previously unknown. The monoepoxides of furans are unstable, isomerizing to 1,4-dicarbonyl compounds;[22] in selected cases the epoxides can be observed at low temperature.[23] The bis-epoxide of methyl 3-furoate has been prepared.[24] It should be noted that the chemical shifts (δ 4.27 and 5.61) for H4 and H5 and the coupling between them (J = 1.5 Hz) in the bis-epoxide compare favorably with the values for H9 and H8 in **2**.

The lack of detectable coupling between H9 and H9a in epoxide **2** requires[25] a torsional angle of ~90° establishing that the epoxide has the exo configuration, i.e., dimethyldioxirane attacks the 8,9-double bond in AFB_1 from the less hindered exo face. Confirmatory evidence for the stereochemistry of epoxidation was obtained from nuclear Overhauser difference spectra; strong nuclear Overhauser effects were observed between protons H8 and H9 and between H6a and H9a, but only a weak effect was seen between anti protons H9 and H9a.

Introduction of ^2H_2O and a trace of ^2HCl into the acetone-d_6 NMR sample of epoxide **2** caused hydrolysis to give *trans*-8,9-diol **5**[26] in essentially quantitative yield. The NMR signals for protons H6a, H8, H9, and H9a of **3** (Figure 1C) appeared at δ 6.65, 5.45, 4.43, and 3.97 with $J_{6a,9a}$ = 5.9 Hz, $J_{8,9}$ = <0.5 Hz, and $J_{9,9a}$ = <0.5 Hz.

Epoxide **2** reacts with DNA with regio- and stereospecificity at the N^7 position of deoxyguanosine. Treatment of calf thymus DNA with **2** (12 h at pH 6.5 and 5 °C) produced extensive covalent reaction. Acid hydrolysis of purine–deoxyribose linkages followed by reverse-phase HPLC purification yielded an adduct identified as 8,9-dihydro-8-(N^7-guanyl)-9-hydroxy-AFB_1 (**6**) by ^1H NMR (Figure 1D); the spectrum was identical with spectra reported for the adduct produced from AFB_1 by microsomal activation and by chemical activation with 3-chloroperoxybenzoic acid.[5,6,27,28] The spectrum shown in Figure 1E was obtained from adduct formed from calf thymus DNA to which AFB_1 had been bound using in situ activation[6] with 3-chloroperoxybenzoic acid.

The preparation of DNA adducts by in situ chemical activation has serious problems. Activation of AFB_1 with peroxy acids requires a two-phase system with the oxidant and aflatoxin in methylene chloride and the DNA in aqueous buffer.[3] A single-phase system is unacceptable due to oxidative modifications of the DNA by the peroxy acid. The two-phase system is limited to nonbiological systems because of the destructive effect of organic solvents on cells. Photooxidative activation[4] requires intense UV light which is mutagenic in its own right. In addition, it is possible that psoralen-type nonoxidative DNA photoadducts are being formed.[29,30] Some research groups have used 8,9-dihalides as surrogates for the epoxide for in vivo studies.[8] Although the dihalides are highly mutagenic, their relevance to the molecular mechanism of action of **2** is questionable since the adducts derived from the dihalides have different structures. Certainly, the availability of AFB_1 epoxide will now facilitate investigations ranging from chemical activation of oncogenes to the total metabolism of this human carcinogen.

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Stereoselective 3 + 2 and Stereospecific 2 + 2 Cycloaddition Reactions of Alkenes and Quinones

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In search of new cycloaddition reactions for the stereoselective preparation of carbocyclic and heterocyclic ring systems,[1] we have found that highly substituted dihydrobenzofurans and bicyclo[4.2.0]octenediones can be obtained stereoselectively via titanium(IV)-catalyzed addition of unactivated alkenes to quinones.[2,3] More importantly, the bicyclo[4.2.0]octenediones are produced stereospecifically. The nature of the product formed is dependent upon substituents present on the alkene and the quinone and on the catalyst.

