Phase-Transfer Catalysis

Highly Enantioselective Epoxidation of 2,4-Diarylenones by Using Dimeric Cinchona Phase-Transfer Catalysts: Enhancement of Enantioselectivity by Surfactants**

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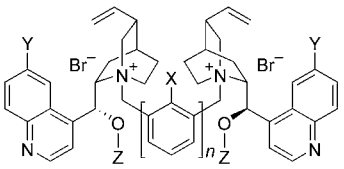
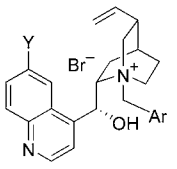
Since the asymmetric epoxidation of allylic alcohols, which was reported by the Sharpless group in 1980, catalytic asymmetric epoxidation has been one of the most important asymmetric methodologies.[1] A number of methods have been developed for the epoxidation of both unfunctionalized olefins and electron-deficient enones.[2] Quite recently, catalytic asymmetric phase-transfer epoxidations by using a cinchona alkaloid-derived quaternary ammonium salt as a chiral phase-transfer catalyst (PTC) have been reported by several research groups.[3] Despite their practical potential, several shortcomings, such as insufficient enantioselectivity, long reaction times, and low reaction temperatures, still remain. Herein we report a highly enantioselective and practical catalytic epoxidation of enones by using cinchona alkaloid-derived dimeric quaternary ammonium salts and the role of surfactants for enantioselectivity.

Recently, we reported a series of novel *meta*-dimeric catalysts, derived from cinchona alkaloids, which were successfully applied in the enantioselective synthesis of α-amino acids.[4] As part of our research, we attempted to apply these catalysts to the asymmetric epoxidation of 2,4-diarylenones. As very versatile intermediates,[3b] the epoxides of 2,4-diarylenones have been applied to the synthesis of various biologically active compounds such as naproxen, ibuprofen, diltiazem, the side chain of Taxol, (+)-clausenamide, as well as styryl lactones ((+)-goniotriol and (+)-goniofufurone).[5]

We first performed the enantioselective phase-transfer epoxidation of *trans*-chalcone (**1a**) by using 5 mol% of the dimeric catalyst **3** along with 30% aqueous H_2O_2 (30 equiv) and 50% aqueous KOH (3 equiv) in diisopropyl ether at 10°C. As shown in Table 1, although the reaction time was somewhat long (48 h), the dimeric catalyst **3** showed moderate enantioselectivity (48% *ee*) compared with the corresponding monomeric catalyst **9**, which provided virtually no enantioselectivity (Table 1, entries 1 and 8). Before we searched for an optimal catalyst for the epoxidation, we needed to reduce the long reaction time, which might cause the low enantioselectivity through non-PTC-mediated epoxidation.

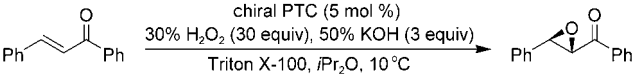


3 *n* = 1 X = H Y = H Z = H
4 *n* = 2 X = H Y = H Z = H
5 *n* = 1 X = F Y = H Z = H
6 *n* = 1 X = H Y = OMe Z = H
7 *n* = 1 X = F Y = OMe Z = H
8 *n* = 1 X = F Y = OMe Z = allyl



9 Ar = Ph Y = H
10 Ar = 9-anthracenyl Y = H
11 Ar = 2,3,4-$F_3C_6H_2$ Y = OMe

Table 1: Catalytic enantioselective epoxidation of *trans*-chalcone.



1a **2a**

Entry	PTC	Triton X-100 [mol%]	*t* [h]	Yield [%]	*ee* [%][a]
1	**3**	0	48	85	48
2	**3**	5	10	89	82
3	**4**	5	8	85	2
4	**5**	5	8	80	92
5	**6**	5	8	90	92
6	**7**	5	3	95	98
7	**8**	5	8	70	6
8	**9**	0	56	65	0
9	**9**	5	15	80	2
10	**10**	5	15	70	3
11	**11**	5	8	95	1

[a] Enantiopurity was determined by HPLC analysis with a chiral column (DAICEL Chiralpak AD), and absolute configuration was determined by comparison of the HPLC retention time with reported data.[3]

Recently, Okino and Takemoto reported a phase-transfer alkylation in a nonorganic solvent as a green chemical process;[6] the method involved the use of a surfactant, Triton X-100. As surfactants generally increase the surface area between the two phases by the formation of micelles,[7] we expected that the reaction would be accelerated in the presence of surfactants. Thus, we tentatively tried Triton X-100 in a phase-transfer epoxidation. Surprisingly, the use of just 5 mol% of Triton X-100 dramatically increased not only the rate of the reaction (five times) but also the enantioselectivity (82% *ee*, Table 1, entry 2). Generally, when the nucleophile and electrophile were not in the same phase, the phase-transfer reaction was considerably slower than the reaction that occurred when both components were in the organic phase. In the case of such a slow enantioselective phase-transfer reaction, the low enantioselectivities may not

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always reflect the low catalytic efficiencies of the employed catalysts. The low reaction rates might not allow the catalysts to perform optimally. Therefore, surfactants might effectively increase enantioselectivity, thus allowing an accurate evaluation of the catalyst capacity in phase-transfer catalytic reactions.

