Substituent Effects on the Stereoselectivity of the Acid-Catalyzed Solvolysis of Rigid 1-Arylcyclohexene Oxides. Further Evidence for a Mechanism Implying Different Benzylic Carbocationic Species

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Abstract: The substituent effect on the stereoselectivity of the acid-catalyzed solvolysis of the conformationally rigid diastereoisomeric 4-*tert*-butyl-1-arylcyclohexene oxides **2** and **3** has been studied. As in the case of the conformationally mobile oxides **1**, the syn/anti adduct ratios obtained in the ring opening reactions (methanolysis and hydrolysis) of both the epoxide **2** and **3** are strongly influenced by the substituent on the aryl: the electron-donating *p*-methyl substituent increases and the electron-withdrawing *m*-chloro reduces the tendency of these epoxides toward syn opening. A linear Hammett-type correlation of the logarithm of the syn/anti ratios with the σ^+ constants, which affords the difference $\rho_{syn} - \rho_{anti}$, was obtained for the rigid epoxides **2** and **3**, analogous to what was found for the corresponding mobile derivatives **1**. The behavior of the epoxides **3a–c** resembles more closely that of the mobile epoxides **1a–c** than does that of derivatives **2a–c** both for the syn diastereoselectivity and for the Hammett-type correlation, confirming that conformationally mobile epoxides **1** preferentially react through a conformation corresponding to **3** rather than the alternative one corresponding to **2**. Furthermore, the fact that the syn diastereoselectivity of the reactions of both the rigid epoxides **2** and **3** is directly linked to the capability of the aromatic system to stabilize the benzylic carbocationic center in the same way as was found for the conformationally mobile oxides **1** further supports the mechanism we previously suggested in order to rationalize the product distribution in these reactions, a mechanism which implies different carbocationic species. The same results point out that an alternative mechanism proposed (*J. Am. Chem. Soc.* **1982**, *104*, 1972) does not apply to 1-arylcyclohexene oxides of type **1**. The alternative mechanism, which implies an equilibrating benzylic carbenium ion pseudoaxially attacked by the nucleophile, was originally suggested on the basis of results obtained on benzocyclohexene oxides of type **14**. It appears that significant differences between the two systems (**1** and **14**) must be present, which require further clarification.

Arene oxides have been demonstrated to be intermediates in the carcinogenesis of polycyclic aromatic hydrocarbons.[1] The knowledge of the mechanism and stereochemistry of the oxirane ring opening processes of such arene oxides and of their simpler models, the 2-aryl-substituted oxiranes,[2] under solvolytic conditions can be important for a better understanding of the more complex transformations which occur under biological conditions.

For several years the mechanism and stereochemistry of the ring opening reactions of oxiranes,[3] and in particular of 2-aryloxiranes,[4] have been extensively investigated in our laboratory. The steric course of the acid-catalyzed ring opening of simple aliphatic or cycloaliphatic oxiranes is almost exclusively anti stereoselective.[3a,5-8] On the contrary, oxiranes bearing either aryls or other unsaturated systems directly linked to the epoxide ring exhibit a high tendency toward syn addition under acidic conditions. However, the steric course of the ring opening can range from complete retention to complete inversion of configuration depending on several factors, such as structure, configuration, and conformation of the epoxide, solvent, nucleophile, temperature, etc.[4,7,9-18] As for 2-aryloxiranes, a clear correlation was found between the capability of the aromatic system to stabilize the carbocationic center during the breaking of the benzylic C–O bond of the protonated oxirane and the percentage of syn opening.[13,16-18] Data from the Hammett free energy relationship,[9] and salt[12] and temperature effects[10] on the stereoselectivity of the acid solvolysis of 1-arylcyclohexene oxides **1** provided proof that the transition state leading to the syn adducts has a higher degree of carbocationic character than the one relative to the anti adducts. Furthermore the temperature effect studies[10] stressed that entropic factors favor syn addition and enthalpic ones anti addition.

The results of the ring opening reactions of 2-aryloxiranes were rationalized through a mechanistic scheme[4,9-12] which can be closely related to the "ion–dipole pair" mechanism,[19] a close analogue of the classic Winstein ion pair scheme of nucleophilic substitution and elimination.[20-22] It should be pointed out that the nucleophilic addition to 1,2-epoxides in acid media is a peculiar

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(3) See, for example: (a) Berti, G.; Canedoli, S.; Crotti, P.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1184. (b) Crotti, P.; Ferretti, M.; Macchia, F.; Stoppioni, A. *J. Org. Chem.* **1984**, *49*, 4706 and references cited therein.

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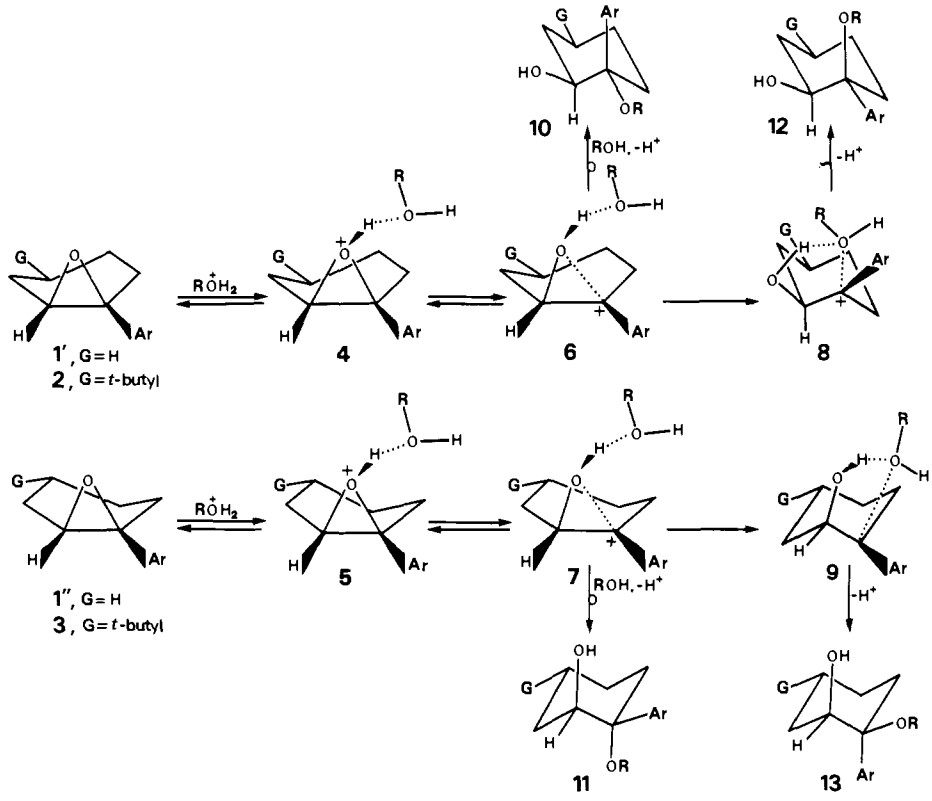
Scheme I



