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Effect of α -fluorination on asymmetric epoxidation of *trans*-olefins using α -fluorinated cyclohexanone dioxiranes

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Abstract

Epoxidations of *trans*- β -methylstyrene, *trans*-stilbene and *trans*-methyl *p*-methoxycinnamate using chiral dioxiranes derived from both enantiopure diastereomers of α -fluoro cyclohexanones, (2*S*, 5*R*)-**3a**–**6a** and (2*R*, 5*R*)-**3e**–**6e** are studied and compared. From ab initio calculations at the HF/6–31G^{*} level of conformational inter-conversion for (2*S*, 5*R*)-**D5a** and (2*R*, 5*R*)-**D5e** dioxiranes it was found that, due to the α -fluorine atom, conformer **K1** is more stable in the case of (2*S*, 5*R*)-**D5a** while conformer **K2** is more stable in the case of (2*R*, 5*R*)-**D5e**. However, in both cases, the more stable conformers, **K1** and **K2**, undergo rapid inter-conversion. Therefore, based on slow epoxidation reactions and rapid ring inversion of six-membered ring dioxiranes the Curtin–Hammett principle holds. Conformation **K2** with axial fluorine having been found to be more reactive, the inversion of configuration observed for the epoxides obtained with ketones **3e**–**6e** (compared with ketones **3a**–**6a**) could be rationalized from competitive reactions of **K2** and **K1** conformations leading to simultaneous production of both (-) and (+) epoxides in the case of ketones **3e**–**6e**.

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1. Introduction

Asymmetric epoxidation of *trans*-olefins by oxone catalysed with chiral ketones [1] which proceed through in situ formation of the corresponding chiral dioxiranes, has been significantly improved since the first attempts by Curci in 1984 [2,3]. A significant activating effect by α -fluorine substitution has been observed [2–5] and then extensively studied [6–15]. We have recently shown that, during epoxidation of methyl *p*-methoxycinnamate (Scheme 1), enantiopure tri-substituted cyclohexanones 1–3 were more efficient, leading to higher ee% and higher yields, when the halogen was axial (1a–3a) than when the halogen was equatorial (1e–3e) [7].

We present here results showing that this trend is encountered also using α -fluorinated ketones **3–6** during epoxidation of other olefins (such as *trans*- β -methylstyrene and *trans*-stilbene) as well as using ketones **4–6** during epoxidation of *trans*-methyl *p*-methoxycinnamate and a comparison of the enantioselectivities¹ (ee% and configurations) observed during epoxidations of the three *trans*-olefins using these ketones of known configuration which differ only from the orientation of the α -fluorine atom, either equatorial (**3e**–**6e**) or axial (**3a**–**6a**).

2. Experimental

2.1. General

Chemical shifts of ¹H and ¹³C NMR are given in 'ppm' (δ) downfield from TMS as an internal standard. TLC was performed on Merck glass plates with silica gel 60 F₂₅₄. Silica gel for column chromatography (Merck) was used for the chromatographic purifications. (+)-Dihydrocarvone,

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¹Being influenced by decomposition of the ketone (through Baeyer– Villiger), availability/solubility and rate of stirring, the percentages of conversion do not constitute a satisfying measure of the efficiency of a ketone and, as a consequence, of fluorine effects.



Scheme 1. Results of epoxidation of *trans*-methyl *p*-methoxy cinnamate [7].

purchased from Fluka, was a 77% (2R, 5R) and 20% (2S, 5R) mixture, having the enantiomeric purity of the starting (–)-carvone, 99% R at C5. All commercially available reagents were used without further purification.

2.2. Computational details

Semi-empirical calculations were carried out using PM3 method with the MOPAC 6.0 program package [26a,b]. The geometries of the transition states for conformational interconversion of the equilibrium structures were obtained using the optimized geometries of the equilibrium structures according to procedure of Dewar et al. [26c] The PM3 results were then used as input for the ab initio molecular orbital calculations, which were carried out using the Gaussian [25]. Geometries for all structures were fully optimized by means of Berny analytical gradients optimization routine [27a,b]. The restricted Hartree–Fock calculations with the split-valence $6-31G^*$ basis set which include a set of d-type polarization functions on all non-hydrogen atoms were used in these calculations [27c]. Vibrational frequencies were calculated all minimum energies and transition states, which were confirmed to have zero and one imaginary frequency, respectively. The frequencies were scaled by a factor of 0.91 [27d] and used to compute the zero-point vibrational energies.

