Regio- and diastereoselection in the oxaziridinium salt oxidation of acyclic allylic acetates

David Poisson, Gilles Cure, Guy Solladié and Gilles Hanquet*

Laboratoire de Stéréochimie associé au CNRS, ECPM, Université Louis Pasteur, 25 rue Becquerel, 67087 Strasbourg, France

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Abstract—Oxaziridinium salt **1** is a versatile oxygen transfer agent towards olefins. An important *threo* selectivity is observed with acyclic allylic acetates due to 1,3-allylic strain ($A^{1,3}$). The π-facial selectivity in the epoxide formation is interpreted as a consequence of an interaction between the residual positive charge on nitrogen and the neighbouring acetate in the transition state. Such an interaction is not strong enough to balance the lowered nucleophilicity of the 2,3 double bond in the geraniol acetate **3a**. © 2001 Elsevier Science Ltd. All rights reserved.

Oxaziridinium salts have been known since 1976[1] as oxygen atom transfer agents towards nucleophiles. Since 1987, several oxaziridinium salts have been described[2] and used for epoxidation in stoichiometric amounts[3] or in catalytic processes.[4] The oxaziridinium salt **1** derived from tetrahydroisoquinoline and its chiral analogue **2** have been extensively studied for oxygen transfer to olefins,[5] *N*-nucleophiles,[6] and *S*-nucleophiles.[7]
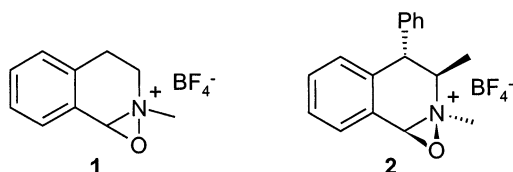
Despite the description of numerous examples of oxaziridinium salt oxidations, little is known to date about the mechanism of the oxygen transfer. Recently Houk[8] proposed a flexible spiro transition state in stereoselective epoxidations.[3c,4,9]

A few years ago,[5] we observed an important *syn*-directing effect of the acetate group in the epoxidation of cyclic allylic substrates by the oxaziridinium salt **1** (de>95% with 2-cyclohexene-1-acetate and 3-methyl-2-cyclohexene-1-acetate). Such interactions were not observed with the corresponding alcohols (de=6/4), the strong electrophilic character of the oxygen atom in the oxaziridinium salt is not compatible with the formation

of hydrogen bonds with the allylic alcohols. In order to explain this selectivity, we postulated a transition state based on an interaction between the residual positive charge on nitrogen and the neighbouring acetate.

Stereoselective hydroxyl directed epoxidations of chiral allylic alcohols have been reported with a variety of oxidizing agents[10] as a result of a π-facial selectivity in epoxide formation from chiral allylic alcohols due to dominant 1,3-allylic strain ($A^{1,3}$) (*threo*-selectivity), with respect to the 1,2-allylic strain ($A^{1,2}$) (*erythro*-selectivity).
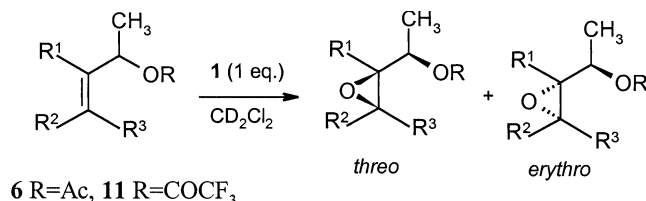
These studies afforded valuable information on the transition state geometry for oxygen transfer processes from metal (peroxy and peroxo) complexes and non-metallic (peracids and dioxirane) oxidants.[11]

In order to get more information about the hypothesis proposed for cyclic allylic acetates, we decided to use the acyclic stereochemical probe **6d** (R=H) described by Adam[10–12] for dioxirane epoxidation and to study the epoxidation of acetates **6a**–**e** with the oxaziridinium salt **1**. We completed this work by studying the regioselectivity obtained in the epoxidation of geranyl acetate **3**, as well as the comparative epoxidation of the allylic acetate **7** versus the homoallylic acetates **8**.[11]

Diastereoselectivity

The stabilization effect due to acetate assistance[5] should direct the epoxidation of chiral acyclic allylic acetates with the oxaziridinium salt **1** as already demonstrated for the allylic alcohol epoxidation by various oxidizing

* Corresponding author. Fax: 33 3 90 24 27 42; e-mail: hanquet@chimie.u-strasbg.fr

Table 1. Diastereoselectivities in the epoxidation of allylic acetates **6** and their corresponding trifluoroacetates **11** by the oxaziridinium salt **1**

6 R=Ac, **11** R=COCF$_3$

Entry	Substrate	R	R^1	R^2	R^3	Epoxides *threo/erythro*[a,b]
1	**6a**	Ac	H	Me	H	50/50
2	**6b**	Ac	H	Me	Me	90/10
3	**6c**	Ac	Me	H	H	65/35
4	**6d**	Ac	Me	H	Me	95/5
						60/40 in acetone-d_6
						65/35 in CD$_3$NO$_2$
5	**6e**[13]	Ac	Me	Me	Me	93/7
						73/27 in acetone-d_6
6	**11b**[c]	COCF$_3$	H	Me	Me	60/40
7	**11c**	COCF$_3$	Me	H	H	58/42
8	**11d**	COCF$_3$	Me	H	Me	65/35
9	**11e**[c]	COCF$_3$	Me	Me	Me	68/32

[a] Reactions are monitored by ^{1}H NMR analysis until complete conversion (>95%). Oxaziridinium salt is quantitatively deoxygenated into its corresponding iminium salt. Structures of epoxy-acetates and trifluoroacetates were confirmed by chemical correlation to the known epoxy-alcohols.[10a]

[b] dr Determined by ^{1}H NMR.

[c] Trifluoroacetates bearing a methyl group at the R^2 position are very sensitive and were prepared in low yields using imidazole trifluoroacetate in dichloromethane.

agents.[10] We have compared the diastereoselectivity of the epoxidation of acetates **6a–e** with that of the corresponding trifluoroacetates **11a–e** in apolar or polar solvents. The results are listed in Table 1.

The large difference in the stereoselectivities for the oxaziridinium salt epoxidation of the allylic acetates (entries 1–5) compared with their corresponding trifluoroacetates (entries 6–9) is consistent with our previous hypothesis.[5] Of more interest is the diastereoselectivity observed with the acetates **6a–e**. Clearly, the diastereoselectivity in the epoxide formation depends on the substitution pattern of the allylic acetates **6**. For substrates without allylic strain (entry 1) no diastereoselectivity is observed, whereas for substrates bearing a methyl group at the R^1 or R^3 position (entries 2 to 5), a *threo* selectivity is observed in the oxaziridinium salt epoxidation. This diastereoselectivity increased from 1,2-allylic strain (entry 3) to 1,3-allylic strain (entries 2, 4 and 5). In the case of **6d**,[12a] which possesses both 1,2 and 1,3-allylic strain, *threo*-selectivity is shown demonstrating the domination of 1,3-allylic strain versus 1,2-allylic strain, without any ambiguity. Clearly, the diastereoselective epoxidations of the chiral allylic acetates (Table 1) provide evidence for an interaction of the acetate group with the cationic transition state. Further support for this proposed association is also gained from the oxaziridinium salt **1** promoted epoxidation of **6d** in acetone or nitromethane and of the trifluoroacetates **11b–e** (entries 6–9). While the acetate function in **6b,d,e** directs oxaziridinium salt attack and

gives the *threo* epoxide, all trifluoroacetate derivatives **11b–e**, which possess a less basic carbonyl, and therefore a lower stabilisation effect in the transition state, yield the corresponding epoxides with a low *threo*-selectivity.

These results can be explained by the transition state depicted in Fig. 1 in which the π-facial selectivity is controlled by the acetate in a geometry with minimization of 1,3-allylic strain (A^{1,3}).

Regioselectivity

Geranyl-acetate is an allylic acetate with two trialkyl substituted double bonds. The next experiments involved a comparison of the π reactivity of the 2,3 and 6,7 double bonds to provide more evidence about acetate assistance. The results are reported in Table 2.
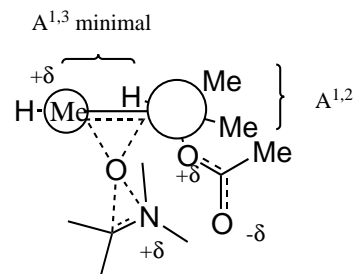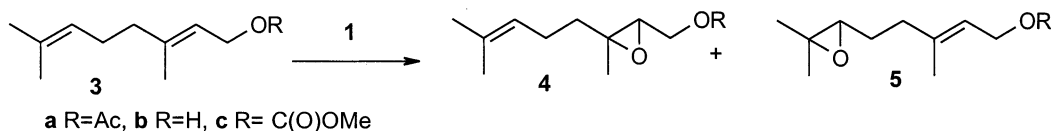

Figure 1.

