Influence of Remote Substituents on the Equatorial/Axial Selectivity in the Monooxygenation of Methylene C−H Bonds of Substituted Cyclohexanes

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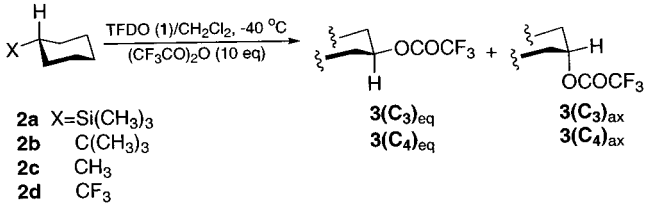
Abstract: The reactivity of individual C−H bonds in the methyl(trifluoromethyl)dioxirane TFDO oxygenation of stereogenic methylene groups in conformationally homogeneous monosubstituted cyclohexanes (**2**) has been determined. The unexpectedly high occurrence of O-atom insertion into C−H_{ax} bonds suggests an *in plane* trajectory attack in the oxygenation while the diastereoselectivity of the reaction is qualitatively interpreted on the basis of the distinct hyperconjugative stabilization by the substituent of diastereomeric transition states due to long-range through bond interactions.

The influence of remote substituents on the reactivity of prochiral moieties is of fundamental interest in organic chemistry and has been the subject of numerous studies, most of which have been devoted to understanding, predicting, and controlling the π-facial selectivity of reactions at sp^2 reactive centers such as ketones or olefins.[1] In contrast, systematic studies on saturated systems are scarce,[2] probably due to the lack of a suitable methodology for the selective functionalization of saturated hydrocarbons with reasonable yields under mild reaction conditions. One exception is the reactivity of methyl(trifluoromethyl)-dioxirane (hereafter TFDO) (**1**) in the oxyfunctionalization of hydrocarbons,[3] which boasts the aforementioned characteristics, thereby permitting the application of this reaction as a mechanistic probe to study the effect of remote substituents in saturated systems. Thus our preliminary results[4] on the study of the *Z/E* selectivity in the oxygenation of 2-substituted adamantanes enabled us to identify the long-range bond hyperconjugative effect of remote substituents on the relative reactivity of diastereotopic tertiary C−H bonds. We now wish to report our results on the influence of remote substituents on the reactivity of the individual C−H bonds of stereogenic methylene groups in conformationally homogeneous monosubstituted cyclohexanes (**2**). This study uses our methodology for the monooxygenation of saturated methyl and methylene groups with TFDO (**1**), which permits efficient control of the TFDO oxygenation reaction at the alcohol stage.[3e] The results show an unexpectedly high occurrence of O-atom insertion into C−H_{ax} bonds and indicate that the electronic nature of the remote substituent determines the equatorial/axial diastereoselectivity of the reaction as well as its regioselectivity.

Scheme 1



Results and Discussion

Oxygenations of conformationally homogeneous trimethylsilylcyclohexane (**2a**), *tert*-butylcyclohexane (**2b**), methylcyclohexane (**2c**), and trifluoromethylcyclohexane (**2d**)[5,6] were carried out at −40 °C by adding an aliquot of a thermostated solution of TFDO in dichloromethane to a dichloromethane solution of the substrate containing 10 equiv of trifluoroacetic anhydride (see Experimental Section). The reactions were treated with potassium carbonate and then analyzed with the aid of gas−liquid chromatography. The products were identified by comparison with authentic samples. Only trace amounts (<0.1%) of ketones were detected. The results are shown in Table 1.

