Trichloroisocyanuric Acid: A Convenient Oxidation Reagent for Phase-Transfer Catalytic Epoxidation of Enones under Non-Aqueous Conditions

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Abstract: Trichloroisocyanuric acid (TCCA) is a cheap, safe and readily available alternative to the commonly used hydrogen peroxide and hypochlorite for the phase-transfer catalytic epoxidation of α,β-enones under non-aqueous conditions. A variety of chalcone derivatives give the corresponding epoxides with quantitative conversion and satisfactory yields in just a few hours under mild conditions. An asymmetric variant of the epoxidation can be carried out in the presence of chiral *N*-anthracenylmethylcinchonidine bromide catalyst giving 73–93% ees and 76–94% yields.

Keywords: enones; epoxidation; organic catalysis; phase-tranfer catalysis; trichloroisocyanuric acid

Introduction

In recent years, methods for the asymmetric epoxidation of electron-deficient olefins, particularly α,β-enones, have attracted widespread attention.[1] The phase-transfer catalytic epoxidation of α,β-enones has been developed rapidly because of its mild reaction conditions, safety and operational simplicity. A variety of oxidants, such as hydrogen peroxide,[2] sodium or potassium hypochlorite,[3] alkyl hydroperoxides,[4] urea-H_2O_2,[5] sodium perborate[6] and sodium percarbonate[7] are used for this epoxidation in a bi- or triphasic system. Recently, we have recognized that trichloroisocyanuric acid (TCCA) can serve as an efficient alternative to these oxidants for the asymmetric epoxidation of α,β-enones with a high enantioselectivity.[8]

TCCA is a cheap, safe, inexpensive and efficient reagent for the oxidation of ethers, thioethers, aldehydes, acetals and alcohols.[9] The decomposition of TCCA under acidic or neutral conditions produces hypochlorous acid.[10] This process can take place under basic conditions as well and produce aqueous hypochlorite salt, which is a mild oxidant for the asymmetric epoxidation of α,β-enones under liquid-liquid phase-transfer catalytic conditions.[8] Interestingly, we found that this epoxidation could occur under non-aqueous conditions when using solid potassium hydroxide instead of its aqueous solution, and the reaction procedure is more convenient for product separation excluding the wet viscid isocyanuric acid.

We now describe the scope of this methodology in which TCCA is used as a cheap, safe, easily handled and readily available oxidant for phase-transfer catalytic epoxidation of enones under solid-liquid biphasic non-aqueous conditions. The epoxidation of chalcone was conducted in a two-phase system made up of oxidant TCCA, a solid inorganic base, a non-asymmetric or an asymmetric phase-transfer catalyst and an organic solvent. The entire process in non-aqueous media was complete in just a few hours with quantitative conversion and satisfactory yields.

Results and Discussion

The epoxidation of chalcone in the presence of a phase-transfer catalyst and KOH in toluene was selected as a model reaction. A variety of catalysts including polyethylene glycols (PEG-4600, PEG-400), tetrabutylphosphonium bromide (TBPB), tetrabutylphosphonium chloride (TBPC), cetyltrimethylammonium bromide (CTMAB), tetrabutylammonium bisulfate (TBABS) and tetrabutylammonium bromide (TBAB) were tested, and these results are summarized in Table 1. Although epoxidation can take place with any catalyst listed in Table 1, it was also found that the epoxidation almost stopped within 24 hours at 0 °C, and that extension of the reaction time could not improve the conversion. This phenomenon may be due to the decomposition of an active hypochlorite salt. The addition of PEG-4600

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as a phase-transfer catalyst gave a low yield (Table 1, entry 1). However, when the same reaction was carried out in the presence of PEG-400, the yield increased to 71% (Table 1, entry 2). Two phosphonium salts gave different yields, and the reason is unclear. Using CTMAB as a phase-transfer catalyst, the yield was good within 24 hours. When using TBABS and TBAB as phase-transfer catalysts, the reactions were quantitatively completed in 4 hours (Table 1, entries 6 and 7). The data clearly show that tetrabutylammonium salt catalysts are more efficient than the PEG and the tetrabutylphosphonium salt catalysts. The amount of TBAB catalyst can be reduced to 5% without reducing the conversion (Table 1, entry 8), while a substantial decrease in the conversion was observed when the amount of catalyst was reduced to 1% (Table 1, entry 9).