type of substitution which implies a preliminary proton transfer to the oxirane oxygen, in which the leaving group (the protonated former oxirane oxygen) is neutral and remains covalently bound close to the reaction center.[11] According to the mechanism suggested[4,9-12] [schematized for 1-arylcyclohexene oxides **1** reacting in both of the two nonequivalent half-chair conformations **1'** and **1''** (see Scheme I); however, for clarity the discussion will for the moment be based only on epoxides **1** which react through conformation **1''** (see later)] the protonated oxirane **5** can lead to an intramolecular intimate ion/dipole pair **7** in which there is an "extended benzylic C–O bond with considerable ionic character".[23] Attack of the nucleophile from the back side[20,22] of the intimate ion/dipole pair **7**, because of the strong shielding at the front side, affords the anti adduct **11**. On the other hand internal rearrangement of the intimate ion/dipole pair **7** with further loosening of the dipole (OH) from the benzylic carbenium ion leads to a nucleophile separated ion/dipole pair **9**, whose collapse with retention of configuration[23,24] affords the syn adduct **13**. The attack on the carbocationic center of the "pseudocyclic" intermediate **9** by the internal nucleophile with retention of configuration rather than by an external one with inversion of configuration appears to be favored by entropic factors.[10] In such a mechanistic scheme the syn diastereoselectivity of these reactions should be related to the competition between the conversion of the intimate ion/dipole pair **7** into the nucleophile separated ion/dipole pair **9** which leads to the syn adduct **13**, and that of the same species **7** into the anti adduct **11**. Any factor increasing the stability of the benzylic carbocationic center should significantly favor the more carbocation-like intermediate **9**, thus increasing the syn/anti ratio.

When the reactions of 1-phenylcyclohexene oxide (**1a**) were compared with those of its rigid *tert*-butyl analogues **2a** and **3a**, both exhibited fair amounts of products arising from syn opening;[4,14] this preference was higher for epoxide **3a** than for **2a**.[4] The

a: Ar = C_6H_5
b: Ar = p-$CH_3C_6H_4$
c: Ar = m-ClC_6H_4

syn stereoselectivity of the reactions of **3a** resembled more closely that of the nonrigid epoxide, suggesting that epoxide **1a** reacts preferentially through conformation **1''**, corresponding to **3**, rather than through the alternative one **1'** corresponding to **2**.[4] Neither examination of molecular models nor experimental evidence revealed conformational preference between conformation **1'** and **1''**; however, an X-ray crystal structure of a *p*-bromo derivative of **1** indicated that the preferred conformation **1'** found in the solid state[25] differed from the one **1''** through which epoxide **1a** appears to react under acidic conditions.[4] Both the differences in stereoselectivity observed for epoxides **2a** and **3a** and the preferential reactivity of epoxide **1a** through conformation **1''** were rationalized according to the mechanism previously suggested (see Scheme I), in terms of the hypothesis that the C–O bond cleavage of 1,2-epoxycyclohexanes in such a way to give an axial hydroxy group ("axial cleavage") should follow a reaction pathway having lower energy requirements than the one leading to the equatorial hydroxy group ("equatorial cleavage").[4,27] Clearly the preferential reactivity of epoxide **1a** through conformation **1''** can be understood in terms of the easier "axial cleavage" hypothesis. The same

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(26) (a) Williams, D. J.; Crotti, P.; Macchia, B.; Macchia, F. *Tetrahedron* **1975**, *31*, 993. (b) Domiano, P.; Macchia, F. *Acta Crystallogr.* **1980**, *B36*, 3067.
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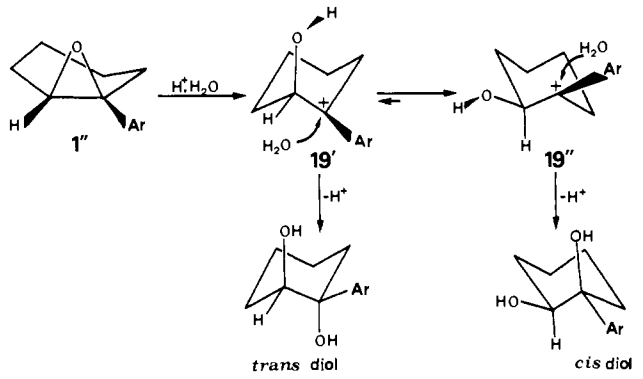
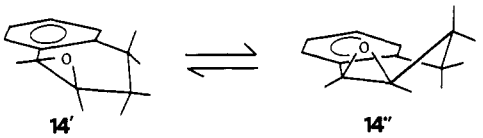
Scheme II



hypothesis can also explain the higher syn stereoselectivity of epoxide **3a** with respect to **2a**. The transformation of the intimate ion/dipole pairs **6** and **7** into the corresponding nucleophile separated ion/dipole pairs **8** and **9** can be considered as part of the ring opening process. According to the easier "axial cleavage" hypothesis, the conversion of **7** into **9** should be easier than that of **6** into **8**. Consequently, the ratio of the conversion rate of **7** into **9** and **7** into **11** should be higher than the corresponding ratio of **6** into **8** and **6** into **10**.

As in the case of 2-aryloxiranes discussed above, the acid-catalyzed solvolysis of benzylic epoxides of type **14** containing a cyclohexane ring fused to a benzene or another polynuclear aromatic system (including arene oxides) also yields mixtures of syn and anti addition products in ratios largely depending on the structure of the epoxide and the reaction conditions.[2b,c,28-32] Also



in the present case the amounts of syn addition were found to increase as the ability of the aryl group to stabilize a positive charge at the benzylic position increased for both tetrahydro and diol epoxides.[2d,28,30,31] On the basis of the results obtained in the acid-catalyzed hydrolysis of conformationally rigid fused benzo-ring epoxides **15** and **16**,[30] a mechanism was proposed to account for product distribution in the solvolysis of mobile tetrahydro and diol epoxides of type **14**.[2d,30] In this rationalization[2d,30] the distribution of the syn and anti addition products is determined by the conformation of the carbenium ion which is "initially formed" from the "predominant ground state conformation" of the epoxide, which can undergo a pseudoaxial attack by the solvent. However, if the carbenium ion "is stable enough to undergo conformational equilibrium prior to capture by solvent", the pseudoaxial attack of the solvent on the alternative carbenium ion can be decisive.

