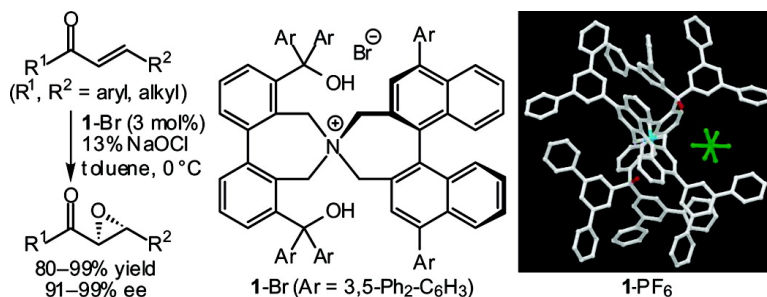## Communication

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Design of New Chiral Phase-Transfer Catalysts with Dual Functions for Highly Enantioselective Epoxidation of α,β-Unsaturated Ketones

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The catalytic asymmetric epoxidation of electron-deficient olefins, particularly α,β-unsaturated ketones, has recently been the subject of numerous investigations and a number of useful methodologies involving different types of catalyst−reagent combinations have been elaborated.[1] Among these, the method utilizing chiral phase-transfer catalysis occupies a unique place, featuring many advantages including operational simplicity, non-metal-containing catalyst, and environmental consciousness.[2] However, successful examples have been very limited since the pioneering work of Wynberg using alkylated *cinchona* alkaloids.[3] In 1998, Lygo showed the effectiveness of a catalyst incorporating a 9-anthracenylmethyl group in the epoxidation of mainly substituted chalcones with commercially available sodium hypochlorite,[4] and the next year Corey reported that use of the same catalyst with freshly prepared 65% potassium hypochlorite at lower temperature (−40 °C) led to improved enantioselectivities.[5] Despite such recent impressive progress,[6] the full potential of this reaction is yet to be realized in terms of both stereoselectivity and general applicability. This situation is largely due to the lack of well-designed, finely tunable chiral catalysts. Herein we wish to disclose our own solution to this problem by introducing a new chiral quaternary ammonium bromide with dual functions, which efficiently catalyzes the epoxidation of a variety of α,β-unsaturated ketones with excellent enantioselectivities under mild reaction conditions (Scheme 1).

Our prime concern in designing a suitable catalyst for phase-transfer-catalyzed asymmetric epoxidation of α,β-unsaturated ketones was to endow it with the ability to recognize the prochiral enone for attaining sufficient reactivity and enantiofacial discrimination. To achieve this, we first planned to introduce certain heteroatom-containing functionality as a substrate recognition site and chose a diarylmethanol group with the expectation that it could appropriately define the position of enones through hydrogen-bonding interaction. With the steric demand of this functionality in mind, we undertook the preparation of a new chiral quaternary ammonium bromide, **1a**, consisting of a flexible biphenyl subunit with a diphenylhydroxymethyl substituent at the 3,3′-position and a simple chiral binaphthyl structure. It was assumed that **1a** adopted a predominantly heterochiral (*R*,*S*) configuration around ambient temperature,[7] and its chiral efficiency was evaluated in the epoxidation of chalcone using commercially available 13% sodium hypochlorite (NaOCl). Thus, vigorous stirring of a mixture of chalcone, **1a** (3 mol %), and 13% NaOCl in toluene at 0 °C for 24 h gave rise to the corresponding epoxy ketone in 69% yield and appreciable enantiomeric excess was attained (66% ee) (entry 1 in Table 1). It should be noted that the reaction with catalyst **2** having no hydroxy group under otherwise identical conditions resulted in almost total loss of the catalytic activity and diminished stereoselectivity (3%, 46% ee) (entry 2).