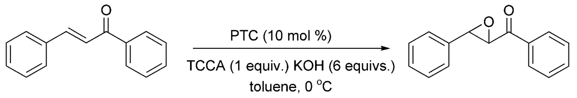
The effects of solvent, base and temperature are presented in Table 2. Several non-polar solvents including methylene chloride, xylene and toluene were tested in the model reaction. Aromatic non-polar solvents such as toluene and xylene turned out to be the suitable solvents (Table 2, entries 2 and 3) for the epoxidation with quantitative conversion in a few hours. Potassium hydroxide as a base gave excellent yields while a relatively weak base such as lithium hydroxide or sodium hydroxide gave lower conversions (Table 2, entries 4 or 5) since the reactivity of potassium hypochlorite was higher than those of lithium hypochlorite and sodium hypochlorite. A stronger base such as cesium hydroxide also gave a poor conversion (Table 2, entry 6) probably due to the high instability of cesium hypochlorite. The optimum temperature of the reaction ranged from 0 to 10 °C. Higher temperatures decreased the conversion probably because of the progressive decomposition of active hypochlorite salts (Table 2, entry 7).

Some examples of the TBAB-catalyzed epoxidation of a series of enones under our non-aqueous conditions are summarized in Table 3. Most of the chalcone derivatives were converted to the desirable products in a few hours with satisfactory yields (Table 3, Entries 1–10). In a number of cases the crude reaction products were most conveniently purified by filtration and recrystallization. However, for some substrates such as 4-methoxychalcone and benzalacetone, undesirable products were obtained. We were able to detect the presence of monochlorinated products of **1k** by GC-MS resulting from electrophilic chlorination. As for **1l**, the reaction mixture turned brown rapidly, probably due to a haloform-type reaction.[11] It is noteworthy that the unsuitable chalcone derivative **1k** was easily converted to the corresponding epoxide without chlorination in a few hours when TCCA was treated with KOH in toluene prior to the addition of the substrate (Table 3, Entry 11). Unfortunately, benzalacetone gave no desired products even under these conditions.

In recent years, methods for the asymmetric epoxidation of electron-deficient olefins, particularly α,β-enones, have attracted widespread attention. In order to illustrate the efficiency of this non-aqueous phase-transfer catalysis, the asymmetric catalyzed epoxidation of enones was also carried out under the developed solid-liquid phase-transfer conditions, and the results are presented in Table 4.

Using the *N*-anthracenylmethyl derivative of *Cinchona* alkaloid as a chiral catalyst, the asymmetric epoxidations of enones proceeded smoothly under solid-liquid phase-transfer conditions to afford the corresponding epoxy ketones. Although 5 mol % of catalyst TBAB is sufficient for the non-asymmetric epoxidation of chalcone, the conversion is incomplete in the presence of

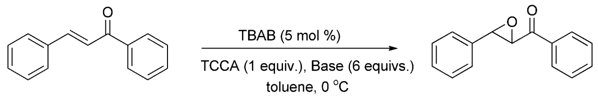
Table 1. Effect of PTC on the epoxidation of chalcone.



Entry	Catalyst	Base	Time [h]	Conversion [%][a]	Yield [%][b]
1	PEG-4600	KOH	24	42	37
2	PEG-400	KOH	24	87	71
3	TBPB[c]	KOH	24	78	71
4	TBPC[d]	KOH	24	57	48
5	CTMAB	KOH	24	92	70
6	TBABS	KOH	3	100	91
7	TBAB	KOH	4	100	92
8	TBAB[e]	KOH	4	100	91
9	TBAB[f]	KOH	24	60	42

[a] The values of conversion and yield were obtained by HPLC analysis.
[b] Yield of isolated product.
[c] 70% TBPB in isopropyl alcohol is used.
[d] 70% TBPC in isopropyl alcohol is used.
[e] A 5% amount of catalyst is used.
[f] A 1% amount of catalyst is used.

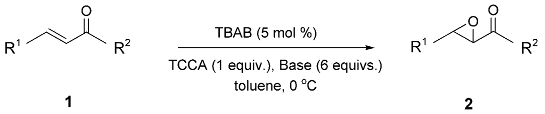
Table 2. Effect of reaction conditions on the epoxidation of chalcone.



Entry	Solvent	Base	T [°C]	Time [h]	Conversion [%][a]	Yield [%][b]
1	CH_2Cl_2	KOH	0	24	85	73
2	Xylene	KOH	0	5	100	84
3	Toluene	KOH	0	4	100	91
4	Toluene	LiOH	0	24	58	25
5	Toluene	NaOH	0	24	58	12
6	Toluene	CsOH	0	24	62	42
7	Toluene	KOH	20	24	88	67
8	Toluene	KOH	10	4	100	91
9	Toluene	KOH	-10	6	100	87

[a] The values of conversion and yield were obtained by HPLC analysis.
[b] Yield of isolated product.