A completely analogous scheme (see Scheme II) has been suggested[30] as an alternative mechanism to our rationalization (see before) of the variation of the syn/anti adduct ratio of the acid-catalyzed hydrolysis of 1-arylcyclohexene oxides.[4,9] In this scheme[30] the epoxides **1** are assumed to react through conformation **1''** affording the fully developed carbenium ion **19'** which could undergo the pseudoaxial attack by the nucleophile yielding the anti adduct. On the other hand, conformational isomerization of the initially formed ion **19'** could give the isomeric ion **19''** which by the same type of attack yields the syn adduct.[30] Accordingly, factors increasing the stability of the benzylic carbenium ion **19'** should favor its conformational inversion to **19''** and therefore the syn with respect to the anti adduct.[30]

Considerations based on some of the many reports we have already published on 1-arylcyclohexene oxides (see before) indicated that the alternative mechanism proposed[30] appeared to suffer from certain deficiencies when applied to our system. For example, the results of the reactions of the conformationally rigid *tert*-butyl epoxides **2a** and **3a** are not easily explained by this mechanism:[30] both epoxides **2a** and **3a** exhibit a high tendency toward syn opening[4,14] (in some conditions the reactions are completely syn stereoselective for both the epoxides[14]). Furthermore the amounts of syn adduct formed in the reactions of **3a** are always higher than in the case of **2a**. In contrast the preferential pseudoaxial attack of the nucleophile on the diastereomeric fully developed benzylic carbenium ions derived from **2a** and **3a**, as expected according to the alternative mechanism,[30] should lead to the syn and to the anti adducts, respectively.

It therefore appeared to be worth while to verify in an unequivocal way whether the tendency toward syn opening of 1-arylcyclohexene oxides under acidic conditions should be related directly to the stability of the different benzylic carbocationic species (in agreement with our hypothesis[4]) or indirectly to it through a conformational equilibrium of the initially formed carbenium ion before the attack of the nucleophile.[30] We thought that the study of 4-*tert*-butyl-1-arylcyclohexene oxides differently substituted on the aromatic ring (**2** and **3**) by a Hammett type approach ought to remove any doubt.

If our mechanism[4] would be operating the syn diastereoselectivity of both the rigid epoxides **2** and **3** should be expected to be directly linked to the capability of the aromatic system to stabilize the benzylic carbocationic center as found for the mobile epoxides **1**. On the contrary, if the alternative mechanism[30] implying a fully developed benzylic carbenium ion pseudoaxially attacked by the nucleophile were involved, the syn diastereoselectivity of the reactions of the rigid epoxides **2a–c** and **3a–c** should either be practically invariable with the substituent on the phenyl or alternatively increase for epoxides **2a–c** and decrease for epoxides **3a–c** as the capability of the aryl group to stabilize positive charge increases.

Therefore the *p*-methyl (**2b** and **3b**) and the *m*-chlorophenyl derivatives (**2c** and **3c**) were prepared and their reactions under acidic conditions (hydrolyses in dioxane-water and methanolyses) compared with those of the unsubstituted compounds **2a** and **3a**.[4] Furthermore, the data obtained with the rigid epoxides **2** and **3** were compared with the corresponding ones of the conformationally mobile 1-arylcyclohexene oxides **1**.

Results

The epoxides **2b,c** and **3b,c** and the reference compounds were prepared (see Scheme III, IV, and V) following as much as possible procedures analogous to those used for the corresponding derivatives without any substituent on the phenyl.[4] In some cases, however, the procedures employed had necessarily to be significantly modified.

The olefin **20c** was prepared as previously described for **20a**[33a] and **20b**[33b] by acid-catalyzed dehydration of the mixture of the corresponding 4-*tert*-butyl-1-arylcyclohexanols obtained by reaction of 4-*tert*-butylcyclohexanone with the appropriate Grignard

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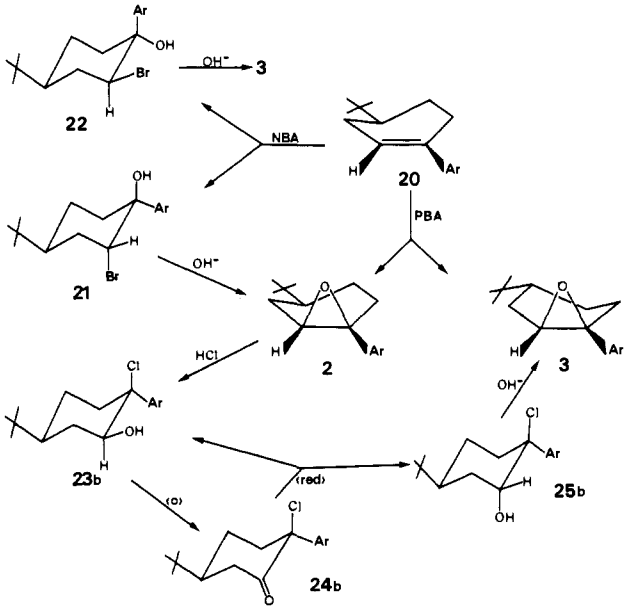
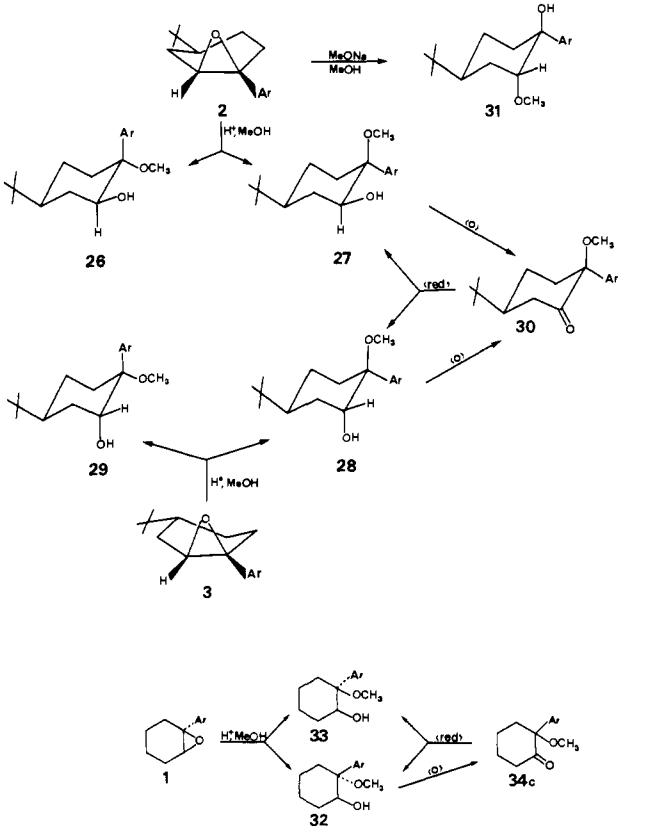
Scheme III



