Asymmetric Epoxidation of *trans*-Olefins via Chiral Dioxiranes: A Possible Contribution of *axial* Approaches in the case of Tri- and Tetrasubstituted α-Fluoro Cyclohexanones

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Dedicated to the memory of Professor H. Mosher[†]

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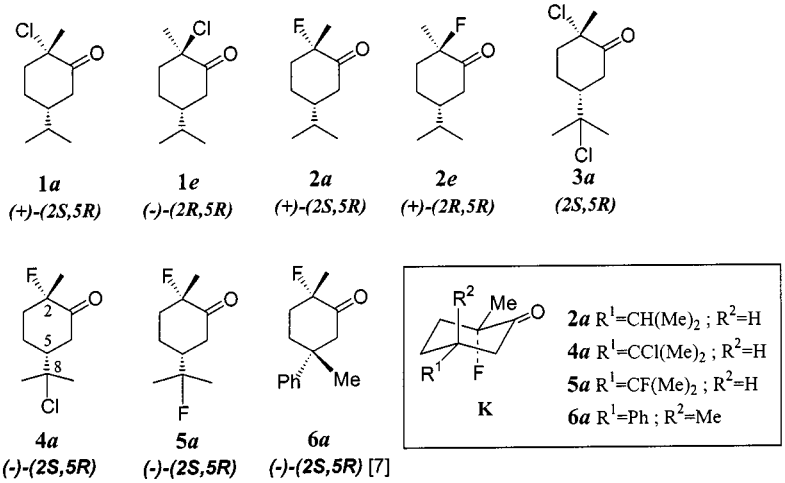
During the asymmetric epoxidation of stilbene and methyl *p*-methoxycinnamate with chiral dioxiranes (derived from 2,2′,5-tri- and 2,2′,5,5′-tetrasubstituted cyclohexanones with an axial fluorine at C2) a 26 to 30% increase in *ee* was observed upon desymmetrization of the axial face of the dioxirane (through disubstitution at C5 or introduction of a fluorine on the equatorial *i*Pr-substituent located at C5), which suggests a contribution of the axial approach of the olefin to the dioxirane (in addition to the main equatorial approach). The two ketones **5a** and **6a**, which do not undergo Baeyer–Villiger oxidation, can be used in substoichiometric amounts and are fully recovered after the reactions, provide epoxides in high yield (75–90%) and high (95:5) to satisfying (83:17 to 87:13) enantiomeric ratios.

Introduction

From our previous results[1] showing that the α-fluoro ketone **2a**, with an *axial* fluorine, was more efficient than ketones with an *equatorial* fluorine (**2e**) or a chlorine (**1a**, **1e**) for the epoxidation of *trans*-disubstituted olefins (with **2a** > **1a** > **2e** > **1e**), and from literature results[2] showing that substitution of the proton of the isopropyl group at C-5 by a halogen atom (such as in compound **3a**) also leads to more efficient ketones, we synthesized the ketones **4a**, **5a** and **6a** with an *axial* fluorine at C-2 and either a halogen at C-8 (**4a** and **5a**) or two substituents at C-5 (**6a**).

While ketones (−)-(2*S*,5*R*)-**4a** and (−)-(2*S*,5*R*)-**5a** were obtained enantiopure [from (+)-(*R*)-dihydrocarvone, ≈99% *R* at C5], ketone **6a** was obtained as a racemate, which was resolved by chiral HPLC;[3] the (−)-isomer used was assigned the (2*S*,5*R*)-configuration by vibrational circular dichroism (VCD).[4]

The most populated conformer of these ketones has then been determined to be **K** (*cf.* above) by 1D and 2D NMR spectroscopy.[3−5]



Results and Discussion

The results of the asymmetric epoxidation of stilbene and methyl *p*-methoxy cinnamate (Scheme 1)[6] with these ke-

