A highly enantioselective phase-transfer catalyzed epoxidation of enones with a mild oxidant, trichloroisocyanuric acid†

Jinxing Ye, Yongcan Wang, Renhua Liu, Guofu Zhang, Qing Zhang, Jiping Chen and Xinmiao Liang*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 161 Zhongshan Road, Dalian 116011, China. E-mail: liangxm@mail.dlptt.ln.cn; jinxingye@dicp.ac.cn; Fax: + 86(0)411 3606605; Tel: + 86(0)411 3699015

The enantioselective epoxidation can be carried out using trichloroisocyanuric acid (TCCA) as oxidant in the presence of chiral quaternary ammonium salt as a phase-transfer catalyst; treatment of chalcone derivatives with TCCA under mild conditions afforded the corresponding epoxy ketones in good yields with moderate to excellent enantioselectivities of up to 96%.

Epoxidation is a key transformation in organic synthesis. The development by Sharpless in the early 1980s of a system which could efficiently and predictably produce either enantiomer of an epoxide from an allylic alcohol using substoichiometric quantities of titanium and tartrate, paved the way for much of today's catalytic asymmetric synthesis.[1] In recent years, methods for the asymmetric epoxidation of electron-deficient olefins, particularly α,β-enones, have attracted widespread attention.[2] Work initiated by Lygo[3] has shown that *N*-anthracenylmethyl derivatives of cinchona alkaloid are capable of catalyzing the epoxidation of enones with remarkable levels of asymmetric control. Early studies have shown the sense of selectivity in asymmetric epoxidation of chalcone **1a** changed depending upon the nature of the stoichiometric oxidants: sodium hypochlorite,[3] hydrogen peroxide,[4] potassium hypochlorite[5] and hydroperoxide.[6] It has been shown that using 8 M KOCl as oxidant allows the reaction to be conducted at −40 °C, leading to very impressive enantioselectivities.[5] However, the concentrated KOCl solution is liable to deteriorate, and needs to be freshly prepared.

Trichloroisocyanuric acid (TCCA, Scheme 1) is a safe, inexpensive and efficient oxidant for the oxidation of ethers, thioethers, aldehydes, acetals and alcohols.[7] To the best of our knowledge, the epoxidation of enones with TCCA has never been explored.[8] In the present study we have characterized commercially available TCCA as a mild, efficient and highly selective oxidant for the asymmetric epoxidation of chalcone derivatives. The epoxidation of chalcone (Scheme 2)‡ § was
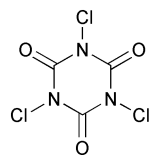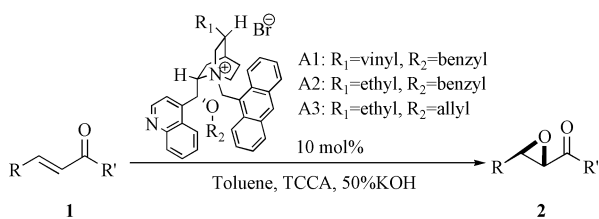
conducted in a two phase system composed of oxidant (TCCA), an inorganic base solution, the *N*-anthracenyl-methyl derivative of cinchona alkaloid and an organic solvent. TCCA in an inorganic base solution can release hypochlorite, which may actually be an efficient oxidant.

Preliminary studies focused on the investigation of the catalytic asymmetric epoxidation of the standard substrate of chalcone in the presence of TCCA (1.67 equiv.), an inorganic base such as KOH (10 equiv.), and a catalytic amount of quaternary salt A1 (0.1 equiv.), which is easily prepared from natural cinchonidine,[3,5] at room temperature. Initially, we investigated the effect of the solvent (Table 1). Although chalcone smoothly disappeared in any selected solvent (not shown in Table 1), the reaction proceeded to afford desired products only in non-polar solvent such as dichloromethane and toluene (entries 1 and 5, Table 1). Low temperature was in favor of enantioselectivity in both dichloromethane and toluene. The enantioseletivities observed in the temperature range from 0 to −30 °C were improved in dichloromethane (entries 2–4, Table 1), and almost maintained in toluene (entries 6–8, Table 1). The results indicated that toluene was the preferred reaction solvent. Substitution of KOH with other weaker inorganic base such as LiOH and NaOH also resulted in the desired products in high yield with 76 and 75% ee (entries 9 and 10, Table 1).

Encouraged by these results, we optimized the amounts of TCCA and quaternary salt based on KOH as an inorganic base. The ratio of TCCA to KOH was fixed to 1 : 6 in order to provide slightly basic reaction conditions. As illustrated in Table 2, epoxidation of chalcone provided epoxide almost quantitatively with approximate enantioselectivity when the amount of TCCA was reduced from 1.67 to 0.5 equivalents (entries 1–4, Table 2). Reduced amounts of oxidant needed longer reaction times.