b, Ar = *p*-$CH_3C_6H_4$; c, Ar = *m*-Cl-C_6H_4

Scheme IV



reagent. The reaction of the *m*-chloro olefin **20c** with peroxybenzoic acid gives a ca. 60:40 mixture of **2c** and **3c**[14a] which were separated by chromatography. Treatment of **20c** with NBA in aqueous dioxane yielded a 86:14 mixture of the two trans bromohydrins **21c** and **22c**, from which pure **21c** was obtained by crystallization; the minor isomer **22c** was isolated by preparative TLC. Dehydrohalogenation of **21c** and **22c** with base gave pure samples of epoxides **2c** and **3c**, respectively. Direct epoxidation of the *p*-methyl olefin **20b** with peroxybenzoic acid under several conditions yielded complex mixtures consisting (^{1}H NMR and IR) of the epoxide **2b** and other products, very likely hydroxybenzoates arising from the ring opening of epoxide **3b** by benzoic

Scheme V

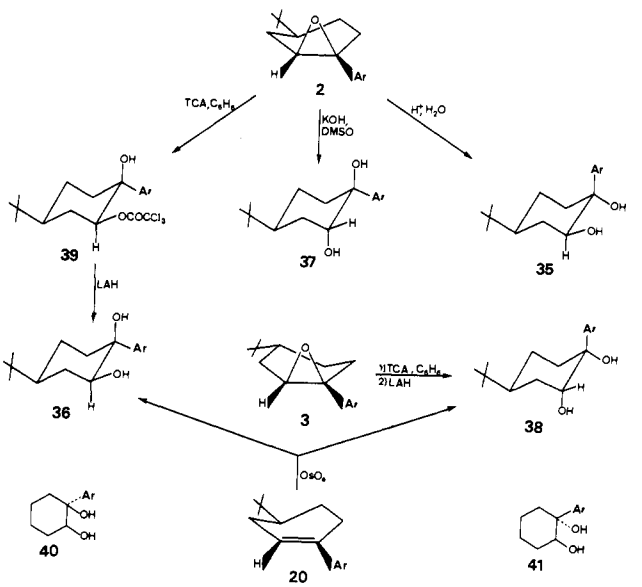


Table I. Stereochemistry of the Ring Opening of Epoxides **1–3(a–c)** under Acid Conditions[mm]

epoxide	solvent	acid	reaction time	% of syn adduct	% anti adduct
1a	MeOH	H_2SO_4	1 h	38.0[a,b]	62.0[b,c]
1b	MeOH	H_2SO_4	10 sec	61.5[d]	38.5[e]
1c	MeOH	H_2SO_4	10 sec	8.1[f]	91.9[g]
2a	MeOH	H_2SO_4	1 h	9.1[b,h]	90.9[b,i]
2b	MeOH	H_2SO_4	10 sec	19.8[j,k]	80.2[k,l]
2c	MeOH	H_2SO_4	10 min	2.9[m]	97.1[n]
3a	MeOH	H_2SO_4	1 h	21.6[b,o]	78.4[b,p]
3b	MeOH	H_2SO_4	10 sec	43.2[q]	56.8[r]
3c	MeOH	H_2SO_4	10 min	6.2[s]	93.8[t]
1a	dioxane–H_2O	H_2SO_4	2 min	56.0[u]	44.0[v]
1b	dioxane–H_2O	H_2SO_4	2 min	76.0[w]	24.0[x]
1c	dioxane–H_2O	H_2SO_4	3 h	23.6[y]	76.4[z]
2a	dioxane–H_2O	H_2SO_4	2 min	24.0[aa]	76.0[bb]
2b	dioxane–H_2O	H_2SO_4	5 min	33.0[cc]	67.0[dd]
2c	dioxane–H_2O	H_2SO_4	3 h	10.8[ee]	89.2[ff]
3a	dioxane–H_2O	H_2SO_4	5 min	45.2[gg]	54.8[hh]
3b	dioxane–H_2O	H_2SO_4	2 min	70.9[ii]	29.1[jj]
3c	dioxane–H_2O	H_2SO_4	15 min	15.9[kk]	84.1[ll]

[a] HE **33a**. [b] Reference 4. [c] HE **32a**. [d] HE **33b**. [e] HE **32b**. [f] HE **33c**. [g] HE **32c**. [h] HE **27a**. [i] HE **26a**. [j] HE **27b**. [k] Epimerization of HE **26b** into **27b** observed with increasing the reaction time; **26b**:**27b** ratio 76:26 (10 min), 67:33 (30 min), 58:42 (60 min). [l] HE **26b**. [m] HE **27c**. [n] HE **26c** accompanied by small amounts (1.9%) of the regioisomer **31c**. [o] HE **29a**. [p] HE **28a**. [q] HE **29b**. [r] HE **28b**. [s] HE **29c**. [t] HE **28c**. [u] D **40a**. [v] D **41a**. [w] D **40b**. [x] D **41b**. [y] D **40c**. [z] D **41c**. [aa] D **36a**. [bb] D **35a**. [cc] D **36b**. [dd] D **35b**. [ee] D **36c**. [ff] D **35c**. [gg] D **38a**. [hh] D **37a**. [ii] D **38b**. [jj] D **37b**. [kk] D **38c**. [ll] D **37c**. [mm] HE = hydroxy ether; D = diol.

acid.[34] Epoxide **2b** was obtained, as for **2c**, by dehydrobromination with a base of the bromohydrin **21b** which was obtained by crystallization of the reaction mixture of **20b** with NBA in aqueous dioxane. The other isomer **3b** was obtained as follows: oxidation of the cis chlorohydrin **23b**, obtained from epoxide **2b** by reaction with HCl in dry $CHCl_3$,[35] gave the ketone **24b** which on reduction with LiAl (*tert*-butoxy)$_3$H yielded a 60:40 mixture of the starting cis chlorohydrin **23b** and of the trans diaxial isomer **25b**. Treatment of this mixture with potassium *tert*-butoxide in dry benzene afforded a crude reaction product from which the pure epoxide **3b** was obtained by crystallization.