For description of ketones 3–5 and 13 cf. ref. [16a,b].

2.3. (2S,5R,7S/R)-2-fluoro-2-methyl-5-(2-methyl-oxiranyl)-cyclohexanone **6a**

To a solution of **13a** (144 mg, 0.847 mmol) in acetone (2 mL), under stirring, at 0 °C, 0.08 M dimethyldioxirane solution in acetone (20 mL, 16 mmol) was added. Upon stirring to completion, as judged by TLC (about 1 h 30 min), the reaction mixture was concentrated. Water was added and the crude extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and concentrated, to give **6a** as a colorless oil (149 mg, 95%); 57/43 mixture of diastereomer **6aI** and **6aII**; IR: 1727 cm⁻¹. ¹H NMR (400 MHz C₆D₆) δ 2.57 (td, J = J = 12.5 Hz, J = 6.0 Hz, 1H, **6aI**, 57%), 2.51 (td, J = J = 13 Hz, J = 6.0 Hz, 1H, **6aI**, 43%), 2.34 (bd, J = 12.5 Hz, 1H, **6aI**, 57%), 2.07 (d = 4.5 Hz, 1H, **6aII**, 43%), 2.02 (d, J = 5.0 Hz, 1H, **6aI**, 57%), 2.01 (d,

J = 4.5 Hz, 1H, **6aII**, 43%), 1.79 (m, 2H, **6aI** and **6aII** overlapped), 1.63 (qd, J = J = J = 12.5 Hz, J = 3.5 Hz, 1H, **6aII**, 43%), 1.54 (qd, J = J = J = 13.0 Hz, J = 4.0 Hz, 1H, **6aI**, 57%), 1.29 (d, J = 22.5 Hz, 3H, **6aI**, 57%), 1.54 (d, J = 22.0 Hz, 3H, 6aII, 43%), 1.26 (m, 2H, 6aII, 43%), 1.17 (m, 2H, 6aI, 57%), 1.00 (m, 1H, 6aII, 43%), 0.90 (m, 1H, 6aI, 57%), 0.86 (s, 6H, 6aI and 6aII overlapped); 13 C NMR (100 MHz C_6D_6) signals of both diastereomers not assigned δ 205.3 (d, J = 25 Hz), 205.1 (d, J = 25 Hz), 95.6 (d, J =172 Hz), 95.5 (d, J = 173 Hz), 57.6, 57.5, 52.2, 52.5, 45.9, 45.5, 40.8 (d, J = 36 Hz), 40.7 (d, J = 36 Hz), 37.9 (d, J =6 Hz), 37.8 (d, J = 6 Hz), 22.8 (d, J = 2 Hz), 22.7 (d, J =2 Hz), 20.3 (d, J = 24 Hz), 20.1 (d, J = 24 Hz), 18.1, 17.6. MS (m/z %) 178 (2), 153 (4), 130 (4), 109 (19), 99 (2), 75 (19), 48 (100). Anal. calculated for C₁₀H₁₅FO₂ C, 64.5; H, 8.1. Found C, 64.4; H, 8.2.

