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Asymmetric Phase-Transfer Mediated Epoxidation of α, β-Unsaturated Ketones Using Catalysts Derived From *Cinchona* Alkaloids

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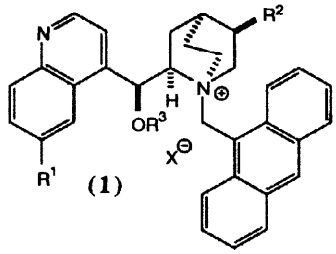
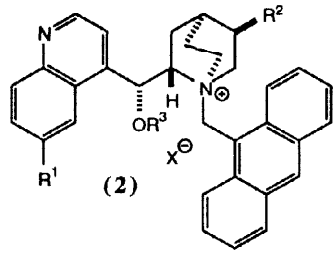
Abstract: The enantioselective epoxidation of α,β-unsaturated ketones utilising *Cinchona* alkaloid-derived quaternary ammonium phase-transfer catalysts bearing an *N*-anthracenylmethyl function are presented. It has been found that the *O*-benzyl derivatives of these catalysts in conjunction with sodium hypochlorite give high stereocontrol and application of this process to the enantioselective synthesis of a range of *trans*-α,β-epoxy ketones (e.e. 69-89%) is presented.

As part of an ongoing programme on the development of new chiral control elements for asymmetric synthesis[1,2] we have recently being studying the use *N*-anthracenylmethylcinchodinium salts (**1a-c, 2a-c**). These materials were shown to be highly effective catalytic agents for the asymmetric phase-transfer alkylation of glycine imines, leading to an efficient method for the synthesis of α-amino acids.[2,3] Here we present initial results regarding the application of these chiral control elements to the asymmetric epoxidation of α,β-unsaturated ketones.



(1)



(2)

(a) R^1 = H, R^2 = CH=CH_2, R^3 = H, X = Cl
(b) R^1 = H, R^2 = CH_2-CH_3, R^3 = H, X = Cl
(c) R^1 = OCH_3, R^2 = CH=CH_2, R^3 = H, X = Cl
(d) R^1 = H, R^2 = CH=CH_2, R^3 = Bn, X = OH
(e) R^1 = H, R^2 = CH_2-CH_2, R^3 = Bn, X = OH

The enantioselective epoxidation of α,β-unsaturated ketones employing chiral catalysts has received considerable attention in recent years.[4] A variety of methods have been developed including the use of polyphasic systems involving hydrogen peroxide in the presence of polyamino acids,[5] alkylperoxides in conjunction with lanthanoid-binaphthol complexes,[6] tartrate-modified metal *tert*-butyl peroxides,[7] and hydrogen peroxide in the presence of chiral platinum (II) complexes.[8] Good enantioselectivities have also been achieved using non-catalytic systems involving molecular oxygen in the presence of diethylzinc/chiral amino alcohols.[9] The use of chiral quaternary ammonium salts as phase-transfer catalysts for this transformation has also been investigated,[10] however to date results have been disappointing (e.e.s generally ≤55%). Our recent observation that phase-transfer catalysts of the type (**1a-c, 2a-c**) were superior to previously reported quaternary ammonium salts for the asymmetric alkylation of glycine-imines promptd us to examine their utility in the phase-transfer mediated oxidation of α,β-unsaturated ketones.

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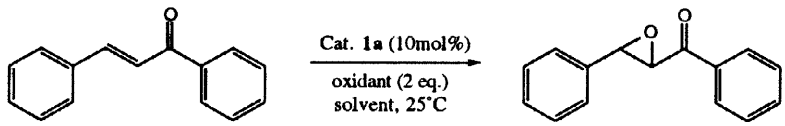
We initially chose to investigate the epoxidation of chalcone (**3**) using catalyst (**1a**) and a variety of reaction conditions were investigated. It was found that epoxidation could be achieved using either hydrogen peroxide or sodium hypochlorite as the stochiometric oxidant, however the enantioselectivities obtained were low (table 1).