(34) The epoxides **2b** and **3b** are relatively unstable with respect to the *m*-chloro and to the unsubstituted derivatives (**2a,c** and **3a,c**). The electron-donating properties of the *p*-methyl group facilitate reactions with cationoid intermediates.

(35) Also reaction of the unsubstituted epoxide **2a** with HCl in low polar solvent was found highly syn stereoselective affording the corresponding chlorohydrin **23a**.[14b]

Table II. $\rho_{syn} - \rho_{anti}$ Values Obtained for the Acid-Catalyzed Hydrolysis and Methanolysis of Epoxides **1–3** According to Equation 1

epoxide	solvent	$\rho_{syn} - \rho_{anti}$	correl coeff (r)	std dev (s)
1	MeOH	−1.79	0.992	0.22
2	MeOH	−1.27	0.999	0.02
3	MeOH	−1.49	0.999	0.00
1	dioxane–H_2O	−1.42	0.998	0.08
2	dioxane–H_2O	−0.86	0.990	0.12
3	dioxane–H_2O	−1.56	0.999	0.03

The acid-catalyzed methanolyses[4] of epoxides **2b** and **3b** gave mixtures mainly consisting of the corresponding *trans*- and *cis*-hydroxy ethers **26b** and **27b**, and **28b** and **29b**, respectively (see Table I), which were separated by preparative TLC. From the acid methanolysis of epoxide **2c** only the main hydroxy ether **26c** (see Table I) was obtained by preparative TLC. The diaxial hydroxy ether **28c** was obtained by crystallization of an acid methanolysis reaction mixture of epoxide **3c** at 25 °C in which **28c** is the major component. When the acid methanolysis of **3c** was carried out in CH_2Cl_2,[4,36] the 57:43 mixture of the trans **28c** and cis isomer **29c** obtained was separated into its components by preparative TLC. Oxidation of the *cis*-hydroxy ether **27b** gave the keto ether **30b**. The same type of compound **30c** was obtained by oxidation of **28c**. Reduction of both ketones **30b** and **30c** with the borane/methyl sulfide complex afforded the corresponding hydroxy ethers **27** and **28** which were separated by preparative TLC; compound **27c** was actually obtained only by this method. The hydroxy ethers **31b** and **31c** were obtained as the only product in the reaction of epoxides **2b** and **2c** respectively with sodium methoxide in methanol.[4,14a] The acid methanolysis of epoxide **1b** and **1c** gave mixtures of the corresponding ethers **32** and **33** (see Table I); from these mixtures pure samples of **32b** and **33b**, and of **32c** were obtained by TLC. Compound **33c** was obtained by oxidation of **32c** to **34c** followed by its $NaBH_4$ reduction of a 45:55 mixture of **32c** and **33c** from which the desired compound was isolated.

The diols **35–39** (**b** and **c**) were obtained as described in Scheme V.[14a] The reactions of epoxides **2b** and **2c** with KOH in aqueous Me_2SO[14a] afforded the corresponding diaxial diols **37b** and **37c**. The cis diols **36b** and **36c** were obtained by $LiAlH_4$ reduction of the corresponding cis monotrichloroacetates **39b** and **39c** obtained by reaction of the same epoxide **2b** and **2c** with trichloroacetic acid in benzene.[14a] Also the reactions of the epoxides **3b** and **3c** with trichloroacetic acid in benzene followed by $LiAlH_4$ reduction[14a] gave the corresponding cis diols **38b** and **38c**. The diequatorial diols **35b** and **35c** were separated from the reaction mixtures of the acid-catalyzed hydrolysis of epoxides **2b** and **2c** in dioxane–water (for **2c**) and in Me_2SO (for **2b**). The cis diols **36b,c** and **38b,c** were also obtained as a 45:55 and a 75:25 mixture in the OsO_4-catalyzed dihydroxylation[37] of olefin **20b** and **20c**, respectively.

In order to effect the acid-catalyzed hydrolyses of epoxides **1–3(a–c)** in homogeneous solutions, the reactions of all the epoxides were carried out in 1:1 dioxane–water solutions, that is, under conditions different from the ones (water) previously used for **1a–3a**.[4,9] The acid-catalyzed methanolyses (methanol) of epoxides **1–3(b–c)** were performed under the same conditions used for the corresponding epoxides without any substituent on the phenyl **1a–3a**.[4] The mixtures of diols (hydrolysis) and methoxy alcohols (methanolysis) were analyzed by GLC. Table I reports the relative percentages of syn and anti adducts formed in the acid-catalyzed methanolysis and hydrolysis of epoxides **1–3(a–c)**. As for the hydrolysis reactions of epoxides **1a–c**, **2a**, and **3a**, the data in 1:1 dioxane–water are consistent with the previously published data obtained in pure water.[4,9] In the methanolysis of the epoxide **2c** the cis and trans benzylic tertiary hydroxy ethers **27c** and **26c** were accompanied by small amounts (1.9%) of the trans regioisomer **31c** which arise by a nucleophile non-benzylic attack through a diaxial ring opening.

