; Kisida, H. *Liebigs Ann. Chem.* **1988**, 721−723. For enantiomeric separation of pterocarpans by HPLC, see: (d) Antus, S.; Bauer, R.; Gottsegen, A.; Wagner, H. *J. Chromatogr.* **1990**, *508*, 212−216. For a recent racemic synthesis: (e) Miki, Y.; Fujita, R.; Matsushita, K.-i. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2533−2536.

(26) Limited SAR studies indicate that C-3/-9 oxygenation may be important for biological activity; see refs 2c,h.

Table 7. Ti−TADDOLate-Promoted Reactions of Quinones 2/3 with 2*H*-Chromenes 45a/b[a]

chromene[b]	quinone	time (h)	product	% yield[c]	% ee[d]
45a	**2**	1.5	**46**	86	84
45a	**3**	27	**47**	64	61
45b	**2**	1.5	**50**	77	75
45b	**3**	0.5	**51**	83	80

[a] All reactions were conducted in CH_2Cl_2 at −78 °C. The Ti−TADDOLate promoter was prepared in the same manner as described for reactions of **1**. [b] 1.1−1.5 equiv with respect to the quinone. [c] Isolated yields. [d] By ^{1}H NMR in the presence of **11**.

products (+)-**46**/**47**. All products were found in 60−84% ee. The enantiomeric purities were determined by ^{1}H NMR analysis in the presence of **11**.[7,11]

Recrystallization of enantiomerically enriched cyclobutane (+)-**46** gave enantiomerically homogeneous material. Treatment of the latter with H_2SO_4 effected its rearrangement to pterocarpan (+)-**48** without loss of enantiomeric purity. Similarly, H^+-promoted rearrangement of a sample of (+)-**47** which was of 61% ee gave pterocarpan (+)-**49** with the same enantiomeric purity. The absolute configuration of synthetic (+)-**50** was assigned on the basis of comparison with its naturally occurring enantiomer.[27a] The stereochemistry of the other pterocarpans prepared herein was then assigned by analogy and by comparison of their optical rotations[27b] (at several different wavelengths) and NMR spectra in the presence of (−)-**11** to those of (+)-**50**. The relative stereochemistry in racemic cyclobutanes (+)-**46**/**47** has been determined previously by ^{1}H−^{1}H NOE experiments,[2c] and their rearrangement to pterocarpans (+)-**48**/**49** establishes the absolute stereochemistry of **46**/**47**.

2-Aryl-3-methyl-2,3-dihydrobenzofuran and bicyclo[3.2.1]octendione structures are also found in numerous other biologically active natural products.[28] The enantioselective reactions described herein offer a convenient asymmetric route to many of these systems and hold considerable potential for additional applications as well.

Experimental Section

General Procedures. Diols-**4**,[5,6] propenylbenzenes **1**/**17**,[2e] 1-anisylcycloalkenes,[2e] and 2*H*-chromenes **45a**/**b**[2c] were prepared as previously described. All reactions were conducted under an atmosphere of N_2 and were monitored by TLC. Melting points are uncorrected. NMR spectra were recorded on samples dissolved in $CDCl_3$, unless indicated otherwise, and data are reported in δ (ppm) relative to TMS or residual $CHCl_3$ as internal standards. Coupling constants are reported in hertz (Hz). IR data are reported in cm^{-1}. Spectral data for (−)-**5a**−**c**, (−)-**6a**−**c**, (+)-**7d**,**e**, (−)-**8a**−**c**, (+)-**9a**,**b**, (+)-**10c**,**d**, (−)-**18**,**19**, (+)-**20**, **-21**, **-25**, **-27**, **-30**, **-46**−**51**, all white solids unless stated otherwise, were identical to those of their racemates previously reported.[2c,e] Optical rotations were taken at ambient temperature.

General Procedure for Cycloadditions of Propenylbenzenes 1 and 2*H*-Chromenes 45a/b with Quinones 2 and 3: Reaction of 1a with 2 Is Representative. (1*R*,6*R*,7*R*,8*R*)-3-Methoxy-8-(3,4-dimethoxyphenyl)-7-methylbicyclo[4.2.0]-oct-3-en-2,5-dione (5a) and (2*S*,3*S*)-6-Methoxy-2-(3,4-dimethoxyphenyl)-3-methyl-2,3-dihydro-5-benzofuranol (6a). To a solution of Ti(O*i*-Pr)$_4$ (2.63 mL, 8.84 mmol) in CH_2Cl_2 (5 mL) at room temperature was added $TiCl_4$ (966 μL, 8.81 mmol) followed rapidly by the addition of a solution of diol (+)-**4** (4.71 g, 8.91 mmol) in CH_2Cl_2 (10 mL). The mixture was then added to a solution of **2** (0.495 g, 3.58 mmol) in CH_2Cl_2 (30 mL) at −78 °C (or −94 °C, see Table 2: the order of addition was not important; in some reactions, a solution of the quinone in CH_2Cl_2 was added to the Ti(IV)−diol-**4** solution). The reaction mixture was stirred at −78 °C (or −94 °C) for 15 min, and then **1a** (644 μL, 3.81 mmol) was added dropwise. The reaction mixture was stirred for 2 h at −78 °C (or the time and temperature indicated in Tables 2 and 7), and then $NaHCO_3$ (8.06 g) and *i*-PrOH (20 mL) were added at −78 °C. The mixture was diluted with water, filtered through Celite, and extracted with CH_2Cl_2 (3 × 250 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Chromatography of the resulting oil on flash silica with 20%, 60%, and then 70% EtOAc/hexanes as eluents gave recovered diol (+)-**4** (routinely >90%, which was pooled for recycling), **6a** (0.105 g, 9%, 41% ee), and **5a** (0.977 g, 86%, 92% ee). Recrystallization of **5a** from EtOAc/hexanes provided enantiomerically homogeneous product; mp 137−138 °C, $[\alpha]_{589}$ = −295 (*c* 12.8 mg/mL, $CHCl_3$). Repeated recrystallizations (up to five) did not increase the specific rotation.

The following reactions were conducted in a similar manner with the same ratios but variable quantities of reactants (for reaction temperatures and times, see Tables 2 and 7).