2.4. (2R,5R,7S/R)-2-fluoro-2-methyl-5-(2-methyloxiranyl)-cyclohexanone **6**e

Synthesized from 13e following identical procedure as for 6a and has been obtained in 95% yield as a 55/45 mixture of diastereomer **6eI** and **6eII**; IR: 1732 cm^{-1} . ¹H NMR (400 MHz C₆D₆) δ 2.25 (2.dm, J = 12.5 Hz, 1H, **6eI** + **6eII**), 2.12 (d, J = 5 Hz, 1H, **6eI** 55%), 2.06 (d, J = 5 Hz, 1H, **6eII** 45%), 2.0 (d, J = 5 Hz, 1H, **6eII** 45%), 1.95 (d, J =5 Hz, 1H, 6eI 55%), 1.90-1.50 (m, 3H, 6eI + 6eII), 1.45-1.27 (m, 3H, **6eI** + **6eII**), 1.15 (d, *J* = 22 Hz, 3H, **6eI** 55%), 1.08 (d, J = 22 Hz, 3H, 6eII 45%), 0.83 (s, 3H, 6eI 55%), 0.81 (s, 3H, 6eII 45%). ¹³C NMR (100 MHz C₆D₆) signals of both diastereomers not assigned δ 204.5 (d, J = 17 Hz), 204.1 (d, J = 17 Hz), 96 (d, J = 185 Hz), 95.9 (d, J =182 Hz), 57.5, 52.2, 51.3, 47.7, 43.8, 42.6, 41.2, 37.4 (d, *J* = 22 Hz), 37.0 (d, J = 22 Hz), 24.6, 24.5, 22.1 (d, J = 22 Hz), 21.9 (d, J = 22 Hz), 19.2, 18.4. Anal. calculated for C₁₀H₁₅FO₂ C, 64.50; H, 8.12. Found C, 64.38; H, 8.21. In both cases diastereomers I and II could not be separated and mixtures were used for the epoxidation reactions.

3. Results and discussion

Ketones **3–6** have been synthesized in three steps from (R)-(+)-dihydrocarvone, Scheme 2, and the diastereomers separated by chromatography [16]. Some isomerisation



Scheme 2. (i) TMSCI, NaI, NEt₃ in pentane/MeCN (ii) selectfluor in DMF (iii) HF-pyridine (30% pyr./70% HF) in THF, 0 $^{\circ}$ C, in a polystyrene flask (iv) dimethyl dioxirane/acetone (v) HCl gas in Et₂O, 0 $^{\circ}$ C and (vi) Pd/C, H₂ (1 bar) in EtOH, rt.

occurs using HF-pyridine, therefore even starting from diastereomerically pure **13a** and/or **13e**, **5a** and **5e** must be purified.

The 1D and 2D NMR data [17] (in benzene-d6) of ketones **3e–6e** fit with the (2*R*, 5*R*)-configuration and conformation **C1** having both the fluorine atom and the *iso*-propyl-type group equatorial as the most populated, while in the case of ketones **3a–6a** the data fit with the (2*S*, 5*R*)-configuration and conformation **C1** having the methyl and the *iso*-propyltype groups equatorial but the fluorine axial as the most populated (Fig. 1). For convenience the ketones will thus be called F-equatorial and/or F-axial (instead of (2*R*, 5*R*) and/or (2*S*, 5*R*), respectively).

The epoxidation reactions have been conducted as previously described [7,9] either in DME/H₂O or in dioxane/ H₂O as solvent. The percentage conversions were determined by a combination of masses and ¹H NMR spectroscopy (400 MHz) of the solvent-free crude products. The epoxides were isolated by flash chromatography on silica



Fig. 1. Absolute configuration and major conformation C1 (determined by ¹H NMR in benzene-*d*6) of ketones **3e–6e** and **3a–6a**.

gel, the ee's were determined by ¹H NMR using Eu(hfc)₃ in CDCl₃ and, all three *trans*-epoxides being known, the absolute configurations were determined using the sign of the optical rotations ($[\alpha]_D$ measured under identical conditions: same solvent, same concentration). None of the ketones studied here underwent Baeyer–Villiger oxidation. Used in sub-stoichiometric amounts (0.3 equiv.) they were recovered almost quantitatively after reaction (through chromatography) and no lactones were detected by NMR (400 MHz) of crude products in none of the reactions.

The results of the asymmetric epoxidation of *trans*- β -methylstyrene 7, *trans*-stilbene 8 and *trans*-methyl *p*-methoxy cinnamate 9 (Scheme 3), with ketones **3e–6e** (having the fluorine atom equatorial in **C1**) are gathered in Table 1. Epoxidation of *trans*- β -methylstyrene 7 with the diastereomeric ketones **3a–6a** (having the fluorine atom axial in **C1**), epoxidation of *trans*-methyl *p*-methoxy cinnamate 9 with ketones **4a** and **6a** as well as epoxidation of *trans*-stilbene **8** with ketone **6a** are gathered in Table 2.