Since methine C−H bonds are more reactive toward dioxiranes than methylene C−H bonds,[3] the regioselectivity in activated substrates such as **2a** and **2c** is thus biased toward

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(5) Conformational energy values ($\Delta G°$) for substituents $Si(CH_3)_3$, $C(CH_3)_3$, CH_3, and CF_3 are respectively −2.5,[6a] −4.9,[6b] −1.74,[6c] and −2.5[6d] kcal mol^{-1}.
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Table 1. Oxidation of Monosubstituted Cyclohexanes **2** with TFDO (**1**) in the Presence of Trifluoroacetic Anhydride[a]

	% attack (rel reactivity)[b]				k_{eq}/k_{ax}[c]	
2	C_1	C_2	C_3	C_4	C_3	C_4
2a	37 (5.5)		50 (1.9)	13 (1.0)	2.92	2.61
2b	1 (0.1)		77 (1.8)	22 (1.0)	1.35	1.10
2c	77 (39.4)	8 (1.1)	11 (1.4)	4 (1.0)	1.34	0.90
2d			33 (0.3)	67 (1.0)	0.44	0.52

[a] Reactions were carried out at −40 °C with a **2**:**1** initial molar ratio of 1:1. O-transfer values ranged between 85 and 97%. [b] Relative to the values of attack on C_4. [c] Results refer to the monohydroxylation of substrates **2**. Values are the average of at least three independent runs. The maximum standard deviation was ±0.034.

oxidation at C_1. In the case of substrates **2b** and **2d**, the reactivity of the methine is inhibited by steric hindrance of the *tert*-butyl substituent in the former and by the inductive electron withdrawing effect of the trifluoromethyl group in the latter. It is noteworthy that the longer length of the Si−C bond relative to the C−C bond significantly reduces the steric hindrance of the trimethylsilyl group toward O-atom insertion at C_1−H.

The C_2 reactivity is strongly affected by the size of the substituent, an effect that is attributable to the steric hindrance to the dioxirane approach caused by the butane-gauche alignment of the substituent relative to the C_2 methylene. In fact, compounds **2a**, **2b**, and **2d**, which all contain bulky substituents, do not react at all at C_2 while the methyl group significantly reduces the reactivity of **2c** at this position (see Table 1). In the case of **2d**, the electron withdrawing effect of the trifluoromethyl group further deactivates C_2.

Methylene groups at C_3 and C_4 (Table 1) exhibit different reactivities in each case, a fact which indicates that inductive electron donor substituents (**2a**, **2b**, and **2c**) favor the electrophilic[7] oxygenation reaction while the inductive electron withdrawing trifluoromethyl group (**2d**) decreases the reactivity. The influence of the inductive effect of the substituent on the reactivity was confirmed by competitive experiments with unsubstituted cyclohexane. *tert*-Butylcyclohexane (**2b**) reacts four times faster ($k_{t-Bu}/k_H = 4.00$) and trifluoromethylcyclohexane (**2d**) fifty times slower ($k_{CF_3}/k_H = 0.02$) than the parent cyclohexane. The reactivity of trimethylsilyl- and methylcyclohexane (**2a** and **2c**) cannot be compared as they react mainly at the tertiary C_1−H bond. Moreover, the results in Table 1 show that, as expected, the inductive substituent effect diminishes as the distance increases. Thus the C_3 position is more reactive than the C_4 position in activated compounds **2a**, **2b**, and **2c**, while the opposite trend is observed in the case of the deactivated compound **2d**.

A significant equatorial/axial diastereoselection is found in the oxygenation at C_3 and C_4 of compounds **2** (Table 1). It is well-known that the product distribution in dioxirane oxygenation reactions largely reflects the steric demand in the transition state.[3] In cyclohexane rings important steric differences apply for C−H_{ax} and C−H_{eq} bonds; therefore, the former are expected to be much less reactive toward oxygenation by dioxiranes. Thus, the extent to which the axial C−H_{ax} bond oxygenation occurs at C_3 and C_4 in compounds **2** is strikingly high (Table 1). Moreover, in the case of **2d**, the oxygenation at C_3 and C_4 occurs preferentially at the C−H_{ax} bonds (69.6 and 65.7% axial attack at C_3 and C_4, respectively). It is worth noting that in

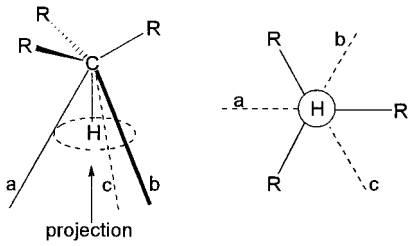

Figure 1. Off-axis limiting approach trajectories (a, b, c) in the attack of dioxirane to a single C−H bond.