1b with **2** gave a 20.3:1 mixture of **5b** (0.255 g, 86%, 90% ee) and an unidentified isomer and **6b** (0.031 g, 11%, 53% ee); the optical rotation of this sample of **5b** was $[\alpha]_{598}$ = −273 (*c* 10 mg/mL, $CHCl_3$).

1c with **2** gave a 19.9:1 mixture of **5c** (0.101 g, 71%) and an unidentified isomer; the major isomer was 86% ee by ^{1}H NMR and the optical rotation of this sample was $[\alpha]_{589}$ = −225 (*c* 10 mg/mL, $CHCl_3$).

1d with **2** gave **7d** (0.089 g, 64%, 84% ee).

1e with **2** gave **7e** (0.150 g, 61%, 90% ee).

1a with **3** gave **8a** (0.407 g, 35%, 88% ee) and **9a** (0.564 g, 48%, 83% ee).

1b with **3** gave **8b** (0.754 g, 72%, 87% ee) and **9b** (0.162 g, 15%, 78% ee).

1c with **3** gave **8c** (0.014 g, 10%, 70% ee) and **10c** (0.084 g, 61%, 92% ee); the optical rotation of this sample of **10c** was $[\alpha]_{589}$ = +52, $[\alpha]_{578}$ = +55, $[\alpha]_{546}$ = +64, $[\alpha]_{436}$ = +65 (*c* 1.8 mg/mL $CHCl_3$).

1d with **3** gave **10d** (0.107 g, 79%, 96% ee); the optical rotation of this sample of **10d** was $[\alpha]_{589}$ = +381, $[\alpha]_{578}$ = +401, $[\alpha]_{546}$ = +478, $[\alpha]_{436}$ = +1080, $[\alpha]_{365}$ = +2914 (*c* 1.5 mg/mL $CHCl_3$).

17 with **2** gave a 10:1 ratio of **18** and **5e** (0.057 g, 42%, 78% ee for the major isomer).

Indene with **2** gave **19** (0.115 g, 85%, 63% ee); the optical rotation of this sample was $[\alpha]_{589}$ = −6.8 (*c* 11 mg/mL, $CHCl_3$).

Indene with **3** gave gave **20** (0.033 g, 24%, 34% ee) and **21** (0.090 g, 68%, 51% ee) as oils. For this sample of **20**, $[\alpha]_{589}$ = +4, $[\alpha]_{578}$ = +2, $[\alpha]_{546}$ = +4, $[\alpha]_{436}$ = +1 (*c* 2.1 mg/mL $CHCl_3$); for **21**, $[\alpha]_{589}$ = +177, $[\alpha]_{578}$ = +186, $[\alpha]_{546}$ = +218, $[\alpha]_{436}$ = +241 (*c* 9.2 mg/mL $CHCl_3$).

45a with **2** gave **46** (0.12 g, 86%, 84% ee).

45a with **3** gave **47** (0.093 g, 64%, 61% ee).

45b with **2** gave **50** (0.116 g, 77%, 75% ee); the optical rotation for this sample was $[\alpha]_{589}$ = +124 (*c* 23.4 mg/mL, $CHCl_3$).

45b with **3** gave **51** (0.135 g, 83%, 80% ee); the optical rotation for this sample was $[\alpha]_{589}$ = +113 (*c* 14 mg/mL, $CHCl_3$).

Recrystallization of the following products from EtOAc/hexanes gave enatiomerically homogeneous samples: **7d**, mp 212−214 °C, $[\alpha]_{589}$ = +368, $[\alpha]_{546}$ = +463, $[\alpha]_{436}$ = +1046, $[\alpha]_{365}$ = +2940 (*c* 2.9 mg/mL, $CHCl_3$). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.70; H, 6.25. **7e**, mp 200−202 °C,

(27) (a) Bezuidenhoudt, B. C. B.; Brandt, E. V.; Ferreira, D. *Phytochemistry* **1987**, *26*, 531−535. A sample of (−)-**50** was kindly provided by Professor Ferreira: natural (−)-**50**, $[\alpha]_{589}$ = −155 (*c* 5.3 mg/mL, $CHCl_3$); synthetic (+)-**50** (75% ee by ^{1}H NMR analysis with **11**), $[\alpha]_{589}$ = +124 (*c* 23 mg/mL). (b) In the pterocarpan series, a dextrorotatory [α] is indicative of (6a*S*,11*S*) configuration, see refs 27 and 24e.

(28) For reviews: (a) Ward, R. S. *Nat. Prod. Rep.* **1997**, *14*, 43−74, and previous reviews in this series. (b) Gottlieb, O.; Yoshida, M. In *Natural Products of Woody Plants I*; Rowe, J. W., Ed.; Springer-Verlag: Berlin, 1989; Chapter 7.3.

$[\alpha]_{589} = +353$, $[\alpha]_{578} = +374$, $[\alpha]_{546} = +446$, $[\alpha]_{436} = +1019$, $[\alpha]_{365} = +2953$ (*c* 4.1 mg/mL, $CHCl_3$). **8a**, mp 133.5−134.0 °C, $[\alpha]_{589} = -166$, $[\alpha]_{578} = -179$, $[\alpha]_{546} = -225$, $[\alpha]_{436} = -918$ (*c* 5.8 mg/mL, $CHCl_3$). Anal. Calcd for $C_{19}H_{22}O_5$: C, 71.98; H, 6.71. Found: C, 71.78; H, 6.87. **8b**, mp 134.0−134.2 °C, $[\alpha]_{589} = -172$, $[\alpha]_{578} = -184$, $[\alpha]_{546} = -229$, $[\alpha]_{436} = -835$ (*c* 12.5 mg/mL $CHCl_3$). Anal. Calcd for $C_{18}H_{20}O_4$: C, 69.08; H, 6.71. Found: C, 68.89; H, 6.88. **18**, mp 127.5−129 °C, $[\alpha]_{589} = -229$ (*c* 5.4 mg/mL, $CHCl_3$). **46**, mp 166−167 °C, $[\alpha]_{589} = +44.4$ (*c* 8.6 mg/mL, $CHCl_3$).

