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Improved procedure for the room temperature asymmetric phase-transfer mediated epoxidation of α , β -unsaturated ketones

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Abstract—Studies into the factors affecting the rate of reaction in the enantioselective epoxidation of α , β -unsaturated ketones utilising *Cinchona* alkaloid-derived quaternary ammonium phase-transfer catalysts are reported. This has led to the identification of improved conditions for the room temperature epoxidation process, which require only 1 mol% catalyst and lead to isolation of the epoxide products in high enantiomeric excess. © 2001 Elsevier Science Ltd. All rights reserved.

The enantioselective epoxidation of α,β -unsaturated ketones has been the subject of considerable investigation in recent years, and a variety of methods involving asymmetric catalysis have been developed.¹ In this context, we recently reported that *N*-anthracenylmethyl derivatives of cinchona alkaloids (e.g. **2**)² could be used for this transformation, leading to the formation of α,β -epoxy ketones in excellent yields and high enantioselectivity (Scheme 1).³ It has also been demonstrated by others that related cinchona alkaloid derivatives can give high enantioselectivity in reaction processes of this type,⁴ and more recently it has been shown that using 65% KOC1 as oxidant allows the reaction to be conducted at lower temperatures, leading to improved enantioselectivities.⁵

In this paper, we wish to report the initial results of a study designed to identify the factors that affect the rate and selectivity in the above epoxidation processes, a study that has led to the development of a significantly improved procedure for the room temperature epoxidation of enones via phase-transfer catalysis.

At the outset of this study we were aware that the efficiency of agitation influenced the rate of reaction;⁶ therefore, in order to minimise this effect we performed all reactions in a standard reaction vessel (round-bot-tom flask) with near identical agitation (magnetic stirring at ca. 1000 rpm).⁷ This particular set-up was chosen because it utilises apparatus that is available in most synthetic chemistry laboratories, and because pre-liminary experiments had confirmed that reproducible

results could be obtained. We chose to employ the epoxidation of chalcone 1a in this study because the reaction could be monitored by both ¹H NMR spectroscopy and HPLC.⁸

Initial investigations indicated that the rate of epoxidation of chalcone **1a** was dependant on the concentration of both sodium hypochlorite and catalyst.⁹ Although the reaction appeared to be approximately first order with respect to hypochlorite concentration in the aqueous phase, the relationship between catalyst concentration and rate of reaction was more complex (Fig. 1).

It was found that for $[cat.]_{org} > 8 \times 10^{-3}$ M, the reaction system appears to become saturated in catalyst (Fig. 1b). This may be a solubility effect, since at higher concentrations undissolved catalyst **2** is visible in the reaction system. By varying the concentration of substrate it was possible to obtain 100% conversion of enone **1a** within 24 h at 25°C with catalyst loading



Scheme 1.

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Figure 1.

down to 0.5 mol%; however, with lower catalyst loadings the concentration of substrate required for rapid reaction led to a significant reduction in enantioselectivity. For example using 10–1 mol% **2**, and an initial chalcone concentration of 0.09–0.34 M in toluene, resulted in the formation of enone **3a** in $86\pm1\%$ e.e., whereas 0.1 mol% **2**, and an initial chalcone concentration of 3.4 M in toluene, gave enone **3a** in 60% e.e. The drop in enantioselectivity observed at higher substrate concentrations could not be accounted for by background epoxidation, and so we speculated that this might be a result of medium effects. In order to test this, a series of experiments were performed using toluene–ethyl acetate mixtures of differing composition (Fig. 2).

It was found that the enantioselectivity was linearly dependant upon the concentration of ethyl acetate in toluene, the highest enantioselectivity being obtained with 100% toluene. This would seem to confirm our earlier observation that polarity of the organic phase significantly influences the level of enantioselectivity,³

and suggests that high concentrations of polar substrates or products may well be detrimental to enantioselectivity.