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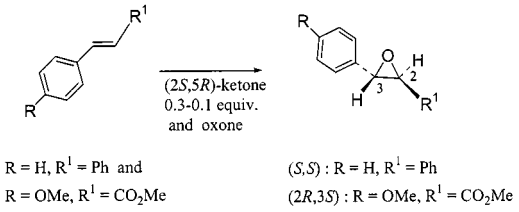
Table 1. Asymmetric epoxidation of stilbene and methyl *p*-methoxycinnamate (reaction time: 8 h, pH = 8.5−9, temp.: 0 °C, * reaction temp.: 20 °C)

	Stilbene				Methyl *p*-methoxycinnamate			
Ketone	**2a**[a]	**4a**[a]	**5a**[a]	**6a**	**2a**[a]*	**4a**[a]	**5a**[a]	**6a***
Enantiom.	(+)	(−)	(−)	(−)	(+)	(−)	(−)	(−)
Conf.	(2*S*,5*R*)	(2*S*,5*R*)	(2*S*,5*R*)	(2*S*,5*R*)	(2*S*,5*R*)	(2*S*,5*R*)	(2*S*,5*R*)	(2*S*,5*R*)
Equiv. of ketone	0.1	0.3	0.3	0.1 0.3	0.3	0.3	0.3	0.3
% conv.	68	78	**90**	**53 95**	99	88	74	**90**
% *ee*	60	86	**90**	**89 90**	40	58	60	**66**
Epox. enantiom.	(−)	(−)	(−)	(−) (−)	(−)	(−)	(−)	(−)
Epox. conf.[b]	(*S*,*S*)	(*S*,*S*)	(*S*,*S*)	(*S*,*S*) (*S*,*S*)	(2*R*,3*S*)	(2*R*,3*S*)	(2*R*,3*S*)	(2*R*,3*S*)

[a] Obtained from (+)-(*R*)-dihydrocarvone, (+)-**2a** has the same chirality **K** as **4a**−**6a**. − [b] For assignment of the absolute configuration of epoxides see ref.[7].

tones are gathered in Table 1. The percentages of conversion were determined by a combination of isolated weights and ^{1}H NMR spectroscopy (200 MHz) of the solvent-free crude products; the epoxides were isolated by flash chromatography on silica gel. The *ee*'s were determined by HPLC (Chiralcel OD) and optical rotations.



Scheme 1

Asymmetric Epoxidation of Stilbene

Most interesting was the 29% increase of *ee* in favor of the same (−)-(*S*,*S*) isomer of stilbene oxide[7] obtained with ketones (−)-(2*S*,5*R*)-**6a**, disubstituted at C-5, relative to the *ee* obtained with ketone (+)-(2*S*,5*R*)-**2a**, monosubstituted at C5 (60% *ee* with **2a** compared to 89% *ee* with **6a**: Table 1, columns 1,4).

Replacing the proton of the isopropyl group located at C-5 by a halogen has the same effect and increases the enantioselectivity toward the same (−)-(*S*,*S*) isomer of the epoxide (Table 1, columns 1−3): from 60% *ee* for H (ketone **2a**) to 86% *ee* for Cl (ketone **4a**) and 90% *ee* for F (ketone **5a**), as also observed by Yang et al.[2] in the case of the α-chloro ketones **3a** and **1a** (85% *ee* with **3a** and 42% *ee* with **1a**).

Asymmetric Epoxidation of Methyl *p*-Methoxy Cinnamate

Although the general trend is identical, with a 26% *ee* increase of the same (−)-(2*R*,3*S*) epoxide[7] upon desymmetrization of the *axial* face of the dioxirane (40% *ee* with **2a** compared to 66% *ee* with **6a**), examination of Table 1 (columns 6−9) shows that a carboxylate group is less efficient than a phenyl group for recognition of the dioxirane chirality: 66% *ee* (Table 1, column 9) instead of 90% *ee* (Table 1, column 5) with ketone **6a**.