General Procedure for Rearrangements of 5/8 to 6/9 with Ti(IV)−diol 4: Rearrangement of 5a to 6a Is Representative. To a solution of Ti(O*i*-Pr)$_4$ (450 μL, 1.51 mmol) in CH_2Cl_2 (1 mL) at room temperature was added $TiCl_4$ (165 μL, 1.50 mmol) followed rapidly by the addition of a solution of diol (+)-**4** (0.793 g, 1.50 mmol) in CH_2Cl_2 (1 mL). The mixture was added to a solution of enantiomerically homogeneous cyclobutane (−)-**5a** (0.720 g, 2.28 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and then allowed to slowly warm to −10 °C (or the temperature indicated in Table 3) over 4 h. $NaHCO_3$ (2.51 g) and *i*-PrOH (5 mL) were added, and the mixture was diluted with water, filtered through Celite, and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Chromatography of the resulting oil on flash silica with 20%, 35%, and then 50% EtOAc/hexanes as eluents gave a >50:1 mixture of **6a** (0.676 g, 94%, 100% ee) and its cis isomer.

Protic acid-catalyzed rearrangements[2] afforded **6a** in 8−12:1 trans:cis ratios, and from the latter experiments, the trans and cis isomers were isolated by HPLC (μporasil, 0.5% 2-propanol/hexanes). Physical and spectral data for *trans*-**6a**: mp 131−132 °C (EtOAc/hexanes); ^{1}H NMR (500 MHz) 1.35 (d, $J = 7$, 3H), 3.39 (dq, $J = 7$, 9, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 5.04 (d, $J = 9$, 1H), 5.25 (s, 1H), 6.49 (s, 1H), 6.73 (d, $J = 1$, 1H), 6.86 (d, $J = 8$, 1H), 6.9−7.0 (m, 2H); ^{13}C NMR (125 MHz) 17.9, 45.3, 55.89, 55.93, 56.2, 93.1, 94.2, 109.1, 109.4, 110.9, 118.9, 123.0, 133.1, 139.9, 146.2, 149.0, 149.2, 152.3; $[\alpha]_{589} = -32$, $[\alpha]_{578} = -33$, $[\alpha]_{546} = -40$, $[\alpha]_{436} = -97$, $[\alpha]_{365} = -282$ (*c* 2.6 mg/mL, $CHCl_3$). Spectral data for *cis*-**6a** (92% ee): ^{1}H NMR (500 MHz) 0.78 (d, $J = 7$, 3H), 3.55 (dq, $J = 7$, 9, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 5.24 (s, 1H), 5.72 (d, $J = 9$, 1H), 6.54 (s, 1H), 6.75 (s, 1H), 6.85 (s, 3H); ^{13}C NMR (125 MHz) 17.1, 41.2, 55.87, 55.88, 56.2, 88.0, 94.1, 109.5, 110.1, 110.8, 118.7, 123.9, 130.7, 139.7, 146.1, 148.4, 148.7, 152.2; $[\alpha]_{589} = +140$, $[\alpha]_{578} = +148$, $[\alpha]_{546} = +172$, $[\alpha]_{436} = +336$, $[\alpha]_{365} = +548$ (*c* 3.1 mg/mL, $CHCl_3$).

The following reactions were conducted in a similar manner (for reaction temperatures, see Table 3).

A sample of enantiomerically enriched **5b** (90% ee) afforded a 14.5:1 ratio of **6b** and its cis isomer (0.197 g, 79%, 93% ee for the major isomer).

A sample of enantiomerically enriched **5c** (86% ee) afforded a 17:1 ratio of **6c** and its cis isomer (0.098 g, 93%, 82% ee for the major isomer).

Enantiomerically homogeneous **8a** afforded pure *trans*-**9a** (0.111 g, 100%, 100% ee) as an oil; $[\alpha]_{589} = +10.3$ (*c* 11.1 mg/mL, $CHCl_3$).

Enantiomerically homogeneous **8b** afforded a 17.0:1 ratio of **9b** and its cis isomer (0.094 g, 83%, 100% ee) as a colorless oil; the optical rotation of this sample was $[\alpha]_{589} = +31.7$ (*c* 9.4 mg/mL, $CHCl_3$).

Recrystallization of **6b** and **6c** from EtOAc/hexanes provided stereo- and enantiomerically homogeneous material: *trans*-**6b**, mp 112.5−114.0 °C; $[\alpha]_{589} = -31.4$ (*c* 6.6 mg/mL, $CHCl_3$); *trans*-**6c**, mp 141−141.5 °C; $[\alpha]_{589} = -47.1$ (*c* 36.2 mg/5 mL, $CHCl_3$).

(+)-(1*R*,5*R*,6*R*,7*R*)-4-Bromo-3-hydroxy-6-methyl-7-(2-methylphenyl)bicyclo[3.2.1]oct-3-en-2,8-dione (12). Bicyclo[3.2.1]-adduct (+)-**7d** (0.053 g, 0.21 mmol) was dissolved in THF (2 mL) at 0 °C, and *N*-bromosuccinimide (0.040 g, 0.22 mmol) was added in small portions. The yellow reaction mixture was stirred for 5 min and then treated with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to a yellow oil. Chromatography using 10% EtOAc/hexanes as eluent afforded (+)-**12** (0.044 g, 63%) as a clear, colorless oil. Crystallization from *i*-PrOH/hexanes gave clear, colorless needles; mp 126−127 °C; TLC $R_f = 0.54$ (30% EtOAc/hexanes); ^{1}H NMR (500 MHz) 7.17−7.12 (m, 3H), 6.78−6.76 (m, 1H), 6.14 (s, 1H), 3.86 (dd, $J = 1.7$, 6.9 Hz, 1H), 3.48 (dd, $J = 5.3$, 6.9 Hz, 1H), 3.38 (d, $J = 1.7$ Hz, 1H), 2.84 (dq, $J = 6.9$, 7.0, 1H), 2.37 (s, 3H), 1.28 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (125 MHz) 196.9, 187.3, 148.3, 137.0, 135.5, 130.8, 127.7, 126.7, 126.4, 118.3, 66.2, 64.2, 46.3, 40.7, 21.7, 20.0; HRMS *m*/*z* 334.0209 (calcd for $C_{16}H_{15}BrO_3$, 334.0205); $[\alpha]_{589} = +300°$ (*c* 1.9 mg/mL, $CHCl_3$).