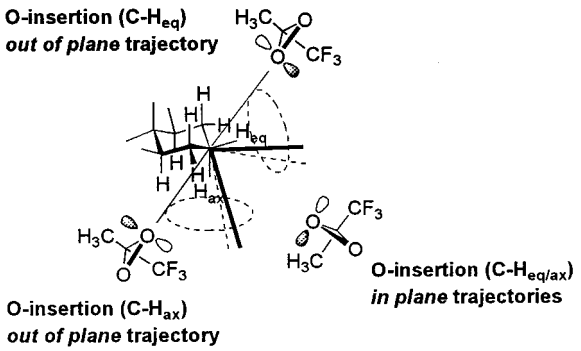

Figure 2. Dioxirane approach trajectories to methylene C−H bonds of cyclohexane. Only significant hydrogen atoms are depicted.

methylcyclohexane (**2c**) the steric influence exerted by the adjacent methyl group prevents the comparative analysis of the diastereoselection found at C_2. The extent of axial attack at positions C_3 and C_4 in the TFDO oxygenation of substrates **2** should allow us to define a preferential trajectory for the approach of dioxirane toward the methylene groups. The theoretical description[7] of the dioxirane oxygenation of saturated hydrocarbons indicates a bimolecular electrophilic interaction between a C−H bond and the dioxirane; the approach of dioxirane has been depicted as occurring somewhat off-axis to the C−H bonds[7] while the lone pair on the electrophilic oxygen acts as the migration terminus for the 1,2-hydrogen shift, thus determining the relative orientation of the molecules in a concerted transition state. Three limiting approach trajectories can be proposed for the oxygenation of a single C−H bond that would follow the perpendicular at the C site to each one of the three planes defined by the carbon atom involved in the C−H bond considered and any two of the three remaining atoms to which it is bonded (Figure 1).

This analysis can be extended to the C−H bonds of the methylene group in cyclohexanes. The geometry of the transition state will be determined by the interaction of the O−O antibonding orbital of dioxirane with the HOMO of the methylene fragment which can be represented as the out-of-phase combination of the σ(CH) local orbitals. In this case the limiting trajectories for the dioxirane attack to each methylene C−H bond will be one *out-of-plane* trajectory and two equivalent *in-plane* trajectories with respect to the plane defined by the six-member ring (Figure 2). The *out-of-plane* approach of dioxirane to the axial C−H_{ax} bond would be severely hindered by repulsive 1,3-diaxial interactions between C−H_{ax} bonds and the dioxirane electrophilic oxygen atom (Figure 2). Since the *out-of-plane* trajectory to attack the equatorial C−H_{eq} bond appears to be much less crowded, the oxygenation along this trajectory should proceed mainly on the equatorial C−H_{eq} bond. Therefore, to explain the different axial selectivities found for substrates **2a**−**d** following an *out-of-plane* trajectory attack, additional factors must be invoked, for instance, an unprecedented specific activation of the methylene C−H_{ax} bonds to

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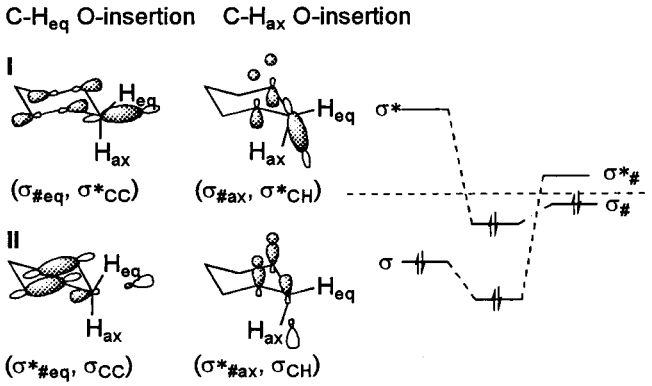

Figure 3. Anh's (**I**) and Cieplak's (**II**) hyperconjugative interactions for O-atom insertion into methylene C−H bonds.