Screening catalysts A1–A3 for the asymmetric epoxidation of chalcone under the same conditions, it was found that catalysts A2 and A3, derived from hydrogenated cinchonidine, gave different enantioselectivity results (89 and 82% ee, respectively).

Scheme 1 Trichloroisocyanuric acid.

Scheme 2

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b308042k/

Table 1 Effect of solvent, temperature and base on the asymmetric epoxidation of chalcone

Entry	Solvent	T/°C	Base	Time/h	Conv.[a] (%)	Ee[b] (%)
1	CH_2Cl_2	r.t.	KOH	48	10	n.d.
2	CH_2Cl_2	0	KOH	24	81	39
3	CH_2Cl_2	−20	KOH	48	49	67
4	CH_2Cl_2	−30	KOH	49	63	71
5	Toluene	r.t.	KOH	8	100	67
6	Toluene	0	KOH	8	100	81
7	Toluene	−20	KOH	16	100	80
8	Toluene	−30	KOH	24	97	82
9	Toluene	0	LiOH	48	94	76
10	Toluene	0	NaOH	36	98	75

[a] The values of conversion (%) were obtained by HPLC analyses.
[b] Determined by HPLC using a Chiralpak® AD-H column with racemic epoxides as standards.

Using conditions developed for the enantioselective catalyzed epoxidation of chalcone, we turned our attention to establishing the generality of the phase-transfer catalyzed asymmetric epoxidation with A2 as catalyst. As shown in Table 3, most chalcone derivatives **1a–j** afforded the corresponding epoxides **2a–j** with good yields and modest to high enantiomeric excesses. It was found that 4-nitro chalcone can be transferred to the epoxide with 96% ee. In a number of cases the crude reaction products were most conveniently purified by recrystallisation, giving the epoxides in excellent enantiomeric purity. However, in the case of 4-methoxy chalcone, 4-methoxy 4′-chloro chalcone and benzalacetone (**1k**, **1l** and **1m**, Table 3), the desired product was not obtained even within 96 h, and some of the recovery materials were the starting chalcones. We were able to detect the presence of monochlorinated products of **1k** and **1l** in GC-MS because of electrophilic chlorination. As for **1m**, the reaction mixture turned brown rapidly, probably due to a haloform type reaction.[9]

Table 2 Optimized effect of solvent, base and temperature on the asymmetric epoxidation of chalcone

Entry	PTC/ equiv.	TCCA/ equiv.	KOH/ equiv.	Time/h	Conv.[a] (%)	Ee[b] (%)
1	0.1	1.67	10.0	8	100	81
2	0.1	1.0	6.0	8	100	83
3	0.1	0.67	4.0	24	100	83
4	0.1	0.5	3.0	48	100	81
5	0.1	0.67	3.0	24	100	82
6	0.1	0.67	2.4	48	88	82
7	0.05	0.67	3.0	96	94	82
8	0.01	0.67	3.0	96	50	77

[a] The values of conversion (%) were obtained by HPLC analyses.
[b] Determined by HPLC using a Chiralpak® AD-H column with racemic epoxides as standards.

Table 3 Asymmetric epoxidation of enones **1a–m** to give the epoxides **2a–m** employing A2 as PTC

Enone	R	R′	Yield[a] (%)	Ee[b] (%)
1a	Ph	Ph	90	89 (96)[c]
1b	Ph	p-MeOC$_6$H$_4$	82	90
1c	p-ClC$_6$H$_4$	p-FC$_6$H$_4$	92	92 (96)[c]
1d	Ph	p-FC$_6$H$_4$	79	88 (99)[c]
1e	p-NO$_2$C$_6$H$_4$	Ph	83	96 (99)[c]
1f	Ph	p-ClC$_6$H$_4$	85	93
1g	p-ClC$_6$H$_4$	Ph	97	84 (99)[c]
1h	o-ClC$_6$H$_4$	Ph	89	64
1i	p-ClC$_6$H$_4$	p-ClC$_6$H$_4$	93	79
1j	p-ClC$_6$H$_4$	p-MeOC$_6$H$_4$	74	93 (98)[c]
1k	p-MeOC$_6$H$_4$	Ph	0	—
1l	p-MeOC$_6$H$_4$	p-ClC$_6$H$_4$	0	—
1m	Ph	Me	0	—

[a] Isolated yield by chromatography. [b] Determined by HPLC using a Chiralpak® AD-H column with racemic epoxides as standards. [c] The ees in parentheses were determined after recrystallisation.