The level of enantioselectivity obtained during epoxidation of *trans*-olefins 7-9 with ketones 3e-6e (having identical absolute configurations, Fig. 1) is very low to nil (Table 1, line 3 and note a).

Inversions of the enantioselectivity, compared with epoxidations using the ketones with an axial fluorine, are



Scheme 3. Epoxidations and absolute configuration of epoxides.

Ketone	β-Methylstyrene 7				Stilbene 8				<i>p</i> -Methoxy cinnamate 9 ^a		
	3e	4e	5e	6e	3e	4 e	5e	6e	4 e	5e	6e
Percentage conversion	100	85	43	25	69	22	70	25	5	17	20
Percentage ee	26	20	0	2	18	23	20	2	nd ^b	10	8
Major enantiopure	(+)	(-)	_	(+)	(+)	(-)	(+)	(+)	_	(+)	(+)
Configuration	RR	SS	_	RR	RR	SS	RR	RR	_	SR	SR
Conditions ^c	А	А	А	А	В	В	В	В	А	А	В

Epoxidation of trans-olefins 7-9 using ketones (2R, 5R)-3e-6e having an equatorial fluorine in the most populated conformer C1

^a Ketone **3e**: 43% yield, 6% ee (+)-(SR), condition B; cf. ref. [7].

^b nd: not determined.

 $^{\rm c}$ A: DME/H2O, 0 $^{\circ}\text{C},$ 1.4 equiv. oxone, 6 h; B: dioxane/H2O, rt, 3 equiv. oxone, 8 h.

Table 2

Epoxidation of *trans*-olefins 7–9 using ketones (2S, 5R)-3a–6a having an axial fluorine in the most populated conformer C1

	β-Methylst	yrene 7	Stilbene 8 ^a	<i>p</i> -Methoxy cinnamate 9 ^b			
Ketone	3a	4a	5a	6a	6a	4a	6a
Percentage conversion	76	71	100	100	100	88	100
Percentage ee	46	72	80	74	88	58	66
Major enantiopure	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Configuration	SS	SS	SS	SS	SS	RS	RS
Condition ^c	А	А	А	А	В	А	В

^a Ketone **3a**: 78% yield, 60% ee (-)-(SS), condition B; ketone **4a**: 80% yield, 86% ee (-)-(SS), condition B; ketone **5a**: 90% yield, 90% ee (-)-(SS), condition B; cf. ref. [9].

^b Ketone **3a**: 97% yield, 40% ee (-)-(*RS*), condition B; ketone **5a**: 74% yield, 60% ee (-)-(*RS*), condition A; cf. ref. [9].

 c A: DME/H2O, 0 $^{\circ}\text{C},$ 1.4 equiv. oxone, 6 h; B: dioxane/H2O, rt, 3 equiv. oxone, 8 h.

observed (compare lines 4 and 5 in Table 1 with the same lines and notes a and b in Table 2) and it appears that only ketone 4 undergoes no inversion on passing from 4a to 4e.

In the case of ketones **3a–6a** (having identical absolute configurations, Fig. 1) the enantioselectivities are significantly higher (compare Table 2 line 3 and notes a and b with Table 1 line 3) and all types of ketones behave in the same way (Table 2, lines 4, 5 and notes a and b) all providing identical enantiomers: epoxides (-)-(SS), (-)-(SS) and (-)-(RS), respectively for olefins **7–9**.

While lower enantioselectivities (decrease in ee%) could be due to contribution of direct epoxidation by oxone which provides racemic epoxide, [18] inversions of enantioselectivity can not be ascribed to direct epoxidation by oxone.