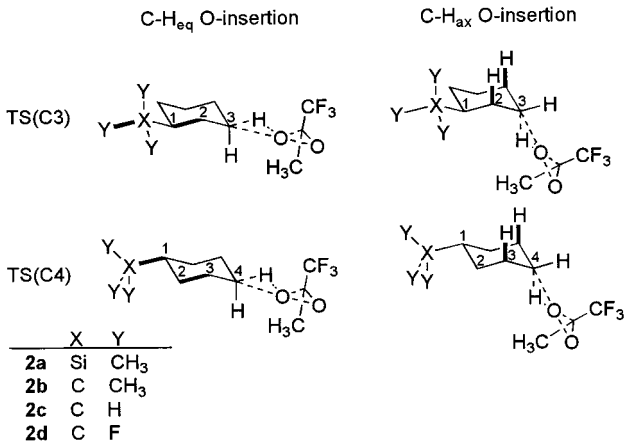

Figure 4. Transmission of the substituent hyperconjugative effect to interacting C−C and C−H bonds in the oxygen atom insertion transition state.

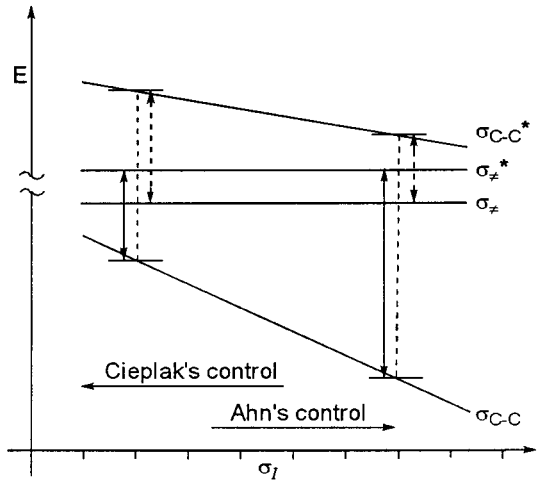

Figure 5. Variation of the hyperconjugative contributions ($\sigma_{\neq}-\sigma^*_{CC}$) and ($\sigma_{CC}-\sigma^*_{\neq}$) as a function of the σ_I value of the hyperconjugating substituent resulting from the more intense substituent effect on filled orbitals.

such an extent that the torsional strain does not play a significant role. In contrast, the *in-plane* approach of TFDO (Figure 2) is sterically unbiased for both diastereomeric methylene C−H bonds, which is in much better agreement with the observed extent of axial attack (Table 1). The equatorial/axial diastereoselection in each case would thus be the result of the distinct activation of the diastereomeric C−H bonds by the substituent.

Our data indicate a significant influence of the electronic nature of the remote substituent on the equatorial/axial selectivity of the reaction. The electron withdrawing trifluoromethyl group favors the oxygenation of the axial $C-H_{ax}$ bonds at C_3 and C_4, while in the case of the electron donor trimethylsilyl group, the oxygenation is biased toward the equatorial $C-H_{eq}$ bond in both positions (Table 1). *tert*-Butyl and methyl groups show a less clear-cut effect, which is in agreement with their weak electronic effect.

The hyperconjugative interactions[1,8−10] in the transition state between the incipient bond and the adjacent C−H and C−C bonds help account for the observed differences in diastereoselectivity. With the *in-plane* trajectory approach, the nascent bond would adopt a pseudoequatorial or pseudoaxial orientation in the transition state, depending on the diastereomeric C−H bond involved, but in any case with a similar torsional strain (see Figure 2). In this way Felkin's[8] destabilization of the transition state, which results from the repulsive interaction between filled orbitals of the incipient bond and the adjacent synperiplanar bonds, should not be expected to play any decisive role in selectivity control.