Thus, *trans*- or *cis*-β-methylstyrenes, **1** or **2**, bearing strong electron-donating groups on the aromatic ring (X = 2- or 4-OMe) stereoselectively produce *trans*-dihydrobenzofurans **6**[4,5] in good yield upon reaction with 2-alkoxy-1,4-benzoquinones **3a–c** or benzoquinone **3d** and $TiCl_4$ or $TiCl_4/Ti(OiPr)_4$ mixtures (Scheme

(21) Oxirane **3**: ^1H NMR (acetone-d_6) δ 1.88 (m, H4), 2.17 (m, H4′), 3.58 (m, H5), 3.61 (m, H3), 3.98 (m, H5′), 5.17 (d, J = 1.8 Hz, H2); ^{13}C NMR (acetone-d_6) δ 27.51 (C4), 56.92 (C3), 65.49 (C5), 82.24 (C2). Oxirane **4**: ^1H NMR (acetone-d_6) δ 1.35–1.48 (m, H5), 1.54–1.65 (m, H5′), 1.87–2.13 (H4 and H4′), 3.13 (m, H3), 3.47 (m, H6), 3.61 (m, H6′), 4.67 (d, J = 2.7 Hz, H2); ^{13}C NMR (acetone-d_6) δ 20.74 (C4 or C5), 22.56 (C5 or C4), 51.58 (C3), 62.95 (C6), 77.20 (C2).

(22) Ravindranath, V.; Burka, L. T.; Boyd, M. R. *Science (Washington, D.C.)* **1984**, *224*, 884–886.

(23) Ruzo, L. O.; Casida, J. E.; Holden, I. *J. Chem. Soc., Chem. Commun.* **1985**, 1642–1643.

(24) Graziano, M. L.; Scarpati, R. *J. Chem. Soc., Chem. Commun.* **1985**, 124–125. Giordano, F.; Graziano, M. L.; Iesce, M. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 773–775.

(25) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.

(26) Swenson, D. H.; Miller, J. A.; Miller, E. C. *Biochem. Biophys. Res. Commun.* **1973**, *53*, 1260–1267.

(27) Groopman, J. D.; Croy, R. G.; Wogan, G. N. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5445–5449.

(28) Croy, R. G.; Essigmann, J. M.; Reinhold, V. N.; Wogan, G. N. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 1745–1749.

(29) Tomic, M. T.; Wemmer, D. E.; Kim, S.-H. *Science (Washington, D.C.)* **1987**, *238*, 1722–1725, and papers cited therein.

(30) Shieh, J.-C.; Song, P.-S. *Cancer Res.* **1980**, *40*, 689–695.

(1) For a compilation of many examples, see: (a) Desimoni, G.; Tacconi, G.; Barco, A.; Piero Pollini, G. *Natural Product Synthesis through Pericyclic Reactions*; ACS Monograph 1980; American Chemical Society: Washington, DC, 1983. See, also: (b) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 563. (c) Lora-Tamayo, M. *Tetrahedron* **1958**, *4*, 17.

(2) Engler, T. A.; Naganathan, S.; Takusagawa, F.; Yohannes, D. *Tetrahedron Lett.* **1987**, *28*, 5267. Various aspects of the present research have been presented; (a) Engler, T. A.; Combrink, K. D. *Abstracts of Papers*, Third Chemical Congress of North America, Toronto, Canada; American Chemical Society: Washington, DC, 1988; ORGN 41. (b) Engler, T. A.; Ray, J. *Abstracts of Papers*, Third Chemical Congress of North American, Toronto. Canada; American Chemical Society: Washington, DC, 1988; ORGN 115. (c) Engler, T. A.; Combrink, K. D. *Abstracts of Papers*, 194th Meeting of the American Chemical Society, New Orleans, LA; American Chemical Society: Washington, DC, 1987; ORGN 280.