(36) Reference 4, note 15.
(37) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

Table III. ^{1}H NMR and IR (in dilute CCl_4 solution in the 3-μm range) Data

		^{1}H NMR, δ		
compd	mp (°C)	CHX ($W_{1/2}$, Hz)	CH_3O	IR OH stretching cm^{-1}
2b	80–81	3.10[a] (4.0)[e]		
2c	38–39	3.13[a] (5.0)[e]		
3b	62–63	3.10[a] (4.0)		
3c	55–56	3.10[a] (4.0)		
21b	119–120	4.57[b] (7.0)		
21c	92–93	4.43[b] (8.0)		
22c	100–101	4.50[b] (22.0)		
23b	106–107	4.10[c] (18.0)		
26b	56–57	4.00[c] (16.0)	3.00	3590[f]
26c	liquid	3.97[c] (18.0)	3.00	3598[f]
27b	113–114	3.43[c] (16.0)	3.20	3590[f]
27c	89–90	3.37[c] (14.0)	3.17	3592[f]
28b	99–100	3.73[c] (6.0)	2.90	3598[g]
28c	94–95	3.76[c] (7.01)	2.96	3606[g]
29b	83–84	4.37[c] (7.0)	2.90	3570[f]
29c	61–62	4.27[c] (8.0)	2.80	3576[f]
31b	104–105	3.37[d] (6.0)	2.97	3606[g]
31c	69–70	3.30[d] (8.0)	3.00	3604[g]
32b	liquid	3.73[c] (7.2)	2.97	3598[g]
32c	67–68	3.73[c] (7.0)	3.00	3610[g]
33b	liquid	3.57[c] (18.0)	3.10	3588[f]
33c	68–70	3.50[c] (18.0)	3.17	3588[f]
35b	150–151	3.83[c] (21.0)		3608[g], 3590[f]
35c	137–138	3.83[c] (20.0)		3604[g], 3590[f]
36b	197–198	4.00[c] (16.0)		3586[g], 3560[f]
36c	153–154	3.93[c] (18.0)		3596[g], 3558[f]
37b	160–162	3.83[c] (7.0)		3604[g]
37c	143–144	3.80[c] (10.0)		3604[g]
38b	105–106	4.33[c] (7.0)		3614[h], 3578[f]
38c	125–127	4.23[c] (8.0)		3612[h], 3582[f]

[a] X = oxirane oxygen. [b] X = Br. [c] X = OH. [d] X = OCH_3. [e] Doublet, coupling constant. [f] OH···O. [g] OH···π. [h] Free OH.

Structures and Configurations

The structures and configurations of all new compounds [*p*-methyl (**b**) and *m*-chloro (**c**) derivatives] prepared were inferred on the basis of their methods of synthesis[4,14a] and on their ^{1}H NMR and IR (in dilute CCl_4 solution) (diols and hydroxy ethers) spectra through direct comparison with the spectra of the compounds having no substituent on the phenyl (**a**) whose structure and configuration had been firmly established.[4,14a] Apart from the different pattern of the signal of the aromatic protons and from the signal of the methyl group present in the *p*-methyl-substituted **b** series, the ^{1}H NMR spectra of all the new compounds of the **b** and **c** series are largely superimposable on those of the corresponding compounds of the **a** series having no substituent on the phenyl.[4,14a] Table III shows the spectroscopic characterization (^{1}H NMR and IR in the 3000–3600-cm^{-1} range in dilute solutions of CCl_4) of the new compounds. Anyway the relative configuration of the epoxides **2b,c** and **3b,c** can be inferred on the basis of the values of the half-bandwidth of the signal of the methynyl proton[4,14a] α to the bromine of the trans bromohydrins **21** and **22** (from which epoxides **2** and **3** can be formed), which are consistent with an equatorial and an axial proton, respectively. Furthermore, the configuration of the epoxides **2b,c** and **3b,c** can also be deduced from the axial and equatorial nature (as from the ^{1}H NMR spectra) of the methynyl proton α to the secondary OH of the methanol addition products under acidic conditions **26** and **27** and **28** and **29**, respectively: here the configuration of the secondary OH must be the same as in the starting epoxide. Finally as regards the relative configuration of the methoxy ethers **26–29b,c** the ^{1}H NMR spectra (half-bandwidth of the methynyl proton α to the secondary OH) define the equatorial and axial nature of the OH group in the couples of compounds **26** and **27** and **28** and **29**, respectively. The oxidation of both **27** and **28** to **30** indicates that they must be epimers on the carbon bearing the secondary OH.

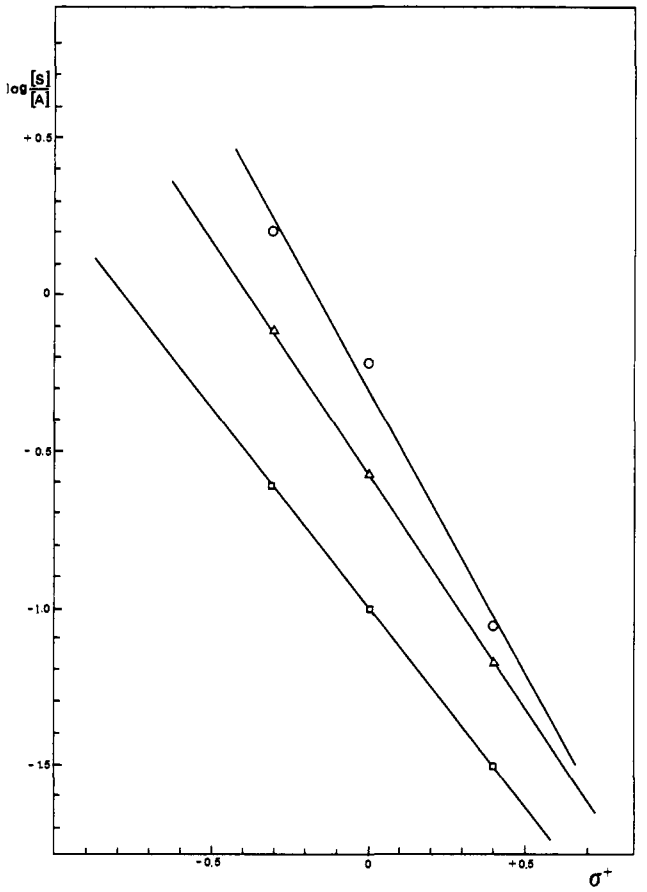


Figure 1. Hammett-Brown $\rho\sigma^+$ plot for acid-catalyzed methanolysis of epoxides **1–3**: O, **1**; □, **2**; △, **3**; [S] = [syn adduct]; [A] = [anti adduct].