Dimethyl (*R*)-2-Methylsuccinate (15).[15−17] A solution of dihydrobenzofuran (+)-**9a** (1.01 g, 3.057 mmol) in AcOH (50 mL) was added to 10% Pd/C (0.522 g). The mixture was stirred under an atmosphere of H_2 for 48 h, then poured into saturated aqueous $NaHCO_3$, and filtered. The filtrate was extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated. Chromatography of the resulting oil on flash silica with 20% and then 40% EtOAc/hexanes as eluents gave a mixture of the quinone and the hydroquinone (0.769 g), which was dissolved in AcOH (30 mL). Ozone was bubbled through the solution for 4 h. The resulting mixture was concentrated, 30% aqueous H_2O_2 was added, and the mixture was heated to reflux for 1 h. The solvent was removed under reduced pressure, THF was added to dissolve the oil, and the mixture was added to a solution of CH_2N_2 in diethyl ether at 0 °C. The mixture was stirred for 1 h and was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Chromatography of the resulting oil on flash silica with 15% EtOAc/hexanes as eluent gave **15** (0.054 g, 11%), TLC R_f (35% EtOAc/hexanes, visualized with iodine) 0.49; ^{1}H NMR (500 MHz) 1.20 (d, $J = 7$, 3H), 2.39 (d, $J = 17$, 6, 1H), 2.73 (dd, $J = 17$, 8, 1H), 2.90 (sextet, $J = 7$, 1H), 3.66 (s, 3H), 3.68 (s, 3H); ORD (*c* 10.7 mg/mL, $CHCl_3$); $[\alpha]_{589} = +4.4$; lit.[29] $[\alpha]_{589} = +4.1$ (*c* 4.1 mg/mL, $CHCl_3$).

(2*S*,3*S*)-4-Allyl-2-(3,4-dimethoxyphenyl)-6-methoxy-3-methyl-2,3-dihydro-5-benzofuranol (16). To a solution of dihydrobenzofuran (−)-**6a** (0.668 g, 2.11 mmol) in acetone (30 mL) was added K_2CO_3 (1.57 g) and allyl bromide (0.75 mL, 8.7 mmol). The mixture was heated to reflux for 48 h and then cooled and poured into saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic extracts were combined, dried (Na_2SO_4), and concentrated. Chromatography of the resulting oil on flash silica with 15% and then 20% EtOAc/hexanes as eluents gave the allyl ether of **6a** (0.601 g, 80%); mp 68.0−68.5 °C (EtOAc/hexanes); TLC R_f (35% EtOAc/hexanes) 0.34; ^{1}H NMR (500 MHz) 1.36 (d, $J = 7$, 3H), 3.39 (m, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.55 (d, $J = 6$, 2H), 5.06 (d, $J = 9$, 1H), 5.26 (dd, $J = 1$, 11, 1H), 5.39 (dd, $J = 1$, 17, 1H), 6.09 (ddd, $J = 6$, 11, 17, 1H), 6.52 (s, 1H), 6.74 (s, 1H), 6.86 (d, $J = 8$, 1H), 6.95 (dd, $J = 2$, 8, 1H), 6.97 (d, $J = 2$, 1H); ^{13}C NMR (125 MHz) 17.9, 45.3, 55.8, 55.9, 56.1, 71.6, 93.2, 95.2, 109.1, 110.9, 111.2, 117.5, 118.8, 122.0, 133.0, 133.9, 142.4, 149.0, 149.1, 150.3, 153.7; HRMS *m*/*z* 356.1628 (calcd for $C_{21}H_{24}O_5$ 356.1624); ORD (*c* 22.0 mg/mL, $CHCl_3$) $[\alpha]_{589} = -4.2$, $[\alpha]_{578} = -4.9$, $[\alpha]_{546} = -6.3$, $[\alpha]_{436} = -22.1$, $[\alpha]_{365} = -100$. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.88; H, 6.80.

A solution of the allyl ether prepared as described above (0.270 g, 0.758 mmol) in *N*,*N*-dimethylaniline (5 mL) was heated to reflux for 4 h. The mixture was cooled to room temperature and poured into aqueous HCl and ice. The mixture was shaken and then extracted with $CHCl_3$ (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Chromatography of the resulting oil on flash silica with 10% and then 15% EtOAc/hexanes as eluents gave **16** (0.220 g, 81%) as a colorless oil; TLC R_f (35% EtOAc/hexanes) 0.39; ^{1}H NMR (500 MHz) 1.40 (d, $J = 7$, 3H), 3.3−3.5 (m, 3H), 3.84

(29) Cohen, S. G.; Milovanovic, A. *J. Am. Chem. Soc.* **1968**, *90*, 3495−3502.

(s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.99 (m, 1H), 5.02 (dd, J = 2, 2, 1H), 5.08 (d, J = 6, 1H), 5.29 (s, 1H), 5.99 (m, 1H), 6.82 (d, J = 8, 1H), 6.85 (d, J = 2, 1H), 6.88 (dd, J = 2, 8, 1H); ^{13}C NMR (125 MHz) 20.2, 30.7, 44.7, 55.68, 55.71, 55.9, 91.7, 92.1, 108.8, 110.9, 114.8, 118.1, 121.3, 121.8, 134.2, 135.7, 137.6, 146.1, 148.8, 149.0, 151.7; HRMS m/z − 356.1627 (calcd for $C_{21}H_{24}O_5$ 356.1624); ORD (c 22.0 mg/mL, $CHCl_3$) $[\alpha]_{589}$ = +66, $[\alpha]_{578}$ = +69, $[\alpha]_{546}$ = +80, $[\alpha]_{436}$ = +147, $[\alpha]_{365}$ = +230.