(3) Enamines, enols, and allylsilanes are known to give benzofuran and dihydrobenzofuran products (3 + 2 cycloadducts) upon reaction with quinones, for examples, see: (a) Allen, G. R. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1973; Vol. 20, p 358. (b) Brimble, M. A.; Gibson, J. J.; Baker, R.; Brimble, M. T.; Kee, A. A.; O'Mahony, M. J. *Tetrahedron Lett.* **1987**, *28*, 4891. (c) Eugster, C. H.; Kuser, P. *Chimia* **1964**, *18*, 358. (d) Eugster, C. H.; Fumagalli, S. E. *Helv. Chim. Acta* **1971**, *54*, 959. (e) Maruyama, K.; Tai, S. *Chem. Lett.* **1985**, 681. (f) Banville, J.; Grandmaison, J. L.; Lang, G.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 80. (g) Brannock, K. C.; Burpitt, R. D. U.S. Patent 3285937; *Chem. Abstr.* **1967**, *66*, 37762p. (h) Bernatek, E. *Acta Chem. Scand.* **1953**, *7*, 677. (i) Giza, C. A.; Hinman, R. L. *J. Org. Chem.* **1964**, *29*, 1453. (j) Grinev, A. N.; Pan, B.-K.; Terent'ev, A. P. *Zh. Obshch. Khim.* **1957**, *27*, 1087; *Chem. Abstr.* **1958**, *52*, 3761e. (k) Maruyama, K.; Naruta, Y.; Uno, H. *Tetrahedron Lett.* **1981**, 5221. For a theoretical discussion on the regioselectivity of these reactions, see: Rozeboom, M. D.; Tegmo-Larsson, I.-M.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338.

(4) All new compounds gave satisfactory spectra (^1H and ^{13}C NMR, IR, mass), elemental analysis, and/or exact mass. Full spectral and crystallographic data will be provided in the full paper.

(5) The methyl signal of the *trans*-2-aryl-3-methyl-2,3-dihydrobenzofurans appears at 1.3–1.4 ppm, whereas the methyl signal of the corresponding *cis*-dihydrobenzofuran isomers appears at ~0.7 ppm, for examples, see: (a) Gregson, M.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Dietrichs, H. H.; Gottlieb, O. R. *Phytochemistry* **1978**, *17*, 1395. (b) Gottlieb, O. R.; Mourao, J. C.; Yoshida, M.; Mascarenhas, Y. P.; Rodrigues, M.; Rosenstein, R. D.; Tomita, K. *Ibid.* **1977**, *16*, 1003. (c) Gottlieb, O. R.; DaSilva, M. L.; Ferreira, Z. S. *Ibid.* **1975**, *14*, 1825. (d) Aiba, C. J.; Fernandes, J. B.; Gottlieb, O. R.; Maia, J. G. S. *Ibid.* **1975**, *14*, 1597. (e) Schmid, E.; Frater, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1625.

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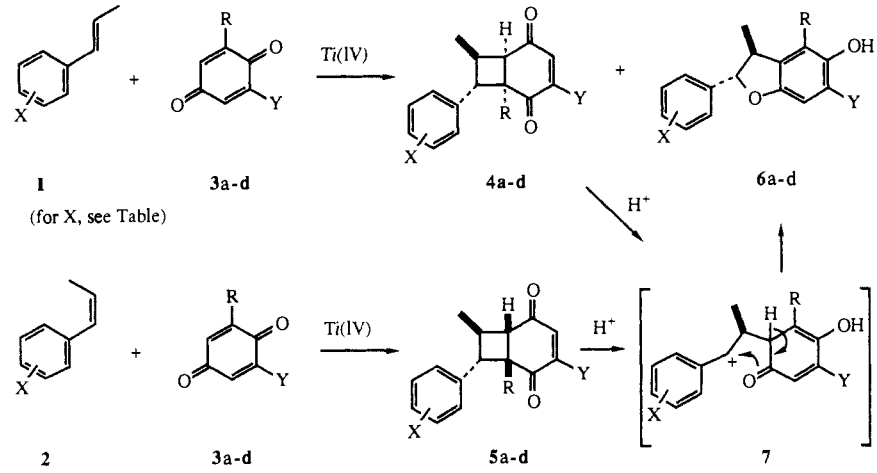
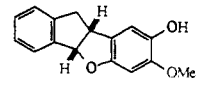
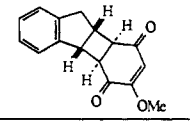
Scheme I[a]



[a] **a**, R = H; Y = OMe; **b**, R = H, Y = OCH_2Ph; **c**, R = Me, Y = OMe; **d**, R = Y = H.