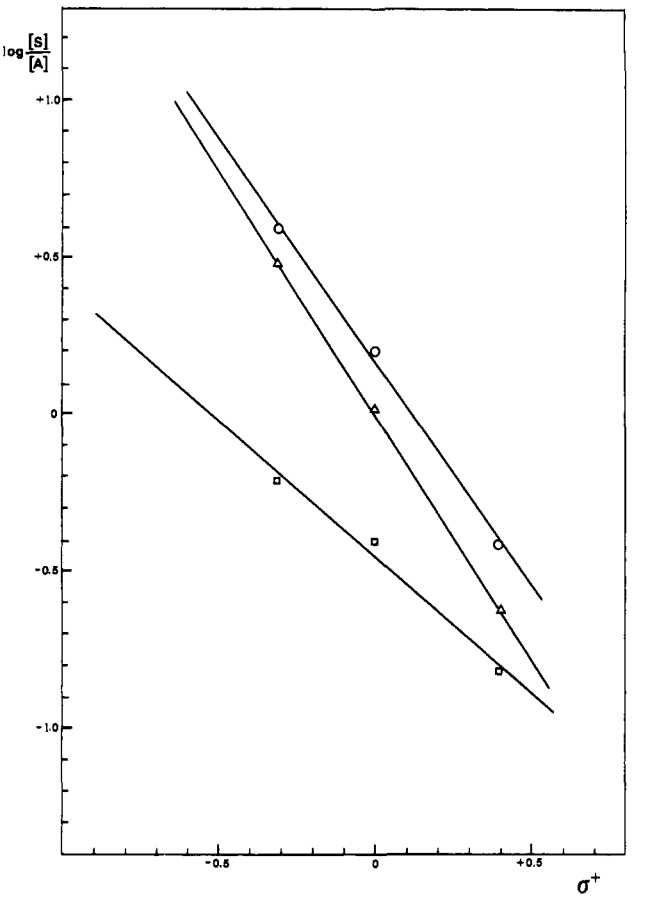


Figure 2. Hammett-Brown $\rho\sigma^+$ plot for acid-catalyzed hydrolysis of epoxide **1–3**: O **1**; □, **2**; △, **3**; [S] = [syn adduct]; [A] = [anti adduct].

Furthermore, the lack of an OH···O interaction in the IR spectrum of **28** in dilute CCl_4[4,14a] indicates a trans diaxial relationship between the OH and the OCH_3 groups in these types of compounds. So the configurations shown must be assigned to **28** and **27**. Consequently, the relative configurations of **26** and **29**, which must differ from **27** and **28**, respectively, only for the configuration of the tertiary OCH_3, can be easily deduced.

Discussion

The behavior of both the rigid *tert*-butyl epoxides **2a–c** and **3a–c** almost parallels that found for the corresponding mobile derivatives **1**.[9] The syn/anti adduct ratios obtained in the ring-opening reactions (methanolysis and hydrolysis) of **2** and **3** are strongly influenced by the substituent on the aryl: the electron-donating *p*-methyl substituent (epoxides **2b** and **3b**) increases and the electron-withdrawing *m*-chloro substituent (epoxides **2c** and **3c**) reduces the tendency of these epoxides toward syn opening. As mentioned above, a particular Hammett-type correlation (eq 1) was applied to the diastereoselectivity of the acid hydrolysis (water) of the mobile 1-arylcyclohexene oxides **1**. Equation 1 was obtained[9] by term-by-term substraction of the Hammett equation relative to the formation of the anti adduct (A) from the one for the formation of the syn adduct (S), under the very likely assumption that the two parallel reactions follow the same kinetic equation and that therefore the rate ratios k_S/k_A can be equated to the concentration ratios [S]/[A]. Acceptable linear correlation was obtained with the σ^+ values affording the difference $\rho_{syn} - \rho_{anti}$ for the two parallel reactions.[9] Also for the hydrolysis (dioxane-water) and methanolysis of the two rigid epoxides **2a–c** and **3a–c** as well as for the corresponding reactions of the mobile derivatives **1a–c**, a linear correlation was found according to eq 1 by using the σ^+ constants[38] (see Figures 1 and 2). The corresponding $\rho_{syn} - \rho_{anti}$ values obtained together with the respective correlation coefficients (r) and the standard deviations (s) are given in Table II. Analogously to what we pointed out in our related study of the epoxides without any substituent on the phenyl (**1a–3a**),[4] the behavior of epoxides **3a–c** resembles more closely that of the mobile epoxides **1a–c** than does that of derivatives **2a–c**. In the present case, however, the similarity concerns the Hammett-type correlation (see Tables I and II and Figures 1 and 2) as well as the syn diastereoselectivity.[4] In particular, we note that the $\rho_{syn} - \rho_{anti}$ values found for epoxides **3** are more negative than the corresponding ones found for epoxides **2** for both methanolysis and hydrolysis.[39]

$$\log \frac{[S][A^0]}{[A][S^0]} = (\rho_{syn} - \rho_{anti})\sigma^+ \qquad (1)$$

As pointed out above, the fact that both the rigid epoxides **2a** and **3a** exhibit in the ring opening definite amounts of syn addition products and that the syn stereoselectivity of the reactions of **2a** and **3a** is higher in the case of **3a** speaks by itself in favor of our mechanism and against the alternative one.[30] However, the results obtained in this paper, that is to say that the syn diastereoselectivity of the reactions of both the rigid epoxides **2** and **3** is directly linked to the capability of the aromatic system to stabilize the benzylic carbocationic center in the same way as found for the conformationally mobile 1-arylcyclohexene oxides **1**, further supports our mechanism implying different carbocationic species, against the alternative one suggested.[30]

(38) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
(39) The $\rho_{syn} - \rho_{anti}$ value is a measure of the sensitivity of the syn/anti ratio to the substituent on the phenyl. The lower $\rho_{syn} - \rho_{anti}$ value found for the reactions of epoxides **2** could be due to a partial steric inhibition of stabilization by the aryl group of the carbocationic species arising from these epoxides;[40] the steric interaction of the equatorial former oxirane oxygen with one of the two ortho hydrogens of the aryl twists the aryl away from the coplanarity with the carbenium ion which is necessary for the best stabilization.[41] In the carbenium ion arising from epoxides **3** the axial former oxirane oxygen does not disturb the coplanarity between the aryl and the carbocation.
(40) Tanida, H.; Matsumura, H. *J. Am. Chem. Soc.* **1973**, *95*, 1586.
(41) Hoffmann, R.; Bissel, R.; Farnum, D. G. *J. Phys. Chem.* **1969**, *73*, 1789. Dubois, J. E.; Hegarty, A. F. *J. Chem. Soc. B* **1969**, 638.

The present data, besides supporting the mechanism (see Scheme I) we suggested in order to rationalize the acid-catalyzed reactions of 1-arylcyclohexene oxides, seem to confirm the hypothesis that conformationally mobile epoxides **1** react preferentially through conformation **1″** corresponding to **3** rather than through the alternative one (**1′**).