Table 2. Epoxidation of geranyl-acetate **3a–c** by the oxaziridinium salt **1**

a R=Ac, **b** R=H, **c** R= C(O)OMe

Entry	Substrate	Equivalents of **1**	Conditions[a]	Conversion%[b]	Products
1	**3a**	0.4	CD$_2$Cl$_2$, 5 min	40	**5a** and traces of **4a**
2	**3a**	1	CH$_2$Cl$_2$, 30 min	97	**5a** only, 92% isolated
3	**3b**	0.4	CD$_2$Cl$_2$, 5 min	40	**5b** only
4	**3c**	0.4	CD$_2$Cl$_2$, 5 min	32	**5c** only

[a] Time required to observe a negative KI (potassium iodide) test.
[b] Determined by ^{1}H NMR analysis on the crude product mixture.

7 n=1, **8** n=2   **9** n=1, **10** n=2

epoxide ratio: allylic/homoallylic= 20/80
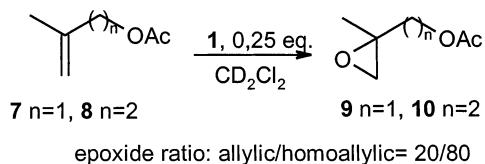
Scheme 1. Competitive epoxidation of a mixture of allylic acetate **7** and homoallylic acetate **8** with the oxaziridinium salt **1**.

Finally, we tested the reactivities of allylic versus homoallylic acetates **8** and **9** in a competitive experiment (Scheme 1).

The results listed in Table 2 (entries 1 and 2) showed that the terminal 6,7 double bond in geranyl acetate is exclusively epoxidized. No di-epoxidation was observed. The nucleophilicity of the 2,3 double bond is therefore strongly lowered by the electron-withdrawing effect of the acetate group. The presence of a more basic carbonyl group such as a carbonate (entry 4) does not induce any change in the regioselectivity. For probably the same reason, the epoxidation of a homoallylic acetate occurs predominantly in the presence of the corresponding allylic acetate (Scheme 1).

Conclusion

The π-facial selectivity observed in the epoxidation of various allylic acyclic acetates by the oxaziridinium salt **1**, provides convincing experimental evidence in favor of the assistance of the acetate group in stabilising the positively charged transition state. These results support our previous results showing such effects in diastereoselective oxaziridinium salt epoxidation of cyclic allylic acetates.[5]

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13. Preparative epoxidation of 3,4-dimethylpent-3-en-2-acetate **6e** by oxaziridinium salt **1**
   100 mg (0.6 mmol) of acetate **6e** was dissolved in 5 mL of dichloromethane. Freshly recrystallized oxaziridinium salt **1** (150 mg, 1 equiv.) was added in one portion to the solution. Stirring was maintained until total disappearance of active oxygen (KI test). The crude solution was concentrated under vacuum, the resulting solid was stirred with diethyl ether (10 mL) and after filtration, the etheral solution was concentrated to give 86 mg (78%

yield) of pure epoxide in a diastereoisomeric mixture (*threo*/*erythro*: 92/8). The diastereoisomers are easily separated by silica gel chromatography using hexane/ether gradient.

^{1}H NMR (400 MHz, CDCl$_3$) *threo* epoxide: 1.25 (d, 3H, $J = 6.5$ Hz); 1.33 (s, 3H); 1.36 (s, 3H); 1.39 (s, 3H); 2.09 (s, 3H); 4.86 (q, 1H, $J = 6.5$ Hz).

^{13}C NMR (100 MHz, CDCl$_3$) *threo* epoxide: 13.1 (Me); 17.4 (Me); 20.9 (Me); 21.6 (Me); 21.7 (Me); 62.0 (C); 65.5 (C); 73.9 (CH); 170.8 (C=O).

^{1}H NMR (400 MHz, CDCl$_3$) *erythro* epoxide: 1.3 (s, 3H); 1.32 (d, 3H, $J = 6.5$ Hz); 1.34 (s, 3H); 1.38 (s, 3H); 2.06 (s, 3H); 4.81 (q, 1H, $J = 6.5$ Hz).

^{13}C NMR (100 MHz, CDCl$_3$) *erythro* epoxide: 13.2 (Me); 16.0 (Me); 20.8 (Me); 21.5 (Me); 21.8 (Me); 64.2 (C); 64.6 (C); 71.2 (CH); 170.4 (C=O).