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Synthesis of (αR,βS)-epoxyketones by asymmetric epoxidation of chalcones with cinchona phase-transfer catalysts

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ABSTRACT

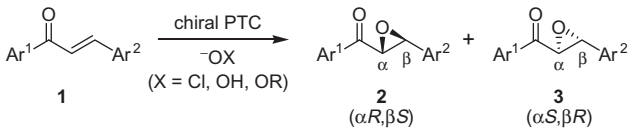
An efficient method to synthetically produce optically enriched (αR,βS)-epoxyketones was developed using a quaternary ammonium salt derived from cinchona alkaloid as the chiral phase-transfer catalyst. (αR,βS)-Epoxyketones were prepared in high optical purities (91–99% ee) by the asymmetric epoxidation of 1,3-diarylenones with aqueous sodium hypochlorite in the presence of a hydrocinchonine-derived chiral phase-transfer catalyst bearing a 2,3,4-trifluorobenzyl group.

Enantiomerically enriched α,β-epoxyketones are considered versatile chiral building blocks in asymmetric organic synthesis and medicinal chemistry.[1] They can be converted to many types of useful chiral compounds such as α-hydroxycarbonyls, β-hydroxycarbonyls, α,β-dihydroxycarbonyls, epoxyalcohols, and β-ketoaldehydes.[1] Asymmetric epoxidation of α,β-unsaturated ketones has been the most widely used method for synthetically producing optically active α,β-epoxyketones.[2] In the last two decades, considerable efforts have been directed toward the asymmetric epoxidation of enone, and the most well-established methods used for this reaction include the use of chiral ligand-metal peroxides, polyamino acid, chiral hydroperoxides, chiral dioxiranes, chiral pyrrolidines, or chiral phase-transfer catalysts.[2]

Asymmetric phase-transfer catalysis has been extensively studied due to its many advantages including operational simplicity, no need for anhydrous reaction conditions, and the high level of asymmetric induction through the use of non-metallic catalyst, and many highly effective reaction systems have been developed.[3] Particularly, with regard to asymmetric phase-transfer-catalyzed epoxidation of acyclic enones such as *trans*-chalcones **1** (Scheme 1), several efficient methods have been developed since the first report by Wynberg and co-worker in 1978.[4] Many types of chiral phase-transfer catalysts (PTCs) have been applied to the asymmetric epoxidation of **1**, and fine tuning of the reaction conditions with various oxidants has been performed. To date, cinchona alkaloid-derived PTCs (cinchona-PTCs) have been the most widely used PTCs by several groups including Lygo,[5] Arai and Shioiri,[6] Corey,[7] Liang,[8] and us.[9] Besides the cinchona-PTCs, other useful chiral PTCs have been developed for this epoxidation such as *N*-spiroammonium salts,[10] azacrown ethers,[11,12] and guanidinium salts.[13,14] In terms of the oxidant, hypochlorite[5,7,10,13] including in situ generation from trichloroisocyanuric acid[8] or hydroperoxide[6,9,12,14]/*tert*-butylperoxide[11] under basic conditions has been employed in most reaction systems.

A class of the cinchona-PTCs containing a *N*-2,3,4-trifluorobenzyl moiety (**4** and **5**, Fig. 1), first introduced by us in 2002,[15] has been shown to possess excellent catalytic efficiency in the asymmetric synthesis of optically active α-amino acid derivatives,[16] α-hydroxycarbonyls,[17] and α,β-epoxysulfones.[18] To demonstrate the potential applicability of **4** and **5** in other asymmetric organic reactions, here, we used these compounds in the asymmetric epoxidation of chalcones **1**.

These reactions were initiated using C(9)–O-allylated cinchona-PTCs (G^2 = allyl in Fig. 1) and sodium hypochlorite.[19] Four basic PTCs (**4a**, **4b**, **5a**, and **5b**) were prepared from natural cinchona alkaloids (cinchonidine for **4a**, quinine for **4b**, cinchonine for **5a**, and quinidine for **5b**) in two sequential steps: N-quaternarization with 2,3,4-trifluorobenzyl bromide followed by C(9)–O-allylation with allyl bromide and KOH.[15–18] The initial screening of the reaction conditions was performed with *trans*-chalcone (**1a**, Ar^1 = Ar^2 = Ph), 11% aqueous sodium hypochlorite (10 equiv) in the presence of the prepared PTC (10 mol %) in toluene at room temperature, and the results are summarized in Table 1. The four basic PTCs (entries 1–4) all promoted the reaction under the given conditions to exclusively produce trans-epoxide (**2a** + **3a**). The



Scheme 1. Asymmetric epoxidation of chalcones **1** under phase-transfer catalytic conditions.