The stereochemical outcomes of epoxidations of *trans*stilbene with ketones **3a–5a** (leading to (–)-(*S*, *S*) stilbene oxide) and *p*-methoxy cinnamate with ketones **3a** and **4a** (leading to (–)-(2*R*, 3*S*) cinnamate oxide) have already been rationalized [7,9] by considering the model shown on Scheme 4: conformation **K1** of the dioxirane (predicted to be the most populated because of the large *i*-Pr group equatorial); *spiro* geometry; [19–22] equatorial approaches of the olefin toward the dioxirane (with some contribution of the axial approaches, although less favored [9]) and $n(F).\pi(Ar)$ or $n(F).CH_3$ repulsion in approach *E*-I (making the corresponding transition state more energetic than the one corresponding to approach *E*-II).

The epoxidations of β -methylstyrene with ketones **3a–6a** (leading to (–)-(*S*, *S*) epoxide), epoxidation of *trans*-methyl

p-methoxy cinnamate **9** with ketones **4a** and **6a** (leading to (-)-(2R, 3S) cinnamate oxide) as well as epoxidation of *trans*-stilbene **8** with ketone **6a** (leading to (-)-(S, S) stilbene oxide), are also correctly rationalized through this



E-II >> E-I (F/Ph n. π repulsion or F/CH₃ repulsion); A-I -A-II when X=H ; A-I ~or slightly>A-II when X = Cl, F, Epox.

Scheme 4. Epoxidation of β -methylstyrene 7 by dioxiranes derived from ketones (2*S*, 5*R*)-**3a**-**6a** having an axial fluorine in the expected most populated conformation K1.

Table 1

Approach on conformation K1 of dioxirane

Approach on conformation K2 of dioxirane



Scheme 5. Epoxidation of trans-stilbene 8 with ketones (2R, 5R)-3e-6e, comparison between conformations K1 and K2.

model using the **K1** conformation for the (2S, 5R)-dioxiranes (Scheme 4).

However, contrary to what is observed (low to nil and in many cases inverted enantioselectivities), the use of this model in the case of stilbene and (2R, 5R)-dioxiranes (derived from ketones **3e–6e**) leads to the prediction that equatorial approach on conformer **K1** will also provide epoxide (–)-(*S*, *S*) as the major isomer (Scheme 5a), and that comparable (if not as high) enantioselectivities should be expected (approach *E*-II being favored over approach *E*-I due to steric CH₃/Ph hindrance in *E*-I). At this point it must be noted that an epoxide of opposite configuration (+)-(*R*, *R*) is expected to be formed from the equatorial approach of stilbene on conformer **K2** (of (2*R*, 5*R*)-dioxiranes) (Scheme 5b).

In spite of the satisfying consistency between the model and the experimental data in the case of (2S, 5R)-dioxiranes, the model suffers from an important weakness: the necessary hypothesis that **K1** is the most populated conformation as well as the most reactive.

Ring inversion in six-membered ring (equilibration between **K1** and **K2** conformations) is known to be a rapid process [23] and the epoxidation reactions slow (about 6 h^2 to be complete), the Curtin–Hammett principle holds and conformation **K2** could well contribute to the reaction if reactive enough.

Interestingly, it has already been shown by Armstrong et al. [22] using quantum mechanical methods, that α -fluoro dioxirane is more reactive when the fluorine is axial than when it is equatorial (E_{act} (TS with F-equatorial) – E_{act} (TS with F-axial) = +2.5 kcal mol⁻¹).

These dioxiranes are generated in situ and cannot be isolated, therefore an NMR study of their conformation in solution is not possible; we have thus performed a modeling of both dioxiranes derived from ketones **5a** and **5e**, respectively (for modelization of other rings cf. [24]). The results

of ab initio calculations at the HF/6–31G^{*} level $[25]^3$ for structure optimization [26,27] and conformational interconversion pathways of (2S, 5R)-**D5a** and (2R, 5R)-**D5e** are shown in Figs. 2 and 3.

The conformation **K1** of (2S, 5R)-**D5a** is by 7.05 kcal mol⁻¹ more stable than the second energy-minimum conformation **K2**. The calculated strain energy barriers for the inter-conversion of conformations **K1** and **K2** to twist-boat are 14.68 and 15.38 kcal mol⁻¹, respectively (Fig. 2) corresponding to rapid processes in consistency with literature results [23].

The degenerate inter-conversion of twist-boat family of (2S, 5R)-**D5a** with itself via the boat intermediate requires 2.35 kcal mol⁻¹.

On the other hand, the most stable conformation of (2R, 5R)-**D5e** is **K2** (isopropyl and F group are axial) and the second energy minimum conformation **K1** is 0.54 kcal mol⁻¹ above that of **K2** (Fig. 3). The calculated strain energy barrier for the inter-conversion of **K2** to **TB2** is 9 kcal mol⁻¹, which is higher than for inter-conversion into **K1**. Also the twistboat family of (2R, 5R)-**D5e** are not degenerate. This corresponds to higher electrostatic repulsion between F and gauche oxygen (which are held closer in the **TB2** than in the **TB1**). The dihedral angle ϕ_{FCCO1} in the **TB1** is -94.3° , while the same dihedral angle is -58.0° in the **TB2** conformer.

Although these calculations have been done for **D5a** and **D5e**, one can reasonably postulate that the trend will be the same for **D3a–e**, **D4a–e** and **D6a–e** with **K1** more populated for **D3a**, **D4a**, **D6a** and **K2** significantly populated for **D3e**, **D4e**, **D6e**.

Thus, from this modeling, conformation **K2** (axial fluorine) of (2R, 5R)-**D3e**-**6e** (derived from ketones **3e**-**6e**) is significantly populated (with [**K2**] \geq [**K1**]) and expected to be more reactive, [22] one can thus expect **K2** to contribute significantly to the reaction. As conformation **K2** leads to the epoxide of opposite configuration (compared with **K1**) a

 $^{^{2}}$ Reactions are monitored by TLC using silicagel 60 F₂₅₄ plates from Merck (eluent: hexana/Et₂O = 9/1).

³ It must be noted that the most stable conformation **K1** of (2S, 5R)-**D5a** was calculated to be 2.61 kcal/mol more stable than the most stable conformation **K2** of (2R, 5R)-**D5e**.



Fig. 2. Ring inversion in dioxiranes: calculated strain energy (kcal mol⁻¹) profile for (2S, 5R)-D5a.



Fig. 3. Ring inversion in dioxiranes: calculated strian energy (kcal mol⁻¹) profile for (2*R*, 5*R*)-**D5e**.

lowering of the ee% and even an inversion of the enantioselectivity (according to the extent of contribution of **K2**) is expected, which is indeed observed.

In (2S, 5R)-**D3a–6a** dioxiranes derived from ketones **3a–6a** conformation **K1** (F-axial) is more populated and more reactive than **K2** (F-equatorial) and will contribute almost exclusively to the reaction providing solely the corresponding enantiomer.

4. Conclusion

According to our calculations, and due to the presence of the α -fluorine atom, conformation **K2** having the fluorine axial is more populated than conformation **K1** (having the

fluorine equatorial) for dioxirane D5e derived from ketones 5e, while it is K1 which has the fluorine axial which is more populated than conformation K2 (having the fluorine equatorial) for dioxirane D5a derived from ketones 5a. According to these calculations it has also been found that K1/K2 inter-conversions should be rapid processes (in the gas phase) consistent with literature results (usually determined in solution) [23]. Moreover, dioxirane conformations having the fluorine axial (K2 for D5e or K1 for D5a) are expected to be more reactive according to Armstrong/Houk ab initio modeling. Based on the hypothesis that all α -fluorinated dioxiranes (D3, D4 and D6) behave as D5, on slow epoxidation reactions, rapid ring inversion of six-membered ring dioxiranes, relative population of conformers K1 and K2 and the Curtin-Hammett principle, the decrease in enantioselectivity and the inversion of configuration observed for the epoxides obtained with ketones 3e-6e (compared to ketones 3a-6a) are due to competitive reactions of K1 and K2 in dioxiranes D3e-D6e and to simultaneous production, in these cases, of both (-) and (+) epoxides with lowering of enantioselectivity and even inversion of enantioselectivity according to the extent of contribution of K2 to the reaction.

It thus appears that activation of ketones (as epoxidation catalysts) by an α -fluorine atom is strongly orientation dependent at least in the cases where flexible dioxiranes are formed.

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