Once we had decreased the reaction time, we continued our search for an optimal catalyst. Five new dimeric catalysts (**4**–**8**) along with three monomeric catalysts (**9**–**11**) were prepared,[8] and their catalytic efficiencies for epoxidation were evaluated in the presence of 5 mol% of Triton X-100. As shown in Table 1, the catalyst based on the naphthyl ligand, **4**, displayed almost no enantioselectivity (Table 1, entry 3), which suggests that the length of the spacer between the two cinchona units influences the binding of the catalyst with chalcone (**1a**) and peroxide. In a series of *meta*-dimeric catalysts based on a central phenyl ring, introduction of substituents in **5** (X = F; entry 4, 92% *ee*) and **6** (Y = OMe; entry 5, 92% *ee*) had an equal effect on the enantioselectivity. These favorable effects were confirmed by an additional increase in enantioselectivity in the case of catalyst **7** (X = F, Y = OMe; entry 6, 98% *ee*). Despite the presence of the F and OMe functional groups in the appropriate positions, use of the corresponding *O*(9)-allyl catalyst **8** led to lower enantioselectivity (entry 7, 6% *ee*), which implies that the free OH group on C9 is essential for the binding process. With the monomeric catalysts (**9**–**11**), neither the surfactant effect nor the effect of the functional groups was observed (Table 1, entries 9–11). These accumulated findings suggested that the *ortho* F group on the phenyl ring, the 6′-methoxy group on the quinoline moiety, and the free OH group on C9 in catalyst **7** play integral roles in the favorable conformation of the binding intermediate, which comprises **7**, **1a**, and the hydrogen peroxide anion.

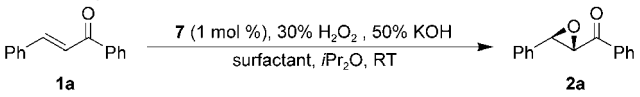
Next, we focused our attention on finding an optimal surfactant. Five commercially available surfactants were chosen. The epoxidation of **1a** was performed by using 1 mol% of **7** along with 30% aqueous H_2O_2 (10 equiv), 50% aqueous KOH (2.0 equiv), and the surfactants in diisopropyl ether at room temperature. Among the surfactants (Table 2, entries 1–5), Span 20 gave the best results in terms of both yield (95%) and enantioselectivity (> 99%). The enantioselectivity was preserved even when only a stoichiometric amount of KOH was present (entry 6), but a decrease in the initial amount of H_2O_2 used resulted in a slight decrease in enantioselectivity (entry 7).

Under the optimal reaction conditions (as in Table 2, entry 6), the reaction of various 2,4-diarylenones with hydrogen peroxide in the presence of **7** was investigated (Table 3). High enantioselectivities (97 to 99% *ee*) were observed for a variety of 2,4-diarylenones, which indicate that the reaction is a very efficient enantioselective method for this epoxidation. However, aliphatic-substituted substrates exhibited relatively low enantioselectivities (data not shown).

Based on the X-ray crystal structure of **7** (see Figure 1),[9] we propose a plausible transition state of the catalytic asymmetric epoxidation (Figure 2). The chalcone is located between the two cinchona units in **7**. The β-phenyl group of chalcone has a π–π stacking interaction with one of the quinoline moieties. The carbonyl oxygen atom is placed as close to the N^+ center as permitted by van der Waals forces. The other N^+ center is ion-paired with the hydrogen peroxide ion through hydrogen bonding with the oxygen of 6′-methoxy group in quinoline. As a consequence, hydrogen peroxide can only approach the β carbon atom of chalcone from the upside in the 1,4-addition to afford the α*S*,β*R* isomer **2**, which is in agreement with the observed results.

In conclusion, we have demonstrated that surfactants can dramatically increase both the reaction rate and enantiose-

Table 2: Optimization of surfactants.

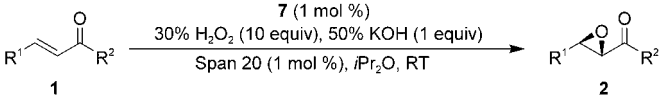


1a **2a**

Entry	H_2O_2 [equiv]	KOH [equiv]	Surfactant[a]	*t* [h]	Yield [%]	*ee* [%]
1	10	2	Triton X-100	3.5	80	90
2	10	2	Tergitol NP 9	3	80	97
3	10	2	Brij 78	2.5	95	94
4	10	2	Tween 20	2	95	99
5	10	2	Span 20	3	95	> 99
6	10	1	Span 20	4	95	> 99
7	5	1	Span 20	4	93	97

[a] The surfactants were purchased from Aldrich Co Ltd. 1 mol% was used in all reactions.