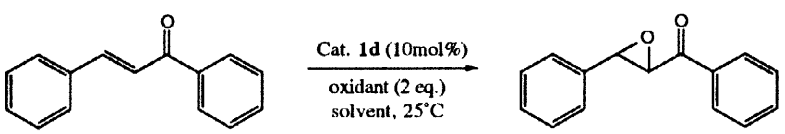


(3) (4)

Solvent	Oxidant	Reaction Time	e.e.[b] (sign of rotation)	Yield[c]
toluene	11% aq. NaOCl	48h	39% (-)	65%
toluene	30% aq. H_2O_2[a]	48h	0%	<10%
dichloromethane	11% aq. NaOCl	48h	23% (-)	71%
dichloromethane	30% aq. H_2O_2[a]	4h	11% (+)	75%

Table 1: [a] - 1 drop of 50% aq. KOH also added. [b] - e.e. values reproducible to ±2%, determined by HPLC on Chiralcel OD-H column. [c] - After purification by chromatography

We were intrigued by the fact that the opposite sense of enantioselectivity was obtained on switching from sodium hypochlorite to hydrogen peroxide (table 1, entries 3-4). This effect has been observed previously with related phase-transfer catalysts,[10b] and would tend to suggest that two (or more) competing reaction pathways are operating under these conditions. This is also reflected in the surprising rate changes observed on changing oxidant and solvent. Control studies on these processes demonstrated that the uncatalysed rate of epoxidation was extremely slow (no reaction observed after 48h at 25°C) and could not account for these observations. We considered that these effects may be associated with interaction of the oxidant with the hydroxy group in the catalyst. Consequently we decided to prepare the corresponding O-benzyl derivative (**1d**). This was readily achieved *via* treatment of (**1a**) with benzylbromide under two-phase conditions,[11] giving the product (**1d**) in good yield (72%). Investigation of catalyst (**1d**) on the epoxidation of chalcone was then examined (table 2).



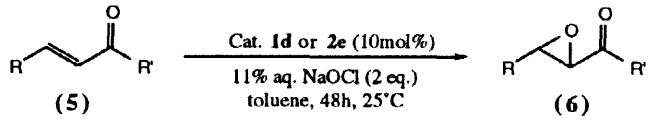
(3) (4)

Solvent	Oxidant	Reaction Time	e.e.[b] (sign of rotation)	Yield[c]
toluene	11% aq. NaOCl	48h	81% (-)	90%
toluene	30% aq. H_2O_2[a]	48h	10% (-)	69%
dichloromethane	11% aq. NaOCl	48h	66% (-)	60%
dichloromethane	30% aq. H_2O_2[a]	48h	2% (-)	<10%

Table 2: [a] - 1 drop of 50% aq. KOH also added. [b] - e.e. values reproducible to ±2%, determined by HPLC on Chiralcel OD-H column. [c] - After purification by chromatography

As can be seen from the results, the *O*-benzyl catalyst (**1d**) shows a remarkable improvement in enantioselectivity when sodium hypochlorite is used as the oxidant. In addition, although low, the enantioselectivity obtained using hydrogen peroxide is now in the same direction. A substantial decrease in reaction rate was also observed when using hydrogen peroxide in conjunction with dichloromethane. These results suggested that derivatisation of the hydroxyl function in the catalyst may well be critical to obtaining high enantioselectivities in these epoxidation reactions. It also appears from these results that toluene is the preferred reaction solvent.

In order to assess the generality of this effect we also prepared the *pseudo*-enantiomeric catalyst (**2e**), the *O*-benzyl derivative of compound (**2b**). We then investigated the utility of catalysts (**1d**) and (**2e**) in the epoxidation of a range of enone substrates (table 3).