Table I. Ti(IV)-Catalyzed Reactions of β-Methylstyrenes with 1,4-Benzoquinones[a]

entry	styrene[b] (trans/cis)	quinone	catalyst $TiCl_4$:$Ti(OiPr)_4$	yield (%) 6	yield (%) 4 + 5	ratio[c] 4/5
1	**1**, X = 4-OMe (14:1)	**3a**	1.6:1 [0.83][d]	72	12	>19:1[f]
2	**1**, X = 2-OMe (3:2)	**3a**	1:0 [1.0]	75	*e*	na[g]
3	**1**, X = 3,4-$(OMe)_2$ (14:1)	**3a**	1.6:1 [0.8]	60	23	>50:1
4	**1**, X = 3,4-$(OMe)_2$ (14:1)	**3b**	1:1 [1.0]	60	24	16:1
5	**1**, X = 4-Me (8:1)	**3a**	3:1 [1.0]	36	49	50:1
6	**1**, X = 4-Me (8:1)	**3a**	1:0 [1.0]	46	5	>19:1[f]
7	**1**, X = H (64:1)	**3a**	1:0 [1.1]	30	19	>50:1
8	**1**, X = 4-Cl (9:1)	**3a**	1:0 [1.0]	43	15	50:1
9	**1**, X = 4-Cl (9:1)	**3a**	3:1 [1.0]	27	24	22:1
10	**2**, X = 3,4-$(OMe)_2$ (1:22)	**3a**	1:1 [1.0]	22	39	1:26
11	**2**, X = 3,4-$(OMe)_2$ (1:22)	**3b**	1.8:1 [1.0]	*h*	49	1:34
12	**2**, X = 4-Me (1:19)	**3a**	4:1 [1.0]	*h*	31	1:13
13	**2**, X = H (1:51)	**3a**	1:0 [1.0]	*h*	21	1:25
14	**1**, X = 4-OMe (14:1)	**3c**	2:1 [1.0]	75	*e*	na
15	**1**, X = 4-Me (8:1)	**3c**	2:1 [1.0]	36	46	>19:1[f]
16	**2**, X = 4-Me (1:19)	**3c**	4:1 [1.0]	59	*e*	na
17	**1**, X = 4-OMe (14:1)	**3d**	1.8:1 [1.15]	68	*e*	na
18	**1**, X = 4-Me (8:1)	**3d**	3:1 [1.0]	21	21	>19:1[f]
19	indene	**3a**	1:0 [1.0]		 54%	
20	indene	**3a**	3:1 [1.0]		 85%	

[a] All reactions were done in CH_2Cl_2 at −78 °C. [b] The molar ratio of styrene to quinone was 1.5–2.0:1 in each case; the trans:cis ratio was determined by capillary VPC. [c] Determined by HPLC. [d] Total equiv of Ti(IV). [e] None of these products were found. [f] An HPLC ratio was not determined; however, only isomer 4 was evident by 300 MHz ^1H NMR. [g] na = not applicable. [h] Part of a complex mixture of 1:1 adducts, none of which are bicyclo[4.2.0]octenediones.

I and Table I). Other *trans*-β-methylstyrenes **1** [X = 3,4-$(OMe)_2$, 4-Me, H, 4-Cl] yield **6** and significant amounts of cyclobutanes **4**.[4] However, *cis*-β-methylstyrenes **2** [X = 3,4-$(OMe)_2$, 4-Me, H] react with 2-alkoxy-1,4-benzoquinone-titanium(IV) complexes to afford the isomeric cyclobutanes **5**[4] as the major isolable products. The structures of **4** and **5** have been unequivocally established by ^1H NMR NOE experiments, chemical modification, and, in one case (entry 4 in Table I), by X-ray crystallography.[6] Cyclobutanes **4** and **5** both afford dihydrobenzofurans **6** in >85% yield upon treatment with protic acid (H_2SO_4/CH_2Cl_2), presumably via **7** (Scheme I).