On the basis of these initial observations, we next pursued the electronic and steric manipulations of this type of catalyst to enhance the chiral recognition ability. Although electronic tuning of the
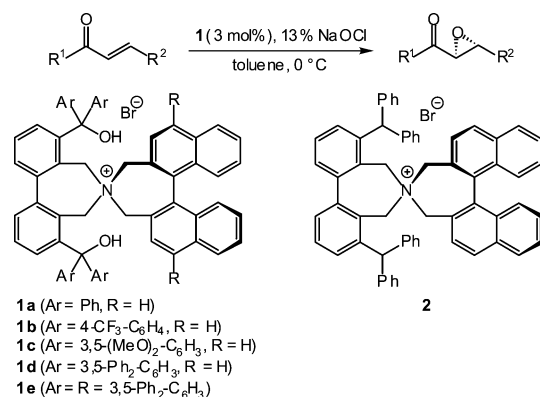
Scheme 1

1a (Ar = Ph, R = H)
1b (Ar = 4-CF₃-C₆H₄, R = H)
1c (Ar = 3,5-(MeO)₂-C₆H₃, R = H)
1d (Ar = 3,5-Ph₂-C₆H₃, R = H)
1e (Ar = R = 3,5-Ph₂-C₆H₃)

Table 1. Structural Modification of **1** for Phase-Transfer Catalytic Asymmetric Epoxidation of Chalcone[a]

entry	catalyst	% yield[b]	% ee[c] (config)[d]
1	**1a**	69	66 (α*S*,β*R*)
2	**2**	3	46 (α*S*,β*R*)
3	**1b**	50	61 (α*S*,β*R*)
4	**1c**	67	64 (α*S*,β*R*)
5	**1d**	61	80 (α*S*,β*R*)
6	**1e**	99	96 (α*S*,β*R*)

[a] The reaction (0.2 mmol scale) was carried out with 13% NaOCl (0.3 mL) in the presence of 3 mol % of **1** or **2** in toluene (0.6 mL) at 0 °C for 24 h. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis of epoxy chalcone using a chiral column (DAICEL Chiralcel OD). [d] Absolute configuration was determined by comparison of the HPLC retention time with that reported.[6d]

diphenylhydroxymethyl moiety subtly affected the reactivity and selectivity of the epoxidation (entries 3 and 4), introduction of the 3,5-diphenylphenyl group as aromatic substituent (Ar) increased the enantioselectivity to 80% ee (entry 5). Fascinatingly, further structural modification by installing a 3,5-diphenylphenyl group on the 4,4′-position of the binaphthyl subunit dramatically improved not only the enantioselectivity but also the catalytic activity, and epoxy chalcone was obtained quantitatively with 96% ee (entry 6).[8]

As shown in Figure 1, a successful single-crystal X-ray diffraction analysis of **1e**-PF₆ uncovered its distinctive three-dimensional molecular architecture and established the heterochiral configuration.[9] The biphenyl and binaphthyl subunits of the core *N*-spiro structure are nearly perpendicular, and this conformational information is transmitted to each substituent, creating an attractive chiral reaction cavity around the central nitrogen cation (blue). Importantly, hexafluorophosphate ion (green) is located inside the cavity being surrounded by the radially spread 3,5-diphenylphenyl groups,
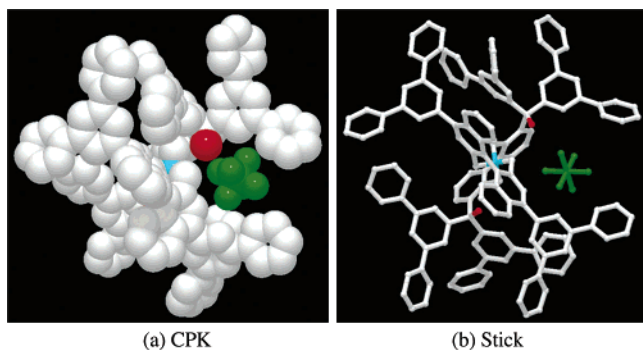
Figure 1. X-ray structure of **1e**-PF$_6$ (N, blue; O, red; PF$_6$, green). Hydrogen atoms and solvent molecules are omitted for clarity.