(5) (6)

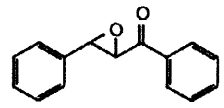
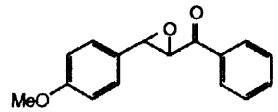
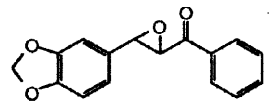
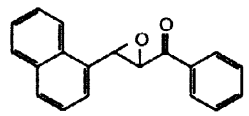
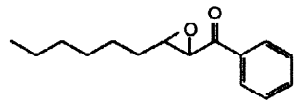
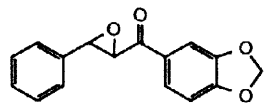
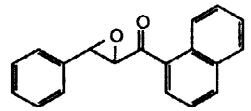
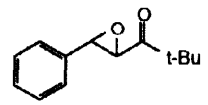
Alkene	Catalyst	Product	d.e.[a]	e.e.[b] (sign of rotation)	Yield[c]
(3)	1d		≥95%	81% (-)	90%
	2e		≥95%	86% (+)	90%
(5a)	1d		≥95%	81% (-)	86%
	2e		≥95%	82% (+)	87%
(5b)	1d		≥95%	82% (+)	92%
	2e		≥95%	83% (-)	97%
(5c)	1d		≥95%	82% (+)	92%
	2e		≥95%	82% (-)	86%
(5d)	1d		≥95%	76% (-)	75%
	2e		≥95%	77% (+)	92%
(5e)	1d		≥95%	86% (-)	93%
	2e		≥95%	89% (+)	95%
(5f)	1d		≥95%	69% (+)	75%
	2e		≥95%	71% (-)	77%
(5g)	1d		≥95%	87% (-)	42% (76%)[d]
	2e		≥95%	85% (+)	40% (74%)[d]

Table 3: [a] - d.e. values estimated by ^{1}H nmr (300MHz). [b] - e.e. values reproducible to ±2%, determined by HPLC on Chiralcel OD-H column. [c] - After purification by chromatography. [d] - Yield in parentheses based on unrecovered starting enone.

The results obtained show that the epoxidation proceeds with good enantioselectivity and a range of substituents are tolerated. In addition the diastereoselectivities for this process are high, giving exclusively the *trans*-epoxides as far as we were able to detect. As expected catalysts (**1d**) and (**2e**) are enantio-complimentary allowing access to either enantiomer of the epoxide with broadly similar selectivity. In general the reactions were complete after 24-48h at 25°C,[12] however in the case of *tert*-butyl ketone (**5g**) the process was considerably slower and only *ca.* 50% conversion was obtained after 5 days at 25°C.

In conclusion, we have developed a straightforward method for the enantioselective epoxidation of α,β-unsaturated ketones utilising *Cinchona*-alkaloid derived phase-transfer catalysts. These catalysts are readily prepared in two steps from commercially-available materials and the epoxidation reactions are cheap and easy to carry out. We are currently seeking to extend the substrate range for this process and examining other uses of these catalysts.

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References and Notes

1. Lygo, B; Crosby, J; Lowdon, T.R; Wainwright, P.G. *Tetrahedron Lett.*, **1997**, *38*, 2343.
2. Lygo, B; Wainwright, P.G. *Tetrahedron Lett.*, **1997**, *38*, 8595.
3. Corey, E.J; Xu, F; Noe, M.C. *J. Am. Chem. Soc.*, **1997**, *119*, 12414.
4. Fruh, T. *Agro. Food Indust. Hi-Tech.*, **1996**, *7*, 31.
5. Juliá, S; Masana, J.; Vega, J.C. *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 929; Juliá, S; Guixer, J; Masana, J; Rocas, J; Colonna, S; Annunziata, R; Molinari, H. *J. Chem. Soc., Perkin Trans I*, **1982**, 1317; Colonna, S; Molinari, H; Banfi, S; Juliá, S; Masana, J; Alverez, A. *Tetrahedron*, **1983**, *39*, 1635; Banfi, S; Colonna, S; Molinari, H; Juliá, S; Guixer, J. *Tetrahedron*, **1984**, *40*, 5207; Bezuidenhoudt, B.C.B; Swanepoel, A; Augustyn, J.A.N; Ferreira, D. *Tetrahedron Lett.*, **1987**, *28*, 4857; Itsuno, S; Sakakura, M; Ito, K. *J. Org. Chem.*, **1990**, *55*, 6047; Baures, P.W; Eggleston, D.S; Flisak, J.R; Gombatz, K.J; Lantos, I; Mendelson, W; Remich, J.J. *Tetrahedron Lett.*, **1990**, *31*, 6501; Flisak, J.R; Gombatz, K.J; Holmes, M.M; Jarmas, A.A; Lantos, I; Mendelson, W.L; Novack, V.J; Remich, J.J; Snyder, L. *J. Org. Chem.*, **1993**, *58*, 6247; Lasterra-Sánchez, M.E; Roberts, S.M. *J. Chem. Soc., Perkin Trans I*, **1995**, 1467; Kroutil, W; Mayon, P; Lasterra-Sánchez, M.E; Maddrell, S.J; Roberts, S.M; Thornton, S.R; Todd, C.J; Tüter, M. *Chem. Commun.*, **1996**, 845, 2495; Lasterra-Sánchez, M.E; Felfer, U; Mayon, P; Roberts, S.M; Thornton, S.R; Todd, C.J. *J. Chem. Soc., Perkin Trans I*, **1996**, 343; Kroutil, W; Lasterra-Sánchez, M.E; Maddrell, S.J; Mayon, P; Morgan, P; Roberts, S.M; Thornton, S.R; Todd, C.J; Tüter, M. *J. Chem. Soc., Perkin Trans. I*, **1996**, 2837; Bentley, P.A; Bergeron, S; Cappi, M.W; Hibbs, D.E; Hursthouse, M.B; Nugent, T.C; Pulido, R; Roberts, S.M; Wu. L.E. *Chem. Commun.*, **1997**, 739.
6. Bougauchi, M; Watanabe, S; Arai, T; Sasai, H; Shibasaki, M. *J. Am. Chem. Soc.*, **1997**, *119*, 2329.
7. Elston, C.L; Jackson, R.W.F; MacDonald, S.J.F; Murray, P.J. *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 410.
8. Baccin, C; Gusso, A; Pinna, F; Strukul, G. *Organomet.*, **1995**, *14*, 1161.
9. Enders, D; Zhu, J; Raabe, G. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1725; Enders, D; Zhu, J. Kramps, L. *Ann.*, **1997**, 1101.
10. (a) Helder, R; Hummelen, J.C; Laane, R.W.P.M; Wiering, J.S; Wynberg, H. *Tetrahedron Lett.*, **1976**, 1831; (b) Hummelen, J.C; Wynberg, H. *Tetrahedron Lett.*, **1978**, 1089; (c) Wynberg, H; Greijdanus, B. *J. Chem. Soc., Chem. Commun.*, **1978**, 427; (d) Wynberg, H; Marsman, B. *J. Org. Chem.*, **1980**, *45*, 158; (e) Pluim, H; Wynberg, H. *J. Org. Chem.*, **1980**, *45*, 2498; (f) Harigaya, Y; Yamaguchi, H; Onda, M. *Heterocycles*, **1981**, *15*, 183; (g) Mazaleyrat, J.P. *Tetrahedron Lett.*, **1983**, *24*, 1243; (h) Baba, N; Oda, J; Kawaguchi, M; *Agric. Biol. Chem.*, **1986**, *50*, 3113; (i) Baba, N; Oda, J; Kawahara, S; Hamada, M. *Bull. Inst. Chem. Res., Kyoto Univ.*, **1989**, *67*, 121; (j) Shi, M; Masaki, Y. *J. Chem. Res. (S)*, **1994**, 250; (k) Shi, M; Kazuta, K; Satoh, Y; Masaki, Y. *Chem. Pharm. Bull.*, **1994**, *42*, 2625.
11. O'Donnell, M.J; Wu, S; Huffman, J.C. *Tetrahedron*, **1994**, *50*, 4507.
12. *Typical Procedure:* A solution of enone (1.0mmol) and the appropriate catalyst (0.1mmol) in toluene (10ml) was treated with 11% aqueous sodium hypochlorite solution (1.2ml, *ca.* 2.0mmol) and the resulting mixture stirred vigorously (*ca.* 1000rpm) at 25°C for 24-48 hours. After this time water (5ml) was added and the layers separated. The aqueous layer was further extracted with ethyl acetate (10ml), and the combined organic extracts dried (Na_2SO_4). Concentration under reduced pressure gave the crude epoxide which was generally purified by chromatography on silica gel.