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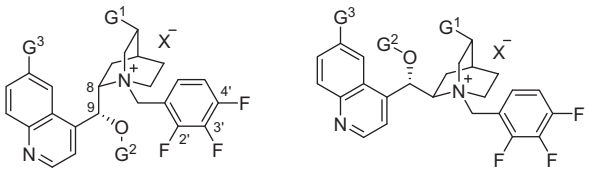


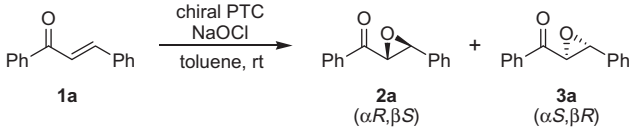
4 (from cinchonidine or quinine) **5** (from cinchonine or quinidine)

G^1 = vinyl or ethyl; G^2 = H, allyl or benzyl
G^3 = H, or methoxy; X = Cl or Br

	G^1	G^2	G^3	X
4a	vinyl	allyl	H	Br
4b	vinyl	allyl	OMe	Br
5a	vinyl	allyl	H	Br
5b	vinyl	allyl	OMe	Br
5c	ethyl	allyl	H	Br

Figure 1. *N*-2,3,4-Trifluorobenzyl-containing cinchona-PTCs.

Table 1
Initial screening[a]

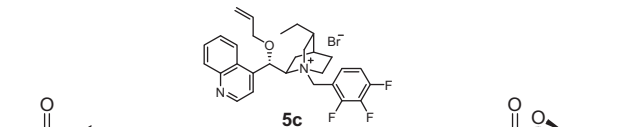


1a **2a** (αR,βS) **3a** (αS,βR)

Entry	PTC	Time (h)	Yield[b] (%)	Major enantiomer[c]	ee[d] (%)
1	**4a**	5	96	**3a**	63
2	**4b**	6	95	**3a**	26
3	**5a**	4	96	**2a**	76
4	**5b**	6	94	**2a**	57
5	**5c**	4	97	**2a**	78

[a] The reaction was carried out with *trans*-chalcone (**1a**, 1.0 equiv) and 11% aqueous sodium hypochlorite (10.0 equiv) in the presence of PTC (10 mol %) in toluene at room temperature.
[b] Yield of isolated product (**2a** + **3a**).
[c] The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[5b,6b,9]
[d] Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralpak-AD) with hexanes/ethanol (volume ratio = 90:10) as the eluent; in this case it was established by analysis of the racemate, of which the enantiomers (**2a** and **3a**) were fully resolved [flow rate: 1 mL/min, detection: 254 nm, retention times: 17.7 min (**2a**), 25.7 min (**3a**)].

Table 2
Tuning of reaction conditions



1a **5c** NaOCl, toluene, temp. **2a** (αR,βS)

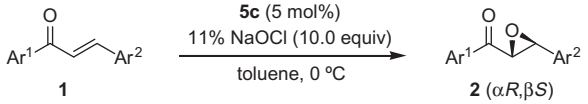
Entry	Temp	Equiv of NaOCl[a]	Mol % of **5c**	Time (h)	Yield (%)	ee (%)
1	rt	10	10	4	96	78
2	rt	10	5	4	95	80
3	rt	10	2	10	91	79
4	rt	5	5	8	97	80
5	rt	2	5	40	90	85
6	0 °C	10	10	24	72	85
7	0 °C	10	5	48	82	91
8	0 °C	5	5	50	81	87
9	0 °C	2	10	48	80	83

[a] 11% Aqueous sodium hypochlorite was used, and consequently, the volume of the aqueous layer in a biphasic system varied with the equivalent of sodium hypochlorite.

fraction of stereoisomers obtained in each case varied with the nature of the cinchona-PTC employed. PTCs **4** produced the (αS,βR)-epoxide (**3a**) as the major enantiomer, while significantly more (αR,βS)-epoxide (**2a**) was obtained when PTCs **5** was used. The level of enantioselectivity was also affected by the PTC, where cinchonine-PTC **5a** provided the highest enantioselectivity (76% ee) among the four PTCs tested. Hydrocinchonine-PTC **5c** led to a slight increase in enantiomeric excess (78% ee, entry 5) and this PTC was chosen to tune the other reaction parameters. Results obtained from varying the reaction conditions (reaction temperature, amount of the oxidant, and catalyst) are shown in Table 2.