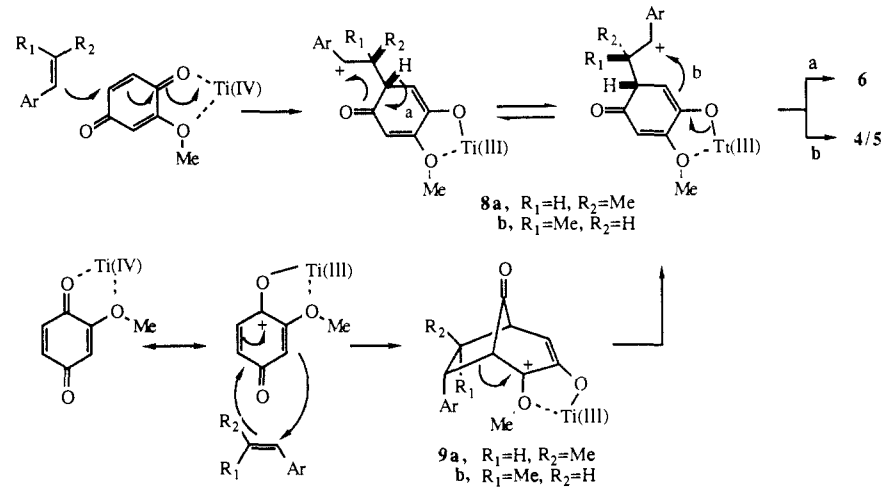
The cyclobutanes **4** and **5** are formed from **1** and **2**, respectively, via highly diastereospecific processes. In several cases, we have determined the extent of specificity in the formation of the 2 + 2 cycloadducts (Table I, entries 3–13). The styrenes used were mixtures of geometrical isomers, and the isomeric products **4** and **5** were the only 2 + 2 cycloadducts found. The ratios of **4** and **5** were determined by HPLC analysis of the crude reaction mixtures obtained after aqueous $NaHCO_3$ workup.

The nature of the Ti(IV) catalyst has a dramatic effect on the type of product obtained in the experiments described herein. In general, $TiCl_4$ gives mainly the dihydrobenzofuran adducts, whereas $TiCl_4/Ti(OiPr)_4$ mixtures produce more of the 2 + 2 cycloadducts. However, the yield and specificity observed in the formation of the cyclobutanes **4**/**5** is critically dependent upon the equivalents of Ti(IV) used and the $TiCl_4$:$Ti(OiPr)_4$ ratio; the results presented in Table I represent the optimum conditions found thus far. In some cases nearly exclusive formation of the dihydrobenzofuran or the cyclobutane adduct can be effected by proper choice of the catalyst, for example, see entries 1 and 2, 5 and 6, 19 and 20.

The formation of the products can be rationalized (Scheme II) via a diastereospecific alkylation of the quinone–titanium(IV) complex by the styrene to afford **8** which collapses via path **a** to

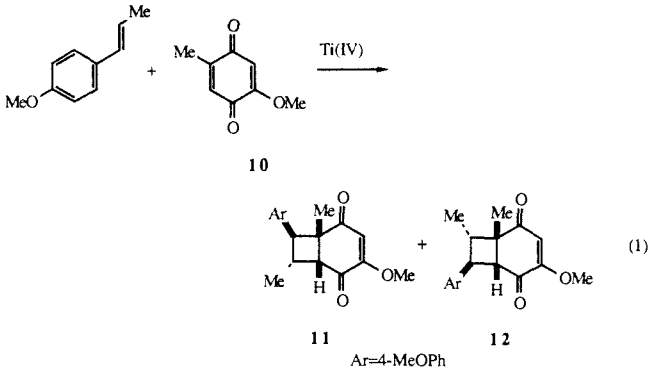
(6) A summary of the NOE data and an ORTEP diagram of **4b** are provided as Supplementary Material.