Table 2. Catalytic Asymmetric Epoxidation of α,β-Unsaturated Ketones under Phase-Transfer Conditions[a]

entry	enone R^1	R^2	react. time (h)	% yield[b]	% ee[c] (config)[d]
1	Ph	Np	24	99	97 (αS,βR)
2	Ph	p-Cl-C$_6$H$_4$	24	99	96 (αS,βR)
3	Ph	p-MeO-C$_6$H$_4$	48	83	96 (αS,βR)
4	p-Cl-C$_6$H$_4$	Ph	24	99	93 (αS,βR)
5[e]	p-Cl-C$_6$H$_4$	n-Hex	41	99	96 (αS,βR)
6	t-Bu	Ph	187	87	89 (αS,βR)
7[f]	t-Bu	Ph	83	99	92 (αS,βR)
8[f]	t-Bu	c-Hex	48	80	96
9[f]	t-Bu	n-Hex	112	80	91

entry			react. time (h)	% yield[b]	% ee[c] (config)[d]
10	n = 1		70	91	99 (αS,βR)
11	n = 2		70	98	96 (αS,βR)

[a] Unless otherwise noted, the reaction (0.1 mmol scale) was conducted with 13% NaOCl (0.15−1.8 mL) in the presence of 3 mol % of **1e** in toluene (0.3 mL) at 0 °C for the given reaction time. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis using a chiral column. [d] Absolute configuration was determined by comparison of optical rotation to literature value except for entry 5 (see the Supporting Information). [e] The reaction was carried out at −20 °C. [f] Use of **1d** as catalyst.

and the hydroxy moiety (red) is situated right above the nitrogen and sticks to the hexafluorophosphate ion. This strongly implies that, after the in situ ion-exchange, hypochlorite ion would be correctly positioned prior to the reaction and the expected hydrogen-bonding interaction would indeed bring enones inside the cavity to provide an ideal proximity to hypochlorite ion for the initial conjugate addition process, resulting in efficient bond formation with rigorous enantiofacial differentiation.

The general applicability of the present system has been thoroughly investigated and the representative results are summarized in Table 2. In the epoxidation of a series of differently substituted chalcone derivatives, the corresponding epoxy ketones were obtained almost quantitatively with excellent enantioselectivities (entries 1−4). The substrates possessing an alkyl substituent either on the double bond or on the carbonyl carbon were also epoxidized cleanly with a high level of asymmetric inductions (entries 5 and 6). Here, it is of interest that the catalyst **1d** was revealed to be superior for the epoxidation of the substrates with an alkyl ketone moiety and that aliphatic α,β-unsaturated ketones are amenable to this condition (entries 7−9). Moreover, β-benzylidene-α-indanone and its tetralone analogue appeared to be good candidates for this asymmetric transformation and virtually complete stereochemical control has been realized (entries 10 and 11).

In summary, we have devised chiral quaternary ammonium bromides that exhibit dual functions and allow practical highly enantioselective epoxidation of various α,β-unsaturated ketones under mild phase-transfer catalytic conditions. This system provides ready access to a wide range of useful synthetic intermediates of high enantiomeric purity. We believe the concept of the present molecular design is applicable to the development of other asymmetric phase-transfer reactions involving the addition of small anionic nucleophiles being supplied as an aqueous inorganic salt to prochiral electrophiles, which are difficult to achieve by the conventional catalyst systems.

Supporting Information Available: Physical characterization of catalysts **1d** and **1e** and all new compounds (PDF); the crystallographic data for **1e**-PF$_6$ (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The catalyst **1e** can be recovered quantitatively by chromatographic separation and reused for this epoxidation at least five times without decrease of catalytic activity and enantioselectivity.
(9) For detailed crystallographic data, see the Supporting Information.

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