In conclusion the reactions of both the rigid epoxides **2** and **3** occur to give definite amounts of syn adduct **12** and **13**, respectively, which both depend, as shown by the Hammett-type treatment, in a similar, although not identical, manner on the substituents on the aryl.

It appears that in the 1-arylcyclohexene oxide system, according to the mechanism we proposed[4,9-12] (see Scheme I), the conformation in which the epoxide reacts can be of some importance, but it cannot be decisive for the product distribution.

It appears very likely that the mechanism through which 2-aryloxiranes react under acidic conditions should be practically independent of the nature of the epoxide and that therefore the rationalization of the product distribution in the reactions both of epoxides of type **1** and **14** and in general of other 2-aryloxiranes should follow the same scheme. On the basis of the results obtained, it appeared to be a logical consequence that our mechanism would be able to rationalize the product distribution in acid solvolysis of benzo-epoxides of type **14**. However, attempts were unsuccessful to rationalize the product distribution of the acid hydrolysis of the rigid benzo-epoxides **15** and **16**[30] through a mechanism analogous to the one proposed for 1-arylcyclohexene oxides[4,9-12] (see Scheme I) in terms of the hypothesis that one of the determining factors in these reactions is the preferential "axial cleavage" of the epoxide ring. Maybe factors other than "axial cleavage" are important in determining the reactivity of such systems. The different conformational rigidity of the aryl in the two systems (1-arylcyclohexene oxides and benzo-epoxides of type **14**) could also be of some importance. Studies are in progress in order to clear up this point.

Experimental Section

Melting points are uncorrected. IR spectra for the determination of OH-stretching bands were taken with a Perkin-Elmer Model 257 double beam grating spectrophotometer in dried (P_2O_5) CCl_4 with use of the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2-cm optical length was employed, and the concentration of the solution was 5×10^{-3} M or lower to prevent intramolecular association. ^1H NMR spectra were determined on ca. 10% $CDCl_3$ solution with a Varian EM 360 with Me_4Si as an internal standard. GLC analyses were performed in the following way: hydroxy ethers **26–29b,c**, **31b,c**, and **32–33b,c**, a Perkin-Elmer Mod. SIGMA 3B (column packed with 10% neopentyl glycol succinate on 80–100 mesh silanized Chromosorb W, 2.0 m × 2.5 mm); **26–29b**, column 200 °C, nitrogen flow 60 mL/min; **26–39c**, column 210 °C, nitrogen flow 60 mL/min; **32–33b,c**, column 190 °C, nitrogen flow 50 mL/min. Diols **35–38a–c** were analyzed on a Carlo Erba Fractovap Model 2300 (column packed with 3% neopentyl glycol succinate on 80–100 mesh silanized Chromosorb W, 1.5 m × 2.5 mm): **35–38a**, column 190 °C, nitrogen flow 40 mL/min; **35–38b,c**, column 205 °C, nitrogen flow 40 mL/min. In every case evaporator and detector were at 270 °C.

Reactions of Epoxides 1–3 in Dioxane–Water and in Methanol in the Presence of Acid. A solution of the epoxide (0.020 g) in a thermostated (25 °C) 1:1 dioxane–aqueous 0.2 N H_2SO_4 (20 mL) or 0.2 N H_2SO_4 in anhydrous methanol (2 mL) was stirred at 25 °C during the time reported in Table I, quenched with solid $NaHCO_3$ and saturated aqueous $NaHCO_3$, and extracted with ether. Evaporation of the washed (water) and dried ether extracts yielded mixtures consisting of hydroxy ethers **26** and **27** from **2**, **28** and **29** from **3**, **32** and **33** from **1** (reaction in methanol), and diols **35** and **36** from **2**, **37** and **38** from **3**, and **40** and **41** from **1** (reaction in dioxane–water) which were analyzed by GLC (see Table I). The solvolysis addition products from each epoxide were completely stable under the exact reaction conditions used. The values given in Table I were the average of at least three measurements done on at least two different runs for each point.

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Registry No. 1a, 4829-01-0; **1b**, 7583-80-4; **1c**, 54637-84-2; **2a**, 17851-86-4; **2b**, 106267-70-3; **2c**, 106267-71-4; **3a**, 4341-22-4; **3b**, 106356-38-1; **3c**, 106356-39-2; **21b**, 106267-72-5; **21c**, 106267-73-6; **22c**, 106267-74-7; **23b**, 106267-75-8; **26b**, 106267-76-9; **26c**, 106267-77-0; **27b**, 106267-78-1; **27c**, 106267-79-2; **28b**, 106267-80-5; **28c**, 106267-81-6; **29b**, 106267-82-7; **29c**, 106267-83-8; **31b**, 106295-68-5; **31c**, 106267-84-9; **32b**, 106267-85-0; **32c**, 106267-86-1; **33b**, 106267-87-2; **33c**, 106267-88-3; **35b**, 106295-69-6; **35c**, 106267-89-4; **36b**, 106267-90-7; **36c**, 106267-91-8; **37b**, 106267-92-9; **37c**, 106267-93-0; **38b**, 106267-94-1; **38c**, 106267-95-2.

Supplementary Material Available: All the experimental details for the preparation of products shown in Schemes III–V and listed in Table III (13 pages). Ordering information is given on any current masthead page.

Chemoselectivity and Stereocontrol in Molybdenum-Catalyzed Allylic Alkylations

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Abstract: Molybdenum-catalyzed allylic alkylations exhibit excellent chemoselectivity. Carbonyl functional groups like esters and ketones need not be protected. The order of reactivity of a normal alkylating agent like an alkyl bromide and an allyl acetate is inverted compared to the uncatalyzed reaction—an observation that means that an alkyl bromide is compatible. In contrast to palladium-mediated reactions, silicon substituents at the allylic or vinylic position of the allylic acetate do not protodesilylate. Control of olefin geometry is exercised. The metal template favors formation of an (*E*)-olefin exocyclic to a ring. Both *E* and *Z* disubstituted allyl acetates give (*E*)-olefinic products. The stereochemistry of substitution with a cyclic allylic acetate depends upon the base and nucleophile. With BSA as base, clean net retention of configuration is observed. On the other hand, both diastereomers of 1-vinyl-1-acetoxycyclohexane give the same product arising from equatorial attack. Mechanistic and synthetic implications are discussed.

Controlling reactivity by the use of metal templates has the promise of enhancing our ability to perform selective transformations and to modify traditional reactivity patterns. For example, metal-catalyzed asymmetric hydrogenation[1] and epoxidations[2]

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