General Procedure for Cycloadditions of Arylcycloalkenes: Reaction of 22 with 2 Is Representative. (−)-(4a*R*,4b*R*,7a*S*,7b*R*)-4,4a,4b,5,6,7,7a,7b-Octahydro-2-methoxy-7a-(4-methoxyphenyl)-1*H*-benzo[3,4]cyclobuta[1,2]cyclopentan-1,4-dione (24) and (+)-(3a*R*,8b*R*)-2,3,3a,8b-tetrahydro-6-methoxy-3a-(4-methoxyphenyl)-1*H*-cyclopenta[*b*]benzofuran-7-ol (25). $TiCl_4$ (270 μL, 2.46 mmol) and a solution of (+)-**4** (1.320 g, 2.50 mmol) in CH_2Cl_2 (2 mL) were added rapidly, in sequence, to a solution of Ti(O*i*-Pr)$_4$ (740 μL, 2.49 mmol) in CH_2Cl_2 (2 mL) at room temperature. The dark mixture was stirred for 15 min and cooled to −78 °C, and a solution of **2** (0.139 g, 1.01 mmol) in CH_2Cl_2 (2 mL) was added. After 15 min, the reaction mixture was treated with a solution of **22** (0.176 g, 1.01 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 20 min, and solid $NaHCO_3$ (1 g) and *i*-PrOH (3 mL) were then added. The mixture was poured rapidly into H_2O (20 mL) and CH_2Cl_2 (10 mL), swirled vigorously, and filtered through Celite (CH_2Cl_2 wash). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), decanted, and concentrated. Chromatography of the resultant brown oil with 10%, 15%, 30%, and then 50% EtOAc/hexanes gave recovered diol-**4** (typically >95%, which was pooled for recycling), (+)-**25** (0.134 g, 42%, 20% ee) as a colorless oil, and (−)-**24** (0.151 g, 48%, 96% ee) as a white solid.

Recrystallization of (−)-**24** from EtOAc/hexanes afforded enantiomerically homogeneous material as colorless needles: mp 174−175 °C; TLC R_f = 0.25 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz) 7.03 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 5.94 (s, 1H), 3.73 (s, 3H), 3.54 (s, 3H), 3.33 (d, J = 8.4 Hz, 1H), 3.29 (dd, J = 3.7, 7.1 Hz, 1H), 2.85 (dd, J = 3.7, 8.4 Hz, 1H), 2.41 (dd, J = 6.1, 13 Hz, 1H), 2.08−1.95 (m, 3H), 1.85−1.77 (m, 1H), 1.64−1.58 (m, 1H); ^{13}C NMR (75 MHz) 199.1, 192.2, 163.8, 158.2, 133.8, 128.1, 113.6 (2C), 58.6, 56.0, 55.1, 51.1, 46.2, 44.4, 42.1, 33.0, 25.2; $[\alpha]_{589}$ = −149 (c 2.3 mg/mL, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.05; H, 6.47. Found: C, 72.60; H, 6.30. NOE data for (−)-**24**: irradiation of H-4a (2.85 ppm) resulted in 10% enhancement of the H-7b signal (3.33 ppm); however, no enhancement of the H-4b signal (3.29 ppm) was observed. Likewise, irradiation of the ortho protons on the aryl ring (7.03 ppm) caused a 6% enhancement of the H-4b signal (3.29 ppm), but no significant enhancement of the H-7b signal.

Enantiomeric purities were determined by (1) ^{1}H NMR (500 MHz) analyses in the presence of **11** (5 equiv by wt with respect to the substrate) in $CDCl_3$ and/or (2) HPLC (Chiralcel OD, 20% 2-propanol/hexanes; 1 mL/min; 254 nm) in which the two enantiomers of each compound appeared as well-separated peaks. Racemic mixtures of **24** were used as standards and were prepared by either (1) combination of (−)-**24** and (+)-**24**, which was made from an identical reaction to the one described above, but with a complex of Ti(IV) with diol-(−)-**4**, or (2) from reactions of the quinone with anisylcyclopentene catalyzed by simple mixtures of $TiCl_4$/Ti(iOPr)$_4$; see the following experimentals.

The following reactions were conducted in a similar manner (for reaction temperatures and times, see Table 4).

23 with **2** gave gave (+)-**27** (0.131 g, 40%, 20% ee) as a colorless oil and (−)-**26** (0.066 g, 20%, 92% ee).

28 with **2** gave starting quinone (0.021 g, 15%), (+)-**30** (0.203 g, 59%, 20% ee), and (−)-**29** (0.087 g, 25%, 57% ee).

Recrystallization of (−)-**26** and (−)-**29** from EtOAc/hexanes afforded enantiomerically homogeneous material as colorless needles: (−)-**26**, mp 217−219 °C; TLC: R_f = 0.11 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz) 7.12 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.88 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.47 (dd, J = 7.2, 7.6 Hz, 1H), 3.34 (d, J = 7.2 Hz, 1H), 3.25 (bt, J = 7.6 Hz, 1H), 2.29 (bd, J = 13 Hz, 1H), 1.96 (dt, J = 3.0, 13 Hz, 1H), 1.88−1.85 (m, 1H), 1.80−1.67 (m, 2H), 1.65−1.52 (m, 2H), 1.50−1.46 (m, 1H); ^{13}C NMR (125 MHz) 198.6, 191.0, 162.7, 158.0, 134.8, 128.2, 113.2, 111.6, 56.1, 55.1, 53.0, 48.3, 44.3, 42.9, 40.0, 24.7, 21.4, 20.3; $[\alpha]_{589}$ = −227 (c 1.1 mg/mL, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.59; H, 6.81. Found: C, 73.49; H, 6.60. NOE data for (−)-**26**: a 6% enhancement of the signal for H-4b (3.25 ppm) was observed upon irradiation of the aryl ortho protons (7.12 ppm), with no significant enhancement of the H-8b signal (3.34 ppm), but a 7% enhancement of the H-8b signal was observed upon irradiation of H-4a (3.47 ppm).

(−)-**29**: mp 249−250 °C; TLC R_f = 0.16 (30% EtOAc/hexanes); HPLC (Chiralcel OD; 20% 2-propanol/hexanes; 1 mL/min; 254 nm), (−)-**29** rt 23−24 min, (+)-**29** rt 19−20 min; ^{1}H NMR (500 MHz) 7.37 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.12 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.61 (d, J = 9.5 Hz, 1H), 3.47−3.39 (m, 2H), 2.09−0.82 (m, 10H); ^{13}C NMR (125 MHz) 198.2, 192.8, 162.9, 157.7, 140.8, 128.3, 115.0, 113.5, 56.3, 55.3, 53.1, 51.9, 44.0, 40.7, 37.0, 31.0, 30.4, 28.2, 24.6; HRMS m/z 341.1751 (M^+ + 1); calcd for $C_{21}H_{24}O_4$, 341.1753); $[\alpha]_{589}$ = −296 (c 1.6 mg/mL, $CHCl_3$). NOE data for (−)-**29**: irradiation of the C-9a aryl ring protons (7.37 ppm) ortho to the attachment to the cyclobutane caused 7% enhancements of both the H-9b doublet (3.62 ppm) and the H-4a/b multiplet (3.4−3.5 ppm, these signals overlap); in addition, irradiation of H-9b gave a 5% enhancement of the H-4a/4b multiplet.