Table 3. Epoxidation of various enones.



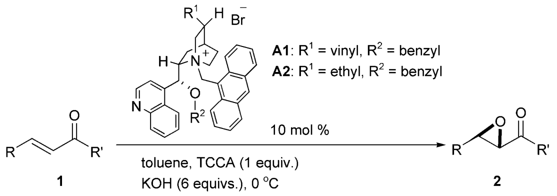
Entry	Enones	R1	R2	Time [h]	Yield [%][a]
1	**1a**	C_6H_5	C_6H_5	4	88
2	**1b**	C_6H_5	4-$CH_3OC_6H_4$	4	85
3	1c	4-ClC_6H_4	4-FC_6H_4	3	94
4	1d	C_6H_5	4-FC_6H_4	5	81
5	1e	4-$NO_2C_6H_4$	C_6H_5	4	77
6	1f	C_6H_5	4-ClC_6H_4	4	91
7	1 g	4-ClC_6H_4	C_6H_5	4	93
8	1 h	2-ClC_6H_4	C_6H_5	4	93
9	1i	4-ClC_6H_4	4-ClC_6H_4	2	80
10	1j	4-ClC_6H_4	4-$CH_3OC_6H_4$	3	72
11	1k	4-$CH_3OC_6H_4$	C_6H_5	5	88
12	1 l	C_6H_5	CH_3	24	0

[a] Yield of isolated product.

5 mol % of chiral *N*-anthracenylmethylcinchonidine bromide catalysts. In the presence of 10 mol % of chiral catalyst **A2**, the asymmetric epoxidation of enones under non-aqueous solid-liquid conditions provided the epoxy ketones in 73–93% ees and 76–94% yields. Although the ees are similar to or slightly lower than those obtained under liquid-liquid conditions,[8] the yields are good in almost all cases. Coupled with the fact that the product separation is more convenient excluding the wet viscid isocyanuric acid, we believe that this new non-aqueous procedure holds considerable promise for the future applications.

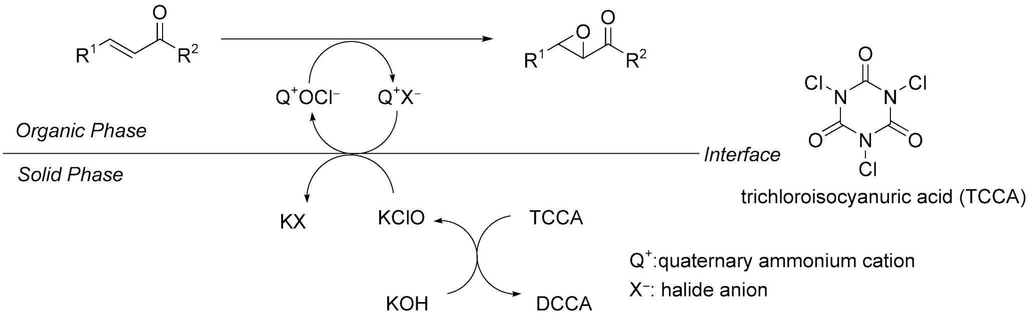
The 4-methoxychalcone also gave a good result using this procedure with 91% ee and 80% yield. In all these examples the *trans*-epoxides were obtained with high diastereoselectivity.[12] This result can be explained in terms of the probable mechanism of the phase-transfer catalysis (Scheme 1). In general, the phase-transfer catalytic epoxidation mediated by a quaternary salt is carried out under liquid-liquid conditions with aqueous H_2O_2, NaClO or KClO. Our phase-transfer catalytic epoxidation with TCCA as a mild and efficient oxidant can proceed smoothly under both aqueous/organic solvent liquid-liquid conditions and non-aqueous solid-liquid conditions at nearly the same reaction rate. Chlorine gas escapes when the reaction is carried out at 30 °C or higher temperatures. Excess of the inorganic base to keep the system basic is required for the quantitative conversion of an enone to an epoxy ketone. On the basis of these findings, and in accord with what is reported for similar cases, we can formulate the mechanism shown in Scheme 1. TCCA should react with inorganic base to form hypochlorite salt, which is transferred to the organ-

Table 4. Asymmetric epoxidation of various enones with **A2** as catalyst.