A 8% increase in *ee* was obtained when the epoxidation was conducted with ketone **6a** on the *tert*-butyl ester of *p*-methoxy cinnamate (74% *ee* vs. 66% for the methyl ester, under identical reaction conditions). In the case of *p*-methoxy cinnamate, ketones **4a** and **5a** are also less efficient than with stilbene.

The stereochemical outcome of epoxidations with **2a** and **6a** [obtention of (−)-(*S*,*S*) stilbene oxide and (−)-(2*R*,3*S*)-cinnamate oxide from the (2*S*,5*R*)-ketones] can be rationalized by considering the *equatorial spiro* approach[8−10] of the olefin to the most populated conformer of the dioxirane, **K**, as usually done in the literature (Figures 1 and 2).

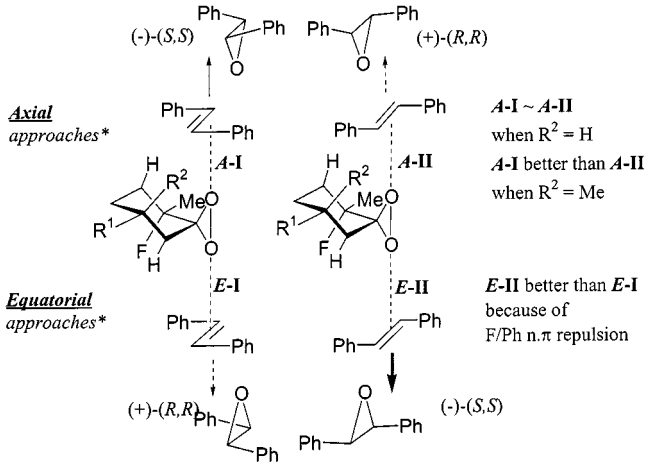


Figure 1. Equatorial and axial approaches of stilbene to the most stable dioxirane conformer

Although *axial* approaches are significantly less favored than *equatorial* ones, they could contribute partly. During such *axial* approaches (Figures 1 and 2), the *axial* methyl at C-5 (R^2 = Me) desymmetrizes this approach making − for steric reasons — approach ***A*I** or ***A*II**/***A*I′** better than ***A*II** or ***A*II**/***A*II′** and one could expect more (−)-(*S*,*S*)- or more (−)-(2*R*,3*S*) epoxide to be formed. As a consequence, an increase in *ee* is expected, which is indeed observed in both cases.

One must also note that the less stable and less populated inverted ring, if reactive enough (Curtin−Hammet principle), could contribute significantly (through *equatorial* ap-

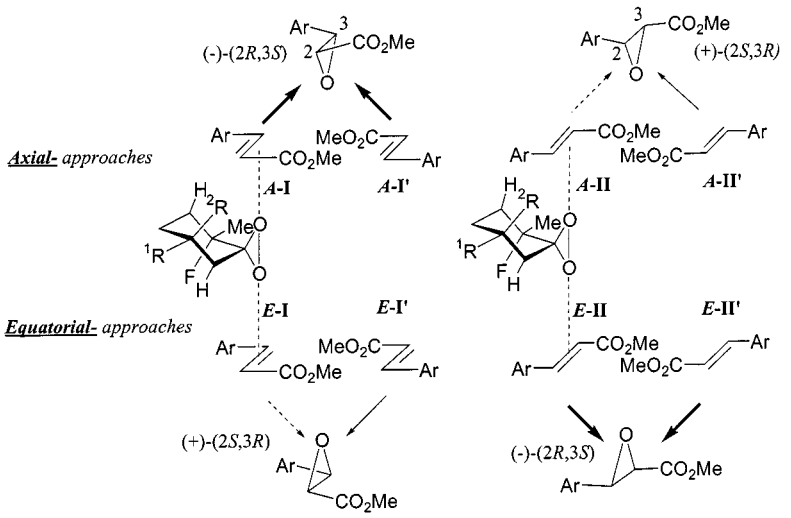


Figure 2. Equatorial and axial approaches of methyl *p*-methoxycinnamate to the most stable dioxirane conformer