***rel*-(4a*R*,4b*R*,7a*S*,7b*R*)-4,4a,4b,5,6,7,7a,7b-Octahydro-2-methoxy-7a-(4-methoxyphenyl)-1*H*-benzo[3,4]cyclobuta-[1,2]cyclopentan-1,4-dione [(+)-24] and *rel*-(3a*R*,8b*R*)-2,3,3a,8b-Tetrahydro-6-methoxy-3a-(4-methoxyphenyl)-1*H*-cyclopenta[b]benzofuran-7-ol [(+)-25].** $TiCl_4$ (0.3 mL, 2.7 mmol) was added to a solution of Ti(O*i*-Pr)$_4$ (0.8 mL, 2.7 mmol) in CH_2Cl_2 (3 mL) at room temperature. The reaction mixture was stirred for 15 min and cooled to −85 °C, and a solution of **2** (0.750 g, 5.4 mmol) in CH_2Cl_2 (5 mL) was added. After 15 min, a solution of **22** (0.940 g, 5.4 mmol) in CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred for 1.5 h at −85 °C and then quenched with solid $NaHCO_3$ (1 g) and *i*-PrOH (5 mL). The mixture was partitioned between H_2O/CH_2Cl_2 (10 mL each) and filtered through Celite. The aqueous layer was separated and extracted with CH_2Cl_2 (6 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Chromatography of the resultant yellow-brown oil with 10%, 15%, 30%, and 50% EtOAc/hexanes gave starting **22** (0.510 g, 54% recovery), (±)-**25** (0.470 g, 28%) as a colorless oil, and (±)-**24** (0.250 g, 15%) as a white solid, mp 147−149 °C. ^{1}H NMR (500 MHz) analyses in the presence **11** (5 equiv by weight with respect to substrate) in $CDCl_3$ showed that signals at 5.96 and 6.43 in *rac*-**24** and *rac*-**25**, respectively, split up into two distinct signals. Chiral HPLC (Chiralcel OD, 20% 2-propanol/hexanes; 1 mL/min; 254 nm) separated the two enantiomers of each compound with the following retention times: (−)-**24**, 27−28 min; (+)-**24**, 22−23 min; (+)-**25**, 11−12 min; (−)-**25**, 9−10 min.

(+)-(4a*S*,4b*S*,7a*R*,7b*S*)-4,4a,4b,5,6,7,7a,7b-Octahydro-2-methoxy-7a-(4-methoxyphenyl)-1*H*-benzo[3,4]cyclobuta-[1,2]cyclopentan-1,4-dione [(+)-24] and (−)-(3a*S*,8b*S*)-2,3,3a,8b-Tetrahydro-6-methoxy-3a-(4-methoxyphenyl)-1*H*-cyclopenta[b]benzofuran-7-ol [(−)-25]. This reaction was carried out in a manner exactly analogous to reaction of **22** with **2** promoted by a complex of Ti(IV) and (+)-**4**. Thus, the complex prepared from $TiCl_4$ (0.093 mL, 0.85 mmol), (−)-**4** (0.45 g, 0.85 mmol), and Ti(O*i*-Pr)$_4$ (0.253 mL, 0.85 mmol) promoted a reaction of **2** (0.05 g, 0.34 mmol) in CH_2Cl_2 (1 mL) with **22** (0.06 g, 0.34 mmol) to afford after chromatography diol (−)-**4** (0.44 g, 98% recovery); (−)-**25** (0.05 g, 48%, 15%ee) as a colorless oil, $[\alpha]_{589}$ = −22 (c 5.0 mg/mL, $CHCl_3$); and (+)-**24** (0.03 g, 31%, 87%ee) as a white solid. Recrystallization of enantiomerically enriched (+)-**24** from EtOAc/hexanes gave enantiomerically homogeneous material as colorless needles; mp 170−171 °C; $[\alpha]_{589}$ = +150 (c 3.0 mg/mL, $CHCl_3$). The products were identified by comparison of their ^{1}H and ^{13}C spectra to those of (−)-**24** and (+)-**25**.

Protic Acid-Catalyzed Rearrangements of Cyclobutanes (−)-24, (−)-26, and (−)-29: Reaction of (−)-24 to (+)-25 Is Representative. *p*-Toluenesulfonic acid (*p*-TsOH, 0.009 g) was added to a solution of (−)-**24** (0.068 g, 0.22 mmol) in CH_2Cl_2 (2 mL) at room temperature. The reaction mixture was stirred for 5 min and then treated with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated. The resultant colorless oil was chromatographed (30% EtOAc/hexanes) to afford (+)-**25** (0.064 g, 94%, >99% ee), mp 74−75 °C (EtOAc/hexanes); $[\alpha]_{589}$ = +110 (*c* 1.9 mg/mL, $CHCl_3$).

In a similar manner, reaction of enantiometically pure (−)-**26** (0.018 g, 0.055 mmol) initially at 0 °C and then room temperature (1 h) gave (+)-**27** (0.018 g, 100%, >99% ee) as a colorless oil; $[\alpha]_{589}$ = +104 (*c* 2.3 mg/mL, $CHCl_3$).

Reaction of enantiomerically pure (−)-**29** (0.017 g, 0.050 mmol) at room temperature (1 h) gave (+)-**30** (0.017 g, 100%, >99% ee), mp 115−116 °C (EtOAc/hexanes); $[\alpha]_{589}$ = +81 (*c* 1.5 mg/mL, $CHCl_3$).