Although we have been able to demonstrate that it is possible to use catalyst loadings down to 0.1 mol% with higher substrate concentrations, based on the above results, we would suggest that an optimal general procedure for the room temperature epoxidation of enones 1 with sodium hypochlorite requires 1 mol% of catalyst and a substrate concentration of 0.34 M.⁷ These conditions have been chosen because they should be directly applicable to a wide range of substrates 1, and the enantioselectivity obtained should be the same as that produced with higher catalyst loading. For a given substrate it may well be possible to further optimise the reaction parameters as outlined above.

In order to illustrate the generality of these conditions, we have investigated epoxidation of a series of enones 1a-e (Table 1). In all cases the epoxidations were complete within 24 h, and high levels of enantioselectiv-

Table 1.

		Cat. 2 (1 mol%)	- 1		
		1 15% aq. NaOCl (2 eq.) toluene, 12-24 h, 25 °C	- 3		
Alkene	Product	% d.e. ^a	% e.e. ^{10,11}	Yield (%)	
1a		≥95	86	98	
1b		≥ 95	≥98 (92) ^b	76	
1c		≥95 F	≥98 (87) ^b	75	
1d		≥95 Br	88	93	
1e		≥95	84	97	

^a Estimated to ±5% by ¹H NMR (400 MHz).

^b After purification by recrystallisation, crude e.e.s are in parentheses.

ity were obtained. We also established that in a number of cases the crude reaction products were most conveniently purified by recrystallisation, giving the epoxides in good overall yield and excellent enantiomeric purity.

In conclusion, the results of this study suggest that ion exchange is the rate-limiting step in the room temperature epoxidation of α,β -unsaturated ketones using sodium hypochlorite and catalyst **2**. Using this information it has been possible to develop optimised reaction conditions that only require 1 mol% of catalyst and allow straightforward access to α,β -epoxyketones with high enantiomeric purity.

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- 7. Typical procedure: A solution of enone (3.4 mmol) and catalyst **2** (0.03 mmol) in toluene (10 ml) in a 25 ml round-bottom flask was treated with 15% aqueous sodium hypochlorite solution (6.8 mmol) and the resulting mixture was stirred vigorously (magnetic stirrer at ca. 1000 rpm) at 25°C for 12–24 hours. After this time water (20 ml) was added and the layers separated. The aqueous layer was further extracted with ethyl acetate (30 ml), and the combined organic extracts dried (Na₂SO₄). Concentration under reduced pressure gave the crude epoxide. Chromatography on silica gel or recrystallisation from

tert-butylmethylether/petroleum ether gave the purified epoxides.

- HPLC retention times (Chiralpak AD, 10% ethanol, 90% hexane): Chalcone 1a (13.2 min), *trans*-chalcone oxide 3a (16.1 min, 23. 9 min), *cis*-chalcone oxide (12.9 min, 13.8 min).
- 9. These data appear to be most consistent with the ratelimiting step being ion exchange between the quaternary ammonium halide and sodium hypochlorite. Catalysts of type 2 have very low solubility in water, so it seems likely that ion exchange takes place in the interfacial region. For related discussion, see: Do, J. S.; Chou, T. C. J. Appl. Electrochem. 1989, 19, 922 and references cited therein.
- Enantiomeric excesses (e.e.s) were determined to ±2% by HPLC analysis (Chiralcel OD-H, *i*-propanol/hexane, epoxides 3b,d,e, Chiralpak AD ethanol/hexane, epoxides 3a,c). In all cases the stereochemically enriched samples were compared with racemic samples generated using tetra-*n*-butylammonium bromide as the catalyst for epoxidation.
- The absolute stereochemistry depicted for the epoxide products 3 is based on the established stereochemistry of compound 3a (Marsman, B.; Wynberg, H. J. J. Org. Chem. 1979, 44, 2312). In this paper it is assumed that the same sense of selectivity applies to the other substrates.