In conclusion, the present study provides the first evidence that TCCA might possess general utility for the catalytic epoxidation of enones. We have developed a mild, efficient phase-transfer catalyzed asymmetric epoxidation of chalcone derivatives with modest to excellent enantioselectivity with TCCA as the oxidant. The procedure reported here is simple and allows for epoxidation under very mild conditions. Further studies aimed at improving the enantioselectivity of epoxidation and reaction scope are currently under investigation.

Notes and references

‡ All chemicals were purchased from Acros and used as received. Chiral catalysts A1, A2 and A3 were prepared according to the references, and the NMR results were consistant with the references.[3,4,5,10]

§ General procedure for catalytic epoxidation of enones under phase-transfer conditions: A solution of enone (1.00 mmol) and chiral PTC (0.100 mmol) in toluene (3 ml) was cooled to 0 °C. TCCA (156 mg, 0.67 mmol) was added slowly by portions and then 50% KOH aq. (0.336 g, 3.00 mmol) was added dropwise *via* syringe. The reaction mixture was stirred at 0 °C until chalcone disappeared (detected by TLC), followed by addition of ether and filtration. The filtrate was washed with water and dried over MgSO$_4$. Evaporation of the solvents and purification of the residue on a silica gel column with 50 : 1 petroleum ether/ethyl acetate as eluent gave the epoxidation product. The enatiomeric excess was determined by chiral HPLC analysis with a Chiralpak® AD-H column.

1 R. A. Johnson and K. B. Sharpless, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, New York, Seoul, Tokyo, 1991, vol. 7, p. 389.

2 For a recent review on the asymmetric epoxidation of electron-deficient alkenes, see: M. J. Porter and J. Skidmore, *Chem. Commun.*, 2000, 1215.

3 (*a*) B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1998, **39**, 1599; (*b*) B. Lygo and P. G. Wainwright, *Tetrahedron*, 1999, **55**, 6289; (*c*) B. Lygo and D. C. M. To, *Tetrahedron Lett.*, 2001, **42**, 1343; (*d*) B. Lygo and D. C. M. To, *Chem. Commun.*, 2003, 2360.

4 (*a*) S. Arai, H. Tsuge and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 7563; (*b*) S. Arai, H. Tsuge, M. Oku, M. Miura and T. Shioiri, *Tetrahedron*, 2002, **58**, 1623.

5 E. J. Corey and F.-Y. Zhang, *Org. Lett.*, 1999, **1**, 1287.

6 W. Adam, P. B. Rao, H-G. Degen, A. Levai, T. Patonay and C. R. Saha-Möller, *J. Org. Chem.*, 2002, **67**, 259.

7 For a recent review on use of trichloroisocyanuric acid, see: U. Tilstam and H. Weinmann, *Org. Process Res. Dev.*, 2002, **4**, 384. For selected examples on the use of trichloroisocyanuric acid see: (*a*) E. C. Juenge and D. A. Beal, *Tetrahedron Lett.*, 1968, **55**, 5819; (*b*) T. Cohen, Z. Kosarych, K. Suzuki and L.-C. Yu, *J. Org. Chem.*, 1985, **50**, 2965; (*c*) T. R. Walters, W. W. Jr. Zajac and J. M. Woods, *J. Org. Chem.*, 1991, **56**, 316; (*d*) G. A. Hiegel and M. Nalbandy, *Synth. Commun.*, 1992, **22**, 1589; (*e*) L. De Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, 2001, **3**, 3041; (*f*) L. De Luca, G. Giacomelli, M. Simonetta and A. Porcheddu, *J. Org. Chem.*, 2003, **68**, 4999.

8 The preparation of racemic epoxides from alkenes by reaction with TCCA in aqueous acetone followed by treatment of the resulting chlorohydrin with aqueous KOH in ether/pentane, see: M. Wengert, A. M. Sanseverino and M. C. S. de Mattos, *J. Braz. Chem. Soc.*, 2002, **13**, 700.

9 (*a*) T. Schlama, L. Alcaraz and C. Mioskowski, *Synlett*, 1996, 571; (*b*) W. S. Johnson, C. D. Gutsche and R. D. Offenhauer, *J. Am. Chem. Soc.*, 1946, **68**, 1648; (*c*) R. Levine and J. R. Stephens, *J. Am. Chem. Soc.*, 1950, **72**, 1642.

10 H.-g. Park, B.-s. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim and S.-s. Jew, *Angew. Chem., Int. Ed.*, 2002, **41**, 3036.