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ARTICLE

Phase-transfer-catalyzed asymmetric desymmetrizations of cyclopentanones†‡

Cite this: DOI: 10.1039/x0xx00000x

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Accepted 00th January 2012

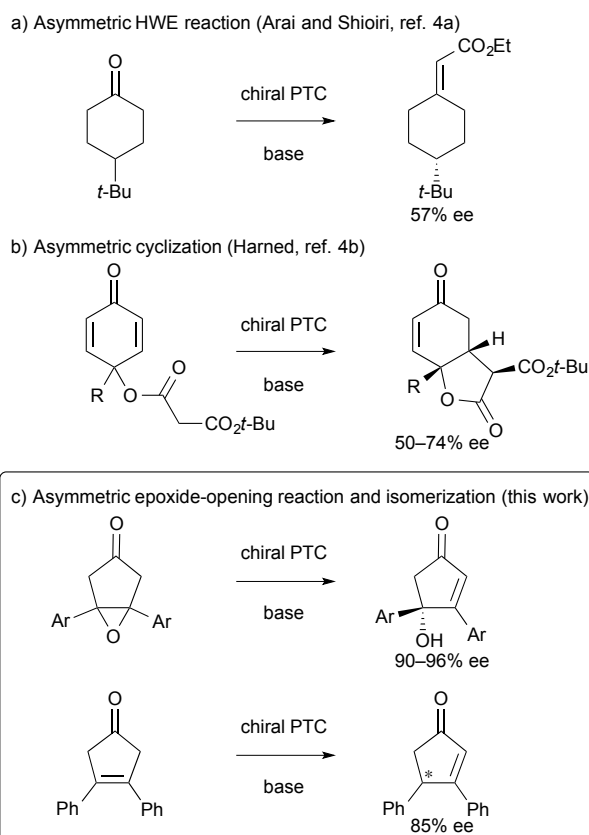
DOI: 10.1039/x0xx00000x

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Although various highly enantioselective transformations have been achieved under phase-transfer conditions, asymmetric desymmetrization of cyclic ketones is still a challenging reaction in the phase-transfer chemistry. In this context, we have developed asymmetric desymmetrization of *meso*-epoxy ketones under phase-transfer conditions. The epoxide-opening reaction was efficiently promoted by chiral bifunctional phase-transfer catalysts to give the corresponding cyclic ketones with high enantioselectivities. Furthermore, this reaction system was applied to asymmetric isomerization of cyclic ketone.

Introduction

Phase-transfer catalysis has long been recