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Asymmetric epoxidation of cinnamic acid derivatives using dioxiranes generated in situ from dehydrocholic acid

Olga Bortolini, Marco Fogagnolo,* Giancarlo Fantin, Silvia Maietti and Alessandro Medici

Dipartimento di Chimica, Università di Ferrara, Via Borsari 46, 44100 Ferrara, Italy

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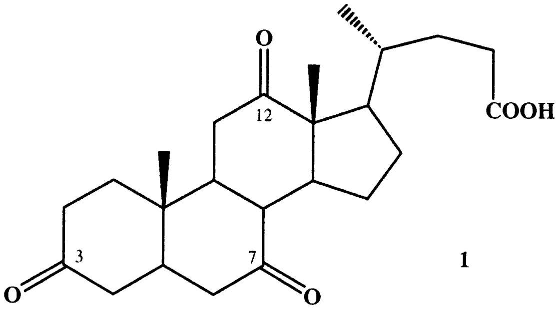
Abstract—The asymmetric epoxidation of different cinnamic acid derivatives in water–$NaHCO_3$ has been achieved using dehydrocholic acid as the optically active ketone and Oxone® as the oxygen source (with product e.e. values of up to 75%).

Dioxiranes[1] generated in situ from Oxone® and chiral ketones have recently emerged as a powerful class of oxidants for the asymmetric epoxidation of various alkenes.[2] In the particular case of electron-deficient olefins,[3] significant results have been obtained using derivatives of (−)-quinic acid[4] and derivatives of tropinone.[5] In principle, any chiral ketone may be used for asymmetric epoxidation, in practice however, its stability and activity in solution is limited by oxidative destruction.[3] Careful choice of this reactant is, therefore, fundamental in order to obtain efficient and highly stereoselective oxygen transfer dioxiranes with high turnover.



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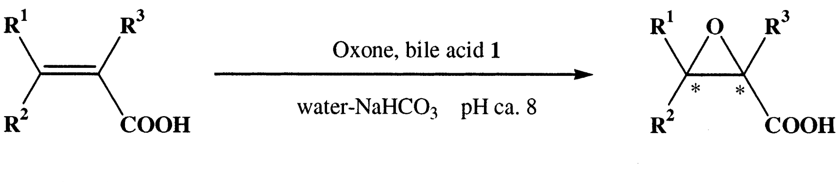
Dehydrocholic acid (3,7,12-triketo-5β-cholan-24-oic acid) **1** is a cheap and commercially available bile acid produced from cholic acid by direct chemical or biological oxidation.[6]

This molecule possesses a chiral steroid skeleton that confers conformational rigidity preventing any distortion and forcing, at the same time, the three keto functions into different directions.[6b] In addition the carboxylic function on the lateral chain makes **1** soluble in slightly basic water and may also be used to anchor the bile acid to a suitable support.[7]

In this communication we describe the catalytic enantioselective oxidation of various cinnamic acid derivatives to the corresponding epoxides (phenylglycidic acids) with Oxone®, using dehydrocholic acid **1** as chiral inducer (Eq. (1)). The process is conveniently performed in water–$NaHCO_3$ in the absence of both co-solvents[8] and phase-transfer agents.[3,9]

The choice of compounds to be oxidized in this study was based on the fact that substituted phenylglycidic acids were used in the synthesis of taxol, taxotene and taxoid, currently considered the most promising anticancer derivatives.[10–12]



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* Corresponding author. Fax: +39-0532-291173; e-mail: brl@unife.it

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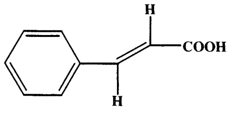
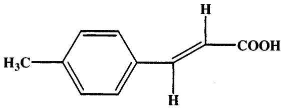
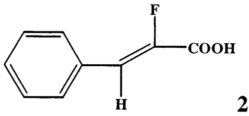
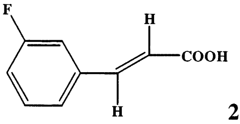
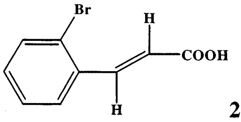
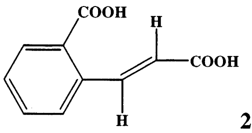
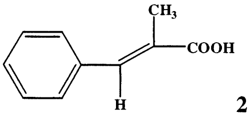
The results of the catalytic asymmetric epoxidation of the prochiral olefins **2a**–**2g** by the in situ generated optically active dioxirane of ketone **1** are collected in Table 1.

At 20°C in 5% aqueous $NaHCO_3$ (5 mL, pH ca. 8), **2a** (0.1 mmol) was rapidly and quantitatively oxidized with Oxone® (0.5 mmol, ketone **1** 0.3 mmol) to the corresponding epoxide **3a** in 36% e.e. (entry 1). Lowering the amount of both the oxidant and the ketone **1** did not produce significant differences in the reaction (entries 2 and 3) proving that the oxidation is truly catalytic. This was also shown by the epoxidations performed with **2a** and **2b** using a ratio of olefin:ketone = 1:0.2 (entries 4 and 9). According to these results, ketone **1** may be recovered in almost quantitative yield at the end of the reaction and its re-use has no effect on the rate and selectivity of subsequent reactions. In the absence of **1**, epoxidation was inefficient, with only 5% conversion to the epoxide product in 24 h (entry 5).