Anh's[9] and Cieplak's[10] hyperconjugative models of the diastereoselection account for the stabilization of the transition state through the interaction of either filled or empty orbitals of the incipient bond with orbitals corresponding to the antiperiplanar adjacent bonds. In Anh's model the discriminating interactions for the oxygen insertion into the $C-H_{eq}$ and $C-H_{ax}$ bonds would be ($\sigma_{\neq eq}$, σ^*_{C-C}) and ($\sigma_{\neq ax}$, σ^*_{C-H}) (Figure 3, **I**), while according to Cieplak's model they would be ($\sigma^*_{\neq eq}$, σ_{C-C}) and ($\sigma^*_{\neq ax}$, σ_{C-H}), respectively (Figure 3, **II**). As the substituent effect is transmitted by hyperconjugation along the adjacent antiperiplanar bonds (Figure 4), it should thus modify the relative energies of the σ_{C-C} and σ^*_{C-C} orbitals leaving the orthogonal σ_{C-H} and σ^*_{C-H} orbitals corresponding to the $C-H_{ax}$ bonds unperturbed. Therefore, the hyperconjugative stabilization of the axial transition states through interaction with antiperiplanar adjacent $C-H_{ax}$ bonds would be roughly constant along the series (Figures 3 and 4). Consequently, the equatorial/axial selectivity would reveal the distinct hyperconjugative stabilization of the equatorial transition states from the corresponding adjacent C−C bonds.

As the electron withdrawing ability of the substituent increases, the energy of the σ_{C-C} and σ^*_{C-C} orbitals decreases (Figures 4 and 5), thus weakening Cieplak's interaction ($\sigma^*_{\neq eq}$, σ_{C-C}) and enhancing Anh's ($\sigma_{\neq eq}$, σ^*_{C-C}). While Cieplak's model predicts an increase of the axial selectivity with the electron withdrawing character of the substituents, Anh's model predicts the opposite trend. This analysis is valid for oxygenations at C4 and C3 (Figure 4). The interpretation of the experimental results in terms of hyperconjugative stabilization of the diastereomeric transition states fits well with Cieplak's model.[10] However, the correlation between equatorial/axial selectivity data and Charton's [11] preferred σ_I constant of the substituents is not linear (Figure 6). In fact, the data corresponding to the oxygenation of trifluoromethylcyclohexane (**2d**) at positions C_3 and C_4 show an equatorial selectivity higher than expected, thus deviating from the trend.[12]

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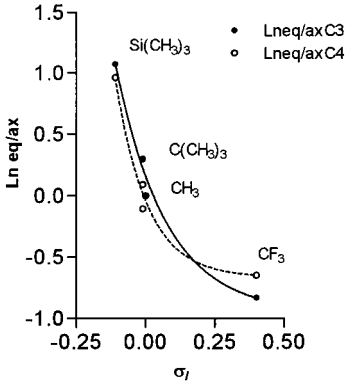

Figure 6. Plot of ln *eq/ax* vs σ_I for monooxygenation at positions C_3 and C_4 of monosubstituted cyclohexanes **2**.

It must be noted that since the progressive increase of the substituent withdrawing effect *simultaneously* weakens Cieplak's interaction and enhances Anh's interaction (Figure 5), there is a σ_I value from which Anh's hyperconjugation becomes noticeable and progressively increases while Cieplak's interaction gradually vanishes. We should therefore expect that on going from electron donor to electron withdrawing substituents, the equatorial selectivity gradually diminishes up to a point where the onset of Anh's hyperconjugation starts to reverse the trend. This balanced operation of both Cieplak's and Anh's hyperconjugation as functions of the σ_I constant of the substituent has been observed experimentally in our preliminary study of the diastereoselectivity in the oxygenation of the 2-substituted adamantane model.[4]