Reactions at low temperature (0 °C, entries 6–9) generally resulted in higher enantioselectivities than at room temperature (entries 1–5) although the chemical yields were slightly lower at longer reaction times. The amounts of sodium hypochlorite did not seem to be closely related to chemical/optical yield. Notably, the enantiomeric excess was maintained with a smaller quantity of the catalyst **5c** (entries 2 and 3), and even an enhanced enantiomeric excess was observed at 0 °C (entry 7).[20] The reaction conditions shown in entry 7 in Table 2 were finally selected to investigate the scope and limitations of this reaction.

Table 3
Synthesis of (αR,βS)-epoxyketones **2** via asymmetric phase-transfer catalytic epoxidation of chalcones **1**[a]



1 **5c** (5 mol%), 11% NaOCl (10.0 equiv), toluene, 0 °C → **2** (αR,βS)

Entry	Chalcones **1**	Ar^1	Ar^2	Time (h)	Epoxides **2**	Yield[b] (%)	ee[c] (%)
1	**1a**	Ph	Ph	48	**2a**	82	91
2	**1b**	4-Me-Ph	Ph	48	**2b**	71	92
3	**1c**	Naphthalene-2-yl	Ph	48	**2c**	63	91
4	**1d**	6-MeO-naphthalene-2-yl	Ph	40	**2d**	81	95
5	**1e**	4-MeO-Ph	Ph	40	**2e**	90	91
6	**1f**	Thiophene-2-yl	Ph	40	**2f**	95	95
7	**1g**	4-F-Ph	Ph	24	**2g**	91	99
8	**1h**	4-F-Ph	4-Cl-Ph	48	**2h**	90	91
9	**1i**	Ph	4-NO_2-Ph	40	**2i**	95	92
10	**1j**	4-F-Ph	4-NO_2-Ph	16	**2j**	90	93
11	**1k**	4-F-Ph	Naphthalene-2-yl	48	**2k**	63	94

[a] The reaction was carried out with *trans*-chalcone (1.0 equiv) and 11% aqueous sodium hypochlorite (10.0 equiv) in the presence of **5c** (5 mol %) in toluene at 0 °C.
[b] Yield of isolated product.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralpak-AD or Chiralcel-OD) with hexanes/ethanol or hexanes/2-propanol as the eluent (flow rate: 1 mL/min, detection: 254 nm); in this case it was established by analysis of the racemate, of which the enantiomers were fully resolved.

As shown in Table 3, this epoxidation system was fairly effective in many cases for 1,3-diarylenones (chalcones **1**).[21] The epoxidation proceeded smoothly within 16–48 h and produced the corresponding (α*R*,β*S*)-epoxyketones **2** with high enantioselectivities and good chemical yields.[22] As mentioned above, many studies have been devoted to the asymmetric epoxidation of enones using cinchona-PTCs,[4–9] but most of the methods developed have focused on only (α*S*,β*R*)-enantiomers with the exception of one.[5a] Here we provide another efficient synthetic method for producing (α*R*,β*S*)-epoxyketones **2** using the cinchona-PTC **5c**.

In conclusion, we developed an efficient method for the synthesis of optically enriched (α*R*,β*S*)-epoxyketones **2** from chalcones **1** via enantioselective phase-transfer catalytic epoxidation with sodium hypochlorite oxidant and the chiral cinchona-PTC **5c** bearing 2,3,4-trifluorobenzyl moiety.

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19. An interesting tendency can be found in the asymmetric epoxidation of chalcones using cinchona-PTCs. A cinchona-PTC with free hydroxy group at C(9) position generally provides better enantioselectivity when an alkaline peroxide is used as the oxidant. On the other hand, a hypochlorite oxidant is well suited for the C(9)-O-alkylated cinchona–PTC.[5–8]
20. Use of C(9)-*O*-benzyl analog of **5c** under the conditions of entry 7 in Table 2 gave the epoxide **2a** at a chemical yield of 80% and 86% ee.
21. *Typical procedure*: A mixture of *trans*-chalcone (**1a**, 35 mg, 0.17 mmol) and PTC **5c** (4.8 mg, 8.5 μmol) in toluene (1 mL) was cooled at 0 °C. 11% Aqueous sodium hypochlorite solution (1.25 mL, 1.7 mmol) was then added to the mixture, and the resulting mixture was stirred vigorously at 0 °C for 48 h. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with brine, and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 50:1) to give the epoxyketone **2a** (31 mg, 82%) as a white solid. HPLC conditions: Chiralpak AD, hexanes/ethanol = 90:10, 1 mL/min, 254 nm, t_R = 17.7 min (**2a**), 25.7 min (**3a**), 91% ee.
22. The epoxidation of enones with alkyl or other non-phenyl groups attached to carbonyl led to only modest enantioselection.