Temperature is an important factor for the oxidations with dioxiranes generated in situ.[4b,13] In our case a decrease of the temperature from 20 to 0°C led to a general increase in product e.e., accompanied by slower reactions. As an example, the lower temperature increased the e.e. from 60 to 75% in the epoxidation of **2b**, but the conversion dropped from 99% to 60% (entries 6 and 8).

An easy work-up characterizes the recovery of epoxides **3a**–**3g**: after the appropriate time (usually 5 minutes), the reaction mixture is simply acidified (HCl 5%) and extracted with ethyl acetate. The epoxides[14] were separated from the ketone **1** by column chromatography, and characterized by ^1H and ^{13}C NMR. The products

Table 1. Asymmetric epoxidation of prochiral cinnamic acid derivatives **2a**–**2g**

entry	substrate	**2** : oxone : **1** (equivalents)[a]	time	convn (%)	e.e. (%)[b]	opt. rotat. sign[c]
1	 **2a**	1:5:3	5 min.	>99	36	(+)[d]
2		1:5:1	5 min.	97	38	
3		1:3:1	5 min.	97[e]	40	
4		1:3:0.2	15 min.	>99	36	
5		1:3:0	24 h.	5	--	
6	 **2b**	1:5:3	5 min.	>99	60	(+)
7		1:5:1	5 min.	98	59	
8		1:3:1	5 min.	60[e,f]	75	
9		1:3:0.2	5 min.	95	55	
10	 **2c**	1:5:1	5 min.	>99	30	(+)
11		1:3:1	15 min.	95[e]	30	
12	 **2d**	1:5:1	5 min.	>99	40	(+)
13		1:3:1	5 min.	90[e]	46	
14	 **2e**	1:5:1	5 min.	>99	46	(+)
15		1:3:1	5 min.	98[e]	55	
16	 **2f**	1:5:1	15 min.	>99	20	(+)
17		1:3:1	15 min.	98[e]	30	
18	 **2g**	1:5:1	5 min.	95	11	(+)
19		1:3:1	5 min.	98[e]	12	

a. Olefin (0.1 mmol), Oxone (0.3-0.5 mmol), ketone **1** (0-0.3 mmol) in aqueous $NaHCO_3$ (5%, 5 mL) 20 °C; b. Determined by GC on Megadex DETTBS on the corresponding methyl esters; c. Solvent $CHCl_3$; d. Abs. config. (2*S*,3*R*)-; e. 0 °C; f. Conversion >99% after 2 h., e.e. = 68%.

were then converted to the corresponding methyl esters by treatment with diazomethane and subjected to GC analysis on a chiral column. The absolute configuration of (2*S*,3*R*)-**3a** was obtained, from the corresponding methyl ester, by comparison with literature values,[15] whereas in the other cases only the signs of the optical rotations are given ($CHCl_3$).

Future efforts will be devoted to the optimization of the ketone structure and to understanding the specific role played by the various keto-functions of the steroid skeleton in the formation of the dioxirane and during the dioxirane-mediated epoxidation. Any activity of the carboxylic group of the bile acid in the oxidation reactions has been excluded.[7,16]

Acknowledgements

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References

1. (a) Adam, W.; Curci, R.; Edwards, J. O. *Chem. Res.* **1989**, *22*, 205; (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.
2. Denmark, S. E.; Wu, Z. *Synlett* **1999**, *S1*, 847.
3. Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215.
4. (a) Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622; (b) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749 and references cited therein.
5. Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621.
6. (a) Bortolini, O.; Medici, A.; Poli, S. *Steroids* **1997**, *62*, 564; (b) *The Bile Acids: Chemistry, Physiology and Metabolism*; Nair, P. P.; Kritchevsky, D., Eds.; Plenum Press: New York, 1971.
7. Fantin, G.; Fogagnolo, M., unpublished results.
8. Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887.
9. Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155.
10. Nicolau, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed.* **1994**, *33*, 15.
11. Yamaguchi, T.; Harada, N.; Ozaki, K.; Hayashi, M.; Arakawa, H.; Hashiyama, T. *Tetrahedron* **1999**, *55*, 1005 and references cited therein.
12. For the non-enantioselective epoxidation of cinnamic acid derivatives with dioxiranes, see for example: Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.
13. Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
14. The isolation and purification of the epoxide **3f** is associated with a partial intramolecular cyclization of this product to the corresponding δ-lactone, see: Carnduff, J.; Leppard, D. G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1329.
15. Plucinska, K.; Kasprzykowski, F.; Kozian, E. *Tetrahedron Lett.* **1997**, *38*, 861.
16. Boehlow, T. R.; Buxton, P. C.; Grocock, E. L.; Marples, B. A.; Waddington, V. L. *Tetrahedron Lett.* **1998**, *39*, 1839.