Applying this model to our data on the equatorial/axial selectivity in the TFDO oxygenation of monosubstituted cyclohexanes, the results found for trifluoromethylcyclohexane (**2d**) would be a consequence of an enhanced equatorial selectivity due to Anh's stabilization of the equatorial transition state. Unfortunately, the necessity of dealing with conformationally homogeneous monosubstituted-cyclohexane rings restricts the number of substituents in this study, thus precluding the determination of the point of minimum equatorial/axial selectivity derived from the balanced operation of both hyperconjugation models.[4] Moreover, although the selectivity of the reaction seems to be determined by the extended hyperconjugation, the flexibility of the monosubstituted cyclohexane model could introduce distinct entropic factors for each diastereomeric transition state, thus deviating the equatorial/axial ratio from the linear trend predicted by the operation of hyperconjugative interactions. It is worth noting that the selectivity induced by the methyl and *tert*-butyl groups suggests that the hyperconjugative effect due to C−H and C−C bonds is roughly the same within the experimental error.

In summary, the oxygenation of methylene C−H bonds in conformationally homogeneous monosubstituted cyclohexanes seems to proceed along an *in-plane* trajectory attack of the dioxirane while the diastereoselectivity of the reaction can be qualitatively interpreted on the basis of the distinct hyperconjugative stabilization of diastereomeric transition states by long-range interactions. For the first time this effect has been evaluated based on a combination of the outstanding selectivity shown by TFDO when reacting with saturated hydrocarbons along with our methodology[3e] for single C−H bond oxygenation of methylene groups. Moreover, the inductive effect of the substituent modulates the reactivity with the distance while the hyperconjugation determines the equatorial/axial selectivity.

Experimental Section

Solvents and reagents were purified by standard procedures.[13] Methyl(trifluoromethyl)dioxirane (**1**) in dichloromethane solution was prepared as described elsewhere.[14] Trimethylsilylcyclohexane[6a] (**2a**) and trifluoromethylcyclohexane[6d] (**2d**) were prepared by hydrogenation of trimethylsilylbenzene and trifluoromethylbenzene following reported procedures.[6a,d] Commercial *tert*-butylcyclohexane and methylcyclohexane were purified by distillation. Alcohols **4b(C$_4$)$_{ax}$**, **4b(C$_4$)$_{eq}$**, **4c(C$_2$)$_{ax}$**, **4c(C$_2$)$_{eq}$**, **4c(C$_3$)$_{ax}$**, **4c(C$_3$)$_{eq}$**, **4c(C$_4$)$_{ax}$**, **4c(C$_4$)$_{eq}$**, **4d(C$_3$)$_{ax}$**, **4d(C$_3$)$_{eq}$**, **4d(C$_4$)$_{ax}$**, and **4d(C$_4$)$_{eq}$** were purchased as cis/trans mixtures or in pure form. Trimethylsilyl-substituted cyclohexanols **4a(C$_3$)$_{eq}$**, **4a(C$_3$)$_{ax}$**, **4a(C$_4$)$_{eq}$**, and **4a(C$_4$)$_{ax}$** were prepared by means of a known procedure for the catalytic hydrogenation of *m*- and *p*-trimethylsilyl-substituted phenols.[15a] 3-*tert*-Butylcyclohexanol was prepared by means of catalytic hydrogenation of 3-*tert*-butylphenol.[15b] Esters of trifluoroacetic acid were prepared by treating the alcohol with an excess of trifluoroacetic anhydride following a reported procedure.[3e,f] Unequivocal determination of GC retention times for the equatorial and axial isomers was performed as reported below. Only the significant ^{1}H NMR data for the synthesized compounds are reported.

***cis*-3-Trimethylsilylcyclohexanol trifluoroacetate [3a(C$_3$)$_{eq}$]:** ^{1}H NMR ($DCCl_3$, 250 MHz) δ (ppm) 4.90 (dt, J_1= 10.9 Hz, J_2 = 4.5 Hz).

***trans*-3-Trimethylsilylcyclohexanol trifluoroacetate [3a(C$_3$)$_{ax}$]:** ^{1}H NMR ($DCCl_3$, 250 MHz) δ (ppm) 5.25 (t, unresolved).