(−)-(3a*S*,3b*R*,4*S*,7a*R*,7b*R*)−(4-Bromophenyl)carbamic Acid, 5-Methoxy-3a-(4-methoxyphenyl)-7-oxo-2,3,3a,-3b,4,7,7a,7b-octahydro-1*H*-cyclopenta[3,4]cyclobuta[1,2]-benzen-4-yl Ester (31). A solution of enantiomerically homogeneous (−)-**24** (0.047, 0.15 mmol) in THF (6 mL) was added to a solution of Red-Al (0.030 mL of a 65+ wt % solution in toluene, 0.15 mmol) in Et_2O (7 mL) maintained at −5 °C. Over 1 h the temperature increased to 5 °C, and the reaction was then quenched by addition of saturated aqueous NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and concentrated. Chromatography of the resultant colorless oil (50% EtOAc/hexanes) gave (3a*R*,3b*R*,7*S*,-7a*R*,7b*S*)-7-hydroxy-6-methoxy-7b-(4-methoxyphenyl)-1,2,3,-3a,3b,7,7a,7b-octahydrocyclopenta[3,4]cyclobuta[1,2]benzen-4-one (0.040, 85%) as a white solid, mp 134−137 °C (EtOAc/hexanes): TLC R_f 0.1 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz) 7.25 (d, *J* = 8.8, 2H), 6.81 (d, *J* = 8.8, 2H), 5.31 (d, *J* = 1.5, 1H), 4.50 (dt, *J* = 8.0, 7.7, 1.5, 1H), 3.78 (s, 3H), 3.53 (s, 3H), 3.07 (dd, *J* = 8.0, 3.5, 1H), 3.01 (t, *J* = 8.0, 1H), 2.60 (dd, *J* = 8.8, 3.5, 1H), 2.37 (dd, *J* = 12.5, 5.0, 1H), 2.03−1.92 (m, 3H), 1.73−1.61 (m, 3H); ^{13}C NMR (75 MHz) 199.1, 175.5, 158.0, 135.4, 130.1, 113.3, 100.7, 66.8, 56.2, 55.2, 53.5, 47.2, 44.4, 42.6, 42.3, 33.2, 25.2; HRMS *m*/*z* 315.1591 (M^+ + 1, calcd for $C_{19}H_{23}O_4$: 315.1596). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.20; H, 7.08.

A solution of the alcohol prepared as described in the preceding paragraph (0.025 g, 0.08 mmol) and 4-bromophenyl isocyanate (0.032 g, 0.16 mmol) in dry benzene (10 mL) was refluxed for 24 h, cooled, and concentrated to a white solid. Chromatography (30% EtOAc/hexanes) afforded (−)-**31** (0.040 g, 98%) as a white solid, mp 219−222 °C (EtOAc/hexanes): TLC R_f 0.36 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz) 7.41 (d, *J* = 8.8, 2H), 7.20 (d, *J* = 7.7, 4H), 6.79 (d, *J* = 7.6, 2H), 6.12 (br s, 1H), 5.63 (dd, *J* = 7.7, 1.0, 1H), 5.41 (s, 1H), 3.77 (s, 3H), 3.54 (s, 3H), 3.15−3.10 (m, 2H), 2.66 (dd, *J* = 9.0, 5.0, 1H), 2.26 (dd, *J* = 10.0, 5.0, 1H), 2.03−1.94 (m, 3H), 1.77−1.64 (m, 2H); ^{13}C NMR (125 MHz) 198.8, 172.9, 157.8, 151.9, 136.5, 132.0, 129.9 (2C), 120.0, 116.1, 112.4, 102.3, 67.1, 56.2, 55.2, 53.5, 47.9, 43.5, 42.5, 40.8, 33.1, 25.3; $[\alpha]_{589}$ = −96 (*c* 2.0 mg/mL, $CHCl_3$).

(−)-(1*S*,4a*S*,4b*R*,9a*R*,9b*R*)-(4-Bromophenyl)carbamic Acid, 2-Methoxy-9a-[4-methoxyphenyl]-4-oxo-4,4a,4b,5,-6,7,8,9,9a,9b-decahydro-1*H*-benzo[3,4]cyclobuta[1,2]cyclohepten-1-yl Ester (32). A solution of enantiomerically homogeneous (−)-**29** (0.035, 0.1 mmol) in THF (5 mL) was added to a solution of Red-Al (0.020 mL of a 65+ wt % solution in toluene, 0.1 mmol) in THF (5 mL) maintained at −5 °C. The reaction temperature increased to 0 °C over 20 min, and the reaction was then quenched by addition of saturated aqueous NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and concentrated. Chromatography of the resultant colorless oil (50% EtOAc/hexanes) gave (4*S*,4a*R*,4b*R*,9a*S*,9b*R*)-4-hydroxy-3-methoxy-4b-[4-methoxyphenyl]-4,4a,4b,5,6,7,8,9,9a,9b-decahydrobenzo[3,4]cyclobuta-[1,2]cyclohepten-1-one (0.032, 91%) as a colorless oil: TLC R_f 0.2 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz) 7.45 (d, *J* = 7.6, 2H), 6.87 (d, *J* = 8.8, 2H), 5.50 (d, *J* = 1.2, 1H), 4.73 (d, *J* = 8.0, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.38−3.31 (m, 2H), 3.03 (t, *J* = 9.9, 1H), 2.92 (d, *J* = 1.7, 1H), 2.15−2.03 (m, 2H), 1.92−1.80 (m, 2H), 1.69−1.63 (m, 2H), 1.37−1.23 (m, 3H), 1.08−1.04 (m, 1H); ^{13}C NMR (125 MHz) 198.8, 175.9, 157.0, 143.7, 128.6, 113.1, 102.2, 65.7, 56.6, 55.2, 53.2, 42.9, 42.8, 41.0, 33.9, 31.6, 29.9, 27.4, 25.2.

A solution of the alcohol prepared as described in the preceding paragraph (0.035 g, 0.1 mmol) and 4-bromophenyl isocyanate (0.030 g, 0.15 mmol) in dry toluene (10 mL) was refluxed for 65 h, cooled, and concentrated to a white solid. Chromatography (30% EtOAc/hexanes) afforded (−)-**32** (0.040 g, 98%) as a white solid, mp 197−199 °C (toluene/hexanes): TLC R_f 0.4 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz) 7.47 (d, *J* = 8.6, 2H), 7.38 (d, *J* = 8.2, 2H), 7.22 (d, *J* = 6.8, 2H), 6.9 (br s, 1H), 6.84 (d, *J* = 8.2, 2H), 5.99 (d, *J* = 7.7, 1H), 5.55 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.42−3.31 (m, 2H), 3.01 (t, *J* = 10.0, 1H), 2.17−2.11 (m, 1H), 1.96−1.84 (m, 2H), 1.69−1.65 (m, 1H), 1.41−1.24 (m, 5H), 1.11−1.07 (m, 1H); ^{13}C NMR (100 MHz) 197.6, 173.3, 157.3, 152.5, 142.6, 136.6, 132.1, 128.0, 120.5, 116.7, 113.5, 103.5, 66.9, 56.8, 55.3, 52.7, 42.9, 42.0, 40.5, 34.2, 31.4, 29.7, 27.3, 25.1; HRMS *m*/*z* 540.1379 (M^+, calcd for $C_{28}H_{30}O_5BrN$: 540.1385); $[\alpha]_{589}$ = −107° (*c* 3.5 mg/mL, $CHCl_3$).