Table 3: Enantioselective phase-transfer catalytic epoxidation of enones.



1 **2**

Entry	R^1	R^2	*t* [h]	Yield [%]	*ee* [%]
1	Ph	Ph	4	95	> 99
2	Ph	4-F-C_6H_4	4	94	98
3	Ph	4-Me-C_6H_4	4	96	97
4	Ph	4-MeO-C_6H_4	1.5	95	> 99
5	Ph	2-naphthyl	6	96	> 99
6	Ph	2-thiophenyl	0.5	95	98
7	2-F-C_6H_4	Ph	1	97	> 99
8	3-F-C_6H_4	Ph	1	96	98
9	3-Me-C_6H_4	Ph	12	95	97

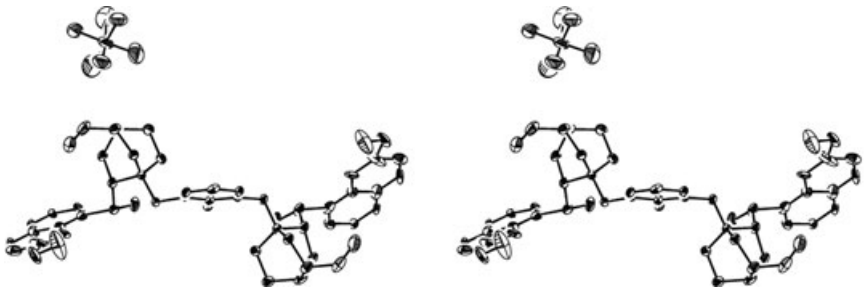


Figure 1. Stereoview of the X-ray crystal structure of **7**-PF_6.

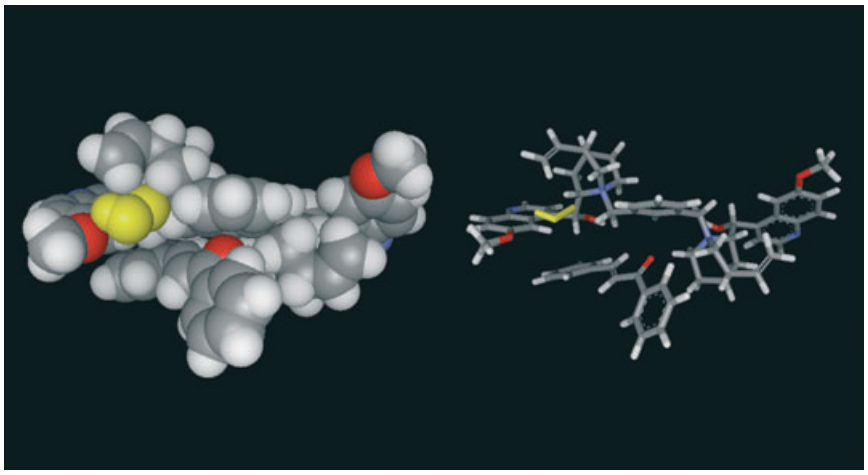


Figure 2. Plausible model of the transition state for the asymmetric epoxidation of **1a** based on the X-ray crystal structure of **7** (HOO^- yellow, C dark gray, H white, N blue, O red).

lectivity of phase-transfer catalytic epoxidation. The best results were obtained with Span 20. The easy preparation of the most effective catalyst, **7**, and the very mild reaction conditions make this method promising for industrial application. Further modification of the dimeric catalysts to extend the substrate scope and mechanistic studies are in progress.

Experimental Section

Aqueous hydrogen peroxide (30%, 0.27 mL; 2.4 mmol) and 50% aqueous KOH (0.027 mL, 0.24 mmol) were added to a mixture of chalcone **1a** (50 mg, 0.24 mmol), catalyst **7** (2.2 mg, 0.0024 mmol), and Span 20 (0.003 mL, 0.0024 mmol) in diisopropyl ether (0.8 mL), and the reaction mixture was stirred vigorously at room temperature until the starting material had been consumed. The resulting suspension was diluted with ether (10 mL), washed with water (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc = 50:1) afforded the desired product **2a** (51.2 mg, 95% yield) as a white solid. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD, hexanes/ethanol = 90:10, flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm; retention times: 16.6 min (minor), 24.0 min (major); > 99.9% *ee*) The absolute configuration was determined by comparison of the HPLC retention time with reported data.[3]

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[9] For detailed crystallographic data, see the Supporting Information.

