Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 15 (2004) 3831–3833
Tetrahedron: *Asymmetry*

Control of the enantioselectivity by keto bile acid derivatives in the epoxidation of alkenes with Oxone

Olga Bortolini,[a,*] Giancarlo Fantin,[b] Marco Fogagnolo[b,*] and Lara Mari[b]

[a]*Dipartimento di Chimica, Università della Calabria, Via Bucci cubo 12 C, 87036 Rende CS, Italy*
[b]*Dipartimento di Chimica, Università di Ferrara, Via Borsari 46, 44100 Ferrara, Italy*

Received 20 October 2004; accepted 5 November 2004

Abstract—The asymmetric epoxidation of unfunctionalized olefins has been achieved using 3-keto bile acids as optically active inducers and Oxone. Opposite enantioselectivities can be obtained depending on the specific substitution of the bile acids.

1. Introduction

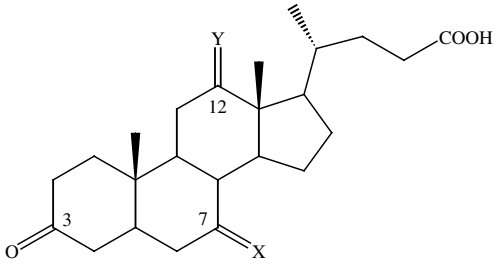
Chiral dioxiranes, generated in situ from Oxone and the appropriate optically active ketones, are documented as oxygen transfer reagent for asymmetric epoxidation.[1,2] In the oxidation of unfunctionalized olefins significant results (ee $\leqslant$98%) have been achieved, among others,[1a] by Shi and co-workers, using fructose derived ketones[3] and Yang et al. employing C_2 symmetric carbonyl compounds.[4]

In two recent papers[5] we have reported an efficient epoxidation protocol based on the use of bile acid derivatives as optically active carbonyl inducers for the enantioselective epoxidation of cinnamic acids with ees up to 95%. More importantly, the control of the enantioselectivity was obtained by specific substitution at carbons C(7) and C(12) of the bile acid. Bile acids, which have carbonyl functions at C(3) and specific and stereochemically appropriate C(7) substitutions, such as **1a** or **1b**, led to the formation of epoxides with a (−) specific rotation sign, whereas C(12) substitution such as **1c** gave rise to the opposite (+) epoxy enantiomer.

Herein, we report our preliminary results on the asymmetric epoxidation of unfunctionalized olefins using the bile acid–Oxone system.

2. Results and discussion

The bile acids that have been used are all inexpensive and commercially available derivatives and have a carbonyl function at carbon C(3), activated by the Oxone, and an α-hydroxy substituent at C(7), **1a**, or at C(12), **1c**, to control the sense of asymmetric induction. The results of the asymmetric oxidations of prochiral alkenes to the corresponding epoxides are shown in Table 1.



1a X = α-OH, H; Y=H, H

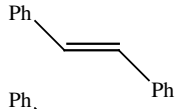
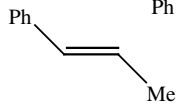
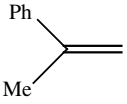
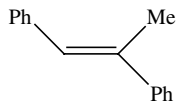
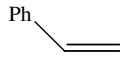
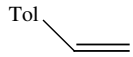
1b X = α-OC(O)$(CH_2)_2$COOH, H; Y=H, H

1c X = H, H; Y= α-OH, H

* Corresponding authors. Fax: +39 0984 493307 (O. Bortolini); e-mail: o.bortolini@unical.it

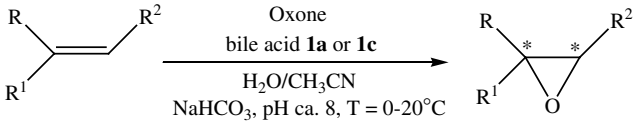
0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2004.11.012

Table 1. Asymmetric epoxidation of unfunctionalized alkenes with keto bile acid derivatives **1a** or **1c** and Oxone at 20 °C[a]

Substrate	Bile acid **1a**			Bile acid **1c**		
	Yield %	Ee %	Config.	Yield %	Ee %	Config.
	90	54	(−)-(1*S*,2*S*)	55	43	(+)-(1*R*,2*R*)
	99 59[b]	37 48[b]	(−)-(1*S*,2*S*)	80 58[b]	15 50[b]	(+)-(1*R*,2*R*)
	99	33	(+)-(*R*)	75	41	(−)-(*S*)
	50	49	(−)-(1*S*,2*S*)	75	44	(+)-(1*R*,2*R*)
	40	30	(−)-(*S*)	45	34	(+)-(*R*)
	95	30	(−)-(*S*)	65	48	(+)-(*R*)

[a] Reaction conditions: substrate (0.08 mmol), Oxone (0.4 mmol), ketone (0.08 mmol), water–CH_3CN (1:1 v/v), EDTA (4×10^{-4} M), pH ca. 8 ($NaHCO_3$).
[b] Reaction performed at 0 °C under otherwise identical conditions.

All the epoxidations were carried out in water–CH_3CN (1:1 v/v) in the presence of EDTA (4×10^{-4} M) as sequestrant of trace metal ions,[6] at pH ca. 8 ($NaHCO_3$), with temperatures in the range 0–20 °C and in the absence of phase-transfer agents (Eq. 1).



(1)

Mono-, *trans*- and *gem*-di-substituted and trisubstituted olefins were epoxidized with yields varying from 40% to 99% using a substrate:Oxone:bile acid ratio of 1:5:1 equiv, in 3 h reaction time. As already pointed out, for all the epoxides, the systematic inversion of the configuration was observed depending on the bile acid used, with ee values ranging from moderate to good. The work-up proved simple and straightforward. The reaction was diluted with water, extracted with ethyl acetate and the yields and ee values obtained by GC analysis on a chiral column (Megadex DETTBS). Absolute configurations were determined on purified epoxides by comparison with literature values.[1a] From the aqueous layer, the bile acid derivatives can be almost quantitatively recovered upon acid treatment and reused without loss of activity. Temperature is an important factor for the oxidation with dioxiranes generated in situ.[5b,7] For example with *trans* β-methyl styrene, by decreasing the temperature from 20 to 0 °C, the ees increase from 37% to 48% and from 15% to 50%, but with a significant decrease of the chemical yields, from 99% to 59% and from 80% to 58% for identical reaction times (Table 1). In the absence of bile acid, the epoxidation was rather inefficient with 5% conversion after 24 h.

Efforts devoted to the optimization of reaction conditions and to the extension of the oxidation protocol to unfunctionalized *cis* olefins are currently in progress.

Acknowledgements

We acknowledge the financial support from the Italian MURST, PRIN 2003 'Efficient and environmentally friendly processes for the selective oxidation of organic 'target' compounds'.

References

1. (a) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497–505; (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000, and references.
2. For recent examples see: (a) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293–296; (b) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435–2446; (c) Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545–7552; (d) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479–3486; (e) Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943–1946; (f) Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* **2002**, *43*, 631–633.
3. (a) Wang, Z-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521–530; (b) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551–11552, and references.
4. (a) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem.*

Soc. **1998**, *120*, 5943–5952; (b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311–11312.
5. (a) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Forlani, R.; Maietti, S.; Pedrini, P. *J. Org. Chem.* **2002**, *67*, 5802–5806; (b) Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113–1115.
6. Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, p 1.
7. Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749–2755.