Entry	Enones	R^1	R^2	Time [h]	Yield [%][a]	ee [%][b]
1[c]	**1a**	C_6H_5	C_6H_5	24	69	86
2	**1a**	C_6H_5	C_6H_5	7	90	87
3[d]	**1a**	C_6H_5	C_6H_5	7	89	82
5	**1b**	C_6H_5	4-$CH_3OC_6H_4$	7	86	91
6	**1c**	4-ClC_6H_4	4-FC_6H_4	6.5	93	93
7	**1d**	C_6H_5	4-FC_6H_4	7	83	90
8	**1e**	4-$NO_2C_6H_4$	C_6H_5	7	76	93
9	**1f**	C_6H_5	4-ClC_6H_4	7	88	92
10	**1 g**	4-ClC_6H_4	C_6H_5	7	94	89
11	**1 h**	2-ClC_6H_4	C_6H_5	7	91	73
12	**1i**	4-ClC_6H_4	4-ClC_6H_4	7	90	86
13	**1j**	4-ClC_6H_4	4-$CH_3OC_6H_4$	7	86	91
14	**1k**	4-$CH_3OC_6H_4$	C_6H_5	8	80	91

[a] Yield of product isolated by chromatography.
[b] Determined by HPLC using Chiralpak® AD-H, OD-H columns with racemic epoxides as standards.
[c] With 5 mol % **A2** catalyst.
[d] With 10 mol % **A1** catalyst.



Scheme 1. Mechanism of the catalytic epoxidation of enones under phase-transfer conditions using TCCA as the oxidant.

ic phase by the phase-transfer catalyst and oxidizes the enone to the corresponding epoxy ketone.

Conclusion

In summary, an operationally simple procedure for the phase-transfer catalytic epoxidation of chalcone derivatives with TCCA under non-aqueous conditions is presented, resulting in quantitative conversion and satisfactory yields in just a few hours. The non-aqueous procedure has certain advantages over previously reported protocols, since TCCA is cheap, safe and convenient in comparison to hydrogen peroxide and hypochlorite, and provides additional options under non-aqueous conditions. We are continuing our investigations on non-aqueous phase-transfer catalysis with TCCA as a mild oxidant in asymmetric tandem reactions, such as the tandem oxidation-epoxidation of allyl alcohols and will report the results in due course.

Experimental Section

General Remarks

The ^{1}H NMR spectra were measured at 400 MHz, with Me_4Si as the internal reference and $CDCl_3$ as the solvent. Column chromatography was performed on silica gel (200–300 mesh). Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel GF-254 plates. Enantiomeric excesses were determined by HPLC using Chiralpak® AD-H, OD-H columns with racemic epoxides as standards. PEG 4600, PEG-400, CTMAB, TBABS and TBAB were purchased from Acros, TBPB and TBPC were kind gifts from Chemconserve. Catalysts **A1** and **A2** were prepared according to reported procedures, and the NMR results were consistent to those of the literature.[2d,3c,3e,13] Enones **1a**, **1c** and **d** were purchased from Acros and **1b**, **1e–k** were prepared *via* aldol condensation according to reported procedures.[14]

Typical Procedure for the Epoxidation of Enones

Procedure A is for the non-asymmetric epoxidation of **1a–j**, Procedure B for non-asymmetric epoxidation of **1k** and Procedure C for asymmetric variants of **1a–k**.

Procedure A: To a solution of chalcone (208 mg, 1.00 mmol) and TBAB (16 mg, 0.05 mmol) in toluene (3 mL) were added TCCA (233 mg, 1.00 mmol) and then KOH (336 mg, 6.00 mmol) in portions at 10 °C. The biphasic mixture was stirred at 10 °C until the chalcone had disappeared (monitored 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 products.

Procedure B: To a suspension of TCCA (233 mg, 1.00 mmol) in toluene (3 mL) was added KOH (336 mg, 6.00 mmol) at below 0 °C, and the mixture was stirred at 10 °C for 15 min. 4-Methoxychalcone (238 mg, 1.00 mmol) and TBAB (16 mg, 0.05 mmol) were then added. The biphasic mixture was stirred at 10 °C until 4-methoxychalcone had disappeared (monitored 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 30:1 petroleum ether/ethyl acetate as eluent gave the epoxidation products.

Procedure C: To a suspension of TCCA (233 mg, 1.00 mmol) in toluene (3 mL) was added KOH (336 mg, 6.00 mmol) under 0 °C, and the mixture was stirred at 0 °C for 15 min. Chalcone (1.00 mmol) and the chiral PTC (66.7 mg, 0.1 mmol) were then added. The biphasic mixture was stirred at 0 °C until the chalcone had disappeared (monitored 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 petroleum ether/ethyl acetate as eluent gave the epoxidation products. Yields and enantiomeric excesses are given in Table **4**.

Characterization data of the racemic and optically active epoxides agree with those published for the racemic and optically active compounds (see supporting information).

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