***cis*-4-Trimethylsilylcyclohexanol trifluoroacetate [3a(C$_4$)$_{ax}$]:** ^{1}H NMR ($DCCl_3$, 250 MHz) δ (ppm) 5.31 (t, unresolved).

***trans*-4-Trimethylsilylcyclohexanol trifluoroacetate [3a(C$_4$)$_{eq}$]:** ^{1}H NMR ($DCCl_3$, 250 MHz) δ (ppm) 4.88 (dt, J_1= 11.3 Hz, J_2 = 4.5 Hz).

***cis*-3-*tert*-Butylcyclohexanol trifluoroacetate [3b(C$_3$)$_{eq}$]:** ^{1}H NMR ($DCCl_3$, 250 MHz) δ (ppm) 4.90 (dt, J_1= 10.9 Hz, J_2 = 4.3 Hz).

***trans*-3-*tert*-Butylcyclohexanol trifluoroacetate [3b(C$_3$)$_{ax}$]:** ^{1}H NMR ($DCCl_3$, 250 MHz) δ (ppm) 5.37 (t, unresolved).

Monooxygenation of Monosubstituted Cyclohexanes 2 with TFDO (1). An equimolar amount of TFDO (**1**) in dichloromethane was added to 1 mL of a 0.1 M solution of **2** in 1 M trifluoroacetic anhydride in dichloromethane cooled to −40 °C. The reaction was stirred at −40 °C until iodometric titration[16] of the mixture showed total consumption of dioxirane (2−6 h). The reaction was then warmed to −10 °C and treated with potassium carbonate for 1 h. The crude reaction mixture was filtered and analyzed by GC. The products were identified by comparison with identical samples prepared as reported above. The results are the average of at least three independent runs.

Unequivocal Determination of GC Retention Times of Equatorial and Axial Isomers of Compounds 3. The ratio of cis/trans isomers of alcohols **4** and their trifluoroacetic esters **3** was determined by ^{1}H NMR analysis and then analyzed by means of GC. When the isomer ratio did not allow the unequivocal determination of retention times (i.e. cis:trans ratio *approximately* 1:1), the mixture of alcohols was fully

(12) One of the referees has pointed out that the deviation from linearity seems greater for oxidations at C_4. As the interactions between the remote equatorial substituent and the equatorial transition state in the oxygenation would seem to be much like those in solvolysis or DAST fluorination reactions the proposition that nonlinearity is due to positive deviation for X = Me_3Si cannot at present be dismissed. (a) Adcock, W.; Coope, J.; Shiner, V. J., Jr.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411. (b) Lambert, J. B.; Salvador, L. A.; So, J.-H. *Organometallics* **1993**, *12*, 697. (c) Adcock, W.; Coton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867. (d) Lambert, J. B.; Ciro, S. M. *J. Org. Chem.* **1996**, *61*, 1940. (e) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265.

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oxidized with dimethyldioxirane[17] and then reduced with sodium borohydride. After this procedure the cis/trans mixtures obtained were enriched in one of the isomers, depending of the substituent. NMR analysis followed by GC analysis permitted unequivocal determination of the retention time for each isomer.

Competitive Oxygenation of Monosubstituted Cyclohexanes 2c and 2d vs Cyclohexane with TFDO (1). An aliquot of a solution of TFDO (**1**) in dichloromethane (2:2:1 molar ratio **2**:cyclohexane:**1**) was added to 1 mL of a 0.1 M equimolecular solution of substrates **2** (cyclohexane and methyl *p*-chlorobenzoate as internal standard) in dichloromethane cooled to −40 °C. The reaction was stirred at −40 °C until iodometric titration[16] of the mixture showed total consumption of dioxirane (2−6 h). The crude reaction mixture was filtered and analyzed by means of GC. The relative reactivity was determined by quantifying the consumption of the starting materials, after applying a statistical correction for the reactive methylene groups in each substrate. The results are the average of at least three independent runs.

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