Scheme II



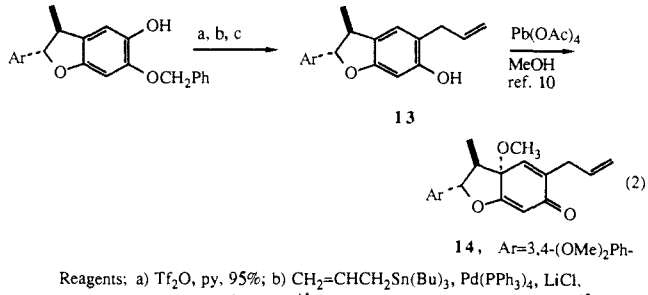
give **6** upon workup or via path **b** to give **4/5**. The stereospecific formation of **8** may be the result of an initial symmetry-allowed 5 + 2 ($4\pi + 2\pi$) cycloaddition between the quinone–titanium(IV) complex and the sytrenes **1/2** to give **9a/b**, respectively, which then rearrange to **8a/b**. Cycloadditions of alkenes and pentadienyl cations have ample literature precedence, and the aryl group of a styrene would be expected to occupy an endo position in similar cycloadditions with the quinone–titanium(IV) complex.[7-9] Intermediates analogous to **9** are known to rearrange under acidic conditions to give dihydrobenzofuran products.[8] Thus, the stereochemistry of the initial cycloaddition explains the specific formation of **4** and **5**.

Reactions of 2-methoxy-5-methyl-1,4-benzoquinone (**10**), with *trans*-β-methylsytrenes are stereoselective but not regioselective (eq 1). Treatment of **10** with a 3:1 mixture of $TiCl_4/Ti(O\mathit{i}Pr)_4$



(1)

(0.8 equiv) and then anethole (**1**) (X = 4-OMe) gives a 2:1 ratio of cyclobutanes **11** and **12** in 76% combined yield. Stereochemical assignments of **11** and **12** are based on ^1H NMR NOE data.[6]



(2)

Reagents: a) Tf_2O, py, 95%; b) $CH_2{=}CHCH_2Sn(Bu)_3$, $Pd(PPh_3)_4$, LiCl, DMF, 100°C, 95%;[11] c) $BF_3\,Et_2O$, DMS/CH_2Cl_2, rt, 67%.[12]

As an application of this new methodology, a total synthesis of (±)-kadsurenone (**14**),[10] a potent platelet activating factor antagonist, has been accomplished (eq 2). Phenol **13** is produced in four steps in 48% overall yield, and **13** has been oxidized directly to **14**. We are continuing to explore the synthetic utility and mechanism of the reactions described herein.

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Supplementary Material Available: Summary of the NOE data on **4b**, **5b**, **11**, and **12** and an ORTEP diagram of **4b** [X = 3,4-$(OMe)_2$] (1 page). Ordering information is given on any current masthead page.

(7) (a) Heilmann, W.; Koschinsky, R.; Mayr, H. *J. Org. Chem.* **1987**, *52*, 1989. (b) Büchi, G.; Chu, P.-S. *Ibid.* **1981**, *46*, 1. (c) Sanchez, I. H.; Yanez, R.; Enriquez, R.; Joseph-Nathan, P. *Ibid.* **1981**, *46*, 2818. (d) Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 5011. (e) Wagner, E. R.; Moss, R. D.; Brooker, R. M.; Heeschen, J. P.; Potts, W. J.; Dilling, M. L. *Ibid.* **1965**, 4233. (f) Mamont, P. *Bull. Chim. Soc. Fr.* **1970**, 1557. (g) McGregor, H. H., Jr. Ph.D. Thesis, Harvard University, 1971 and references cited in the above.

(8) (a) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (b) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717. (c) de Alvarenga, M. A.; Brocksom, U.; Gottlieb, O. R.; Yoshida, M.; Filho, R.; Figliuolo, R. *J. Chem. Soc., Chem. Commun.* **1978**, 831.

(9) (a) Mori, M.; Hayamizu, A.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1259. (b) Ojima, I.; Yatabe, M.; Fuchikami, T. *J. Org. Chem.* **1982**, *47*, 2051 and ref 8.

(10) Ponpipom, M. M.; Bugianesi, R. L.; Brooker, D. R.; Yue, B.-Z.; Hwang, S.-B.; Shen, T.-Y. *J. Med. Chem.* **1987**, *30*, 136.

(11) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

(12) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull. Jpn.* **1980**, *28*, 3662.

A Stereoselective Contrasteric Conversion of Epoxides to *cis*-Oxazolidin-2-ones

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The stereocontrolled introduction of heteroatoms represents a common synthetic challenge. The formation of vicinal amino alcohols via intermediate epoxides[1,2] is an attractive strategy

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