proaches) or partly (through *axial* approaches) to the epoxidation. However, if one envisages *equatorial* (and *axial*) approaches to the inverted ring of the dioxirane (Figure 3), it appears that stilbene oxide with the opposite (+)-(*R,R*)-configuration should be formed. A contribution of the inverted ring in the case of ketone **6a** would thus lead to a decrease in *ee* and one can, therefore, reasonably conclude that the large increase in *ee* observed (+29/+30% for stilbene and +26% for *p*-methoxy cinnamate) could only arise from some contribution of an *axial* approach to the most populated conformer (Figures 1 and 2), and not from an approach to the inverted ring of the dioxirane (Figure 3).

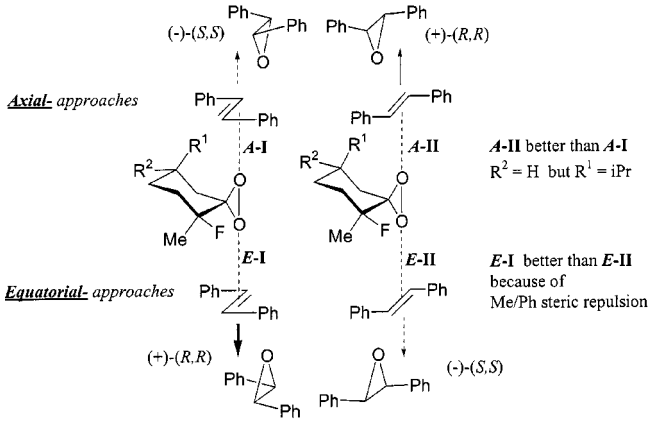


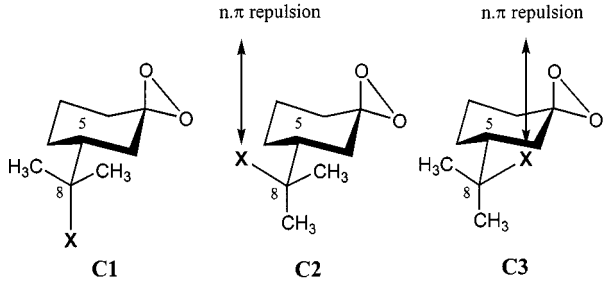
Figure 3. Equatorial and axial approaches of stilbene to the less stable conformer of the dioxirane (inverted ring)

The stereochemical course of these epoxidations thus suggests that:

equatorial approach to *axial* fluorine > *axial* approach to *axial* fluorine (Figure 1) > *equatorial*/*axial* approach to *equatorial* fluorine (Figure 3).

This observation is not in contradiction with previous ab initio calculations,[11] which were conducted on a cyclohexanone with only a fluorine atom at the α-position. In the dioxirane corresponding to ketone **6a**, when the fluorine atom is *equatorial* (inverted ring) a methyl group is in the *axial* position instead of a proton and this *axial* methyl destabilizes the *equatorial* approaches making them less stable with a possible inversion of the order of stability and *equatorial* approaches to *equatorial* fluorine could become more difficult than an *axial* approach to *axial* fluorine instead of *equatorial* approaches to *equatorial* fluorine being easier than an *axial* approach to *axial* fluorine, as found by an ab initio simulation of α-fluorocyclohexanone.[11]

The increase in enantioselectivity observed when replacing the proton of the isopropyl group located at C-5 by a halogen could also be rationalized by a non-negligible contribution of *axial* approaches. Molecular models show that during type ***A*II** (Figure 1) *axial* approaches to conformations **C2** (and **C3**) of the dioxiranes derived from **4a** and **5a**, the phenyl ring of the olefin is located above the "haloisopropyl" moiety and close to the halogen atom thus making n-π electronic repulsions possible and, perhaps, of significant intensity. ***A*II** being thus disfavored compared to ***A*I**, less (+)-(*R,R*) epoxide is expected to be formed and the *ee* should increase as observed.