(+)-[(3a*R*,8b*R*)-2,3,3a,8b-Tetrahydro-6-methoxy-3a-(4-methoxyphenyl)-1*H*-cyclopenta[*b*]benzofuran-7-yl]-4-bromobenzoate (33). NaH (60% dispersion in mineral oil; 0.027 g, 0.68 mmol) was washed with hexanes and THF (10 mL) was added. The slurry was treated with a solution of enantiomerically pure (+)-**25** (0.046 g, 0.15 mmol) in THF (10 mL), and the reaction mixture stirred at room temperature for 20 min. A solution of *p*-bromobenzoyl chloride (0.033 g, 0.15 mmol) in THF (5 mL) was added dropwise; the reaction mixture was stirred for 15 min and then diluted with H_2O (20 mL) and poured into CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography of the resultant colorless oil using 20% EtOAc/hexanes furnished (+)-**33** (0.069 g, 94%) as a white solid. Recrystallization from EtOAc/hexanes gave colorless prisms, mp 120−121 °C: TLC R_f = 0.42 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz) 8.05 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.87 (s, 1H), 6.53 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.76 (d, *J* = 8.6 Hz, 1H), 2.41 (dd, *J* = 5.7, 14 Hz, 1H), 2.18−2.05 (m, 2H), 1.94−1.84 (m, 2H), 1.74 (apparent nonet, *J* = 6.2 Hz, 1H); ^{13}C NMR (125 MHz) 164.6, 158.8, 158.3, 151.2, 136.9, 133.3, 131.8, 131.7, 128.6, 128.5, 125.9, 122.1, 118.3, 101.3, 94.2, 56.1, 55.3, 54.7, 42.6, 36.2, 25.1; HRMS: *m*/*z* 494.0717 (calcd for $C_{26}H_{23}O_5Br$, 494.0729); $[\alpha]_{589}$ = +44 (*c* 7.62 mg/mL, $CHCl_3$).

General Procedure for the Rearrangement of (−)-24 with Ti(IV)−TADDOLates. $TiCl_4$ (0.005 mL, 0.05 mmol) and a solution of **4** (0.025 g, 0.05 mmol) in CH_2Cl_2 (1 mL) were added rapidly, in sequence, to a solution of Ti(O*i*-Pr)$_4$ (0.014 mL, 0.05 mmol) in CH_2Cl_2 (1 mL) at room temperature. The dark-red reaction mixture was stirred for 15 min and cooled to −78 °C, and a solution of (−)-**24** (0.010 g, 0.032 mmol) in CH_2Cl_2 (1 mL) was added. Aliquots (0.1−0.2 mL) were drawn at the times and temperatures indicated in Table 6 and quenched with a slurry of *i*-PrOH (2 mL)/solid $NaHCO_3$ (1 g) maintained at the quench temperature. The resultant mixtures were partitioned between H_2O/CH_2Cl_2 (5 mL each) and filtered through Celite, and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in *i*-PrOH, quinone **2** was added, and the mixture was analyzed by HPLC (Chiralcel OD; 20% 2-propanol/hexanes; 1 mL/min; 254 nm). The relative response factors for each compound were determined by analysis of a mixture of **2**, *rac*-**24**, and *rac*-**25** by both ^{1}H NMR and HPLC. After complete conversion of (−)-**24** (as indicated by HPLC) the reaction was worked up as described above and chromatographed to give (+)-**25** (0.008 g, 82% from reac-

tion with (−)-**4**, and 0.006 g, 79% from (+)-**4**, yields adjusted to take into account the aliquots removed). The enantiomeric purity was determined by HPLC and by ^{1}H NMR as described above.

In the reaction involving (+)-**4**, complete conversion of (−)-**24** was observed after 60 min, when the reaction temperature had reached 10 °C. In reactions involving (−)-**4**, complete conversion of (−)-**24** was observed after 20 min, when the reaction temperature had reached −60 °C.

Protic Acid-Catalyzed Rearrangements of (+)-46/47 to (+)-48/49. Both reactions were conducted in a similar manner. Thus, concentrated H_2SO_4 (2 drops) was added to a solution of enantiomerically pure (+)-**46** (0.029 g, 0.11 mmol) in CH_2Cl_2 (3.6 mL). The reaction mixture was stirred for 5 min and then poured into saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with brine (50 mL) and concentrated to give (+)-**48** (0.026 g, 90%, >99% ee). The % ee was determined by ^{1}H NMR (500 MHz) analysis in the presence of **11** in $CDCl_3$ (the singlet at δ 6.49 ppm in the racemate split into well-resolved signals); $[\alpha]_{589} = +163$ (*c* 16 mg/mL, $CHCl_3$).

In a similar manner, enantiomerically enriched (+)-**47** (61% ee, 0.083 g) gave, after chromatography (30% EtOAc/hexanes), (+)-**49** (0.072 g, 86%), which was 61% ee by ^{1}H NMR analysis in the presence of **11**; the specific rotation of this sample was $[\alpha]_{589} = +136$ (*c* 7.2 mg/mL, $CHCl_3$).

Acknowledgment. We thank Professor Daneel Ferreira for a sample of (−)-**50**, and Professor Fusao Takusagawa and Mr. Larry Seib for X-ray structure determinations. Financial support was provided by NIH (GM 39820) and NSF (CHE-9116576, OSR-9255223, OSR-9550487) and the University of Kansas General Research and J.R. and Inez Jay Funds. Fellow- and granteeships from the Alfred P. Sloan Foundation (T.A.E.), NIH (M.A.L., GM 07775), and Eli Lilly and Company (T.A.E.) are acknowledged with gratitude.

Supporting Information Available: ORTEP drawings, crystallographic data, tables of atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for (+)-**12**, (−)-**31**, (−)-**32**, and (+)-**33**; IR and mass spectral data for new compounds; copies of NMR spectra of all new compounds characterized by HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982164S