Conclusion

The new ketones **5a** and **6a** provide epoxides in high yield (75−90%) and high (90%) to satisfying (66−74%) *ee*. Moreover, they do not undergo Baeyer−Villiger oxidation under the reactions conditions used and are quantitatively recovered.

As previously observed,[1] fluorine is better than chlorine: ketone **5a** leading to a higher percentage of conversion and higher *ee* than ketone **3a** (0.3 equiv. **5a**: conv. = 90%, *ee* = 90%; 1 equiv. **3a**: conv. = 74%, *ee* = 85%). It is worth noting that the classical model (Figures 1 and 2) allows rationalization/prediction of the absolute configuration of the epoxides obtained and of the changes in *ee* upon modification of the ketone structure. At the moment, one can reasonably postulate that desymmetrization of the *axial* face of α-fluoro-α-methyl cyclohexanones (through disubstitution at C-5 or through modification of the *equatorial* substituent at C-5), increases the enantioselectivity of epoxidation, suggesting that *axial* approaches may contribute partly. Contribution of *equatorial* (*axial*) approaches to the inverted ring (less populated conformer) do not contribute significantly, but might be responsible for the fact that the *ee*'s do not exceed 90%; rigid α-fluoro ketones are therefore under synthesis.

Experimental Section

General Remarks: The synthesis and characterization of ketones **4a**−**6a** is described in ref.[3] The stilbene oxide and methyl *p*-methoxy cinnamate epoxide obtained had the same NMR spectra as the racemic compounds purchased from Aldrich. Reactions were monitored by TLC using Merck's glass plates with silica gel 60 F_{254}. Silica gel Si 60 (40−60 μm) from Merck was used for the chromatographic purifications. Determination of the *ee* of both epoxides was performed on CHIRALCEL OD: Stilbene oxide, mobile phase = *i*PrOH/hexane (10:90), flow rate = 1 mL/min, t_R (min) = 5.4 (−)-(*S*,*S*) isomer and 7.0 (+)-(*R*,*R*) isomer); and methyl *p*-methoxy cinnamate epoxide, mobile phase = *i*PrOH/hexane (35:65), 1 mL/min, t_R(min) = 5.7 (−)-(2*R*,3*S*) isomer and 7.0 (+)-(2*S*,3*R*) isomer. Optical rotations were determined with a Perkin−Elmer 341 polarimeter. Rotations were determined in EtOH (c = 1) for stilbene oxide (ref.:[12] $[\alpha]_D^{20} = -299$, ≈100% *ee*) and in MeOH (c = 0.5) for the methyl *p*-methoxy cinnamate epoxide (ref.:[13] $[\alpha]_D^{20} = -212$, ≈100% *ee*).

Epoxidation: Distilled water (6 mL) and a solution (4 mL) of acetic acid (0.5 mL) and 0.1 M aqueous K_2CO_3 (100 mL) were added whilst stirring to a solution of 1 mmol of the desired olefin and 0.1 or 0.3 mmol of ketone (0.1 or 0.3 equiv.) in DME (16 mL). The mixture was cooled to the desired temperature and a solution of Oxone® (1.850 g, 3 mmol, 6 equiv. of oxidant) in distilled water (7 mL) was added dropwise over 8 hours. During the addition of the Oxone®, the pH was controlled and regulated (≈8.5−9) by addition of a solution of 1 M K_2CO_3. The reaction mixture was then immediately quenched by addition of CH_2Cl_2 (30 mL) and water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4 and analyzed by NMR spectroscopy. After chromatographic purification the ketone was recovered and the isolated epoxide analyzed (NMR spectroscopy, optical rotation and chiral HPLC). Stilbene oxide and methyl- or *tert*-butyl *p*-methoxycinnamate oxides are well-known compounds; all their physical characteristics are identical to those of the literature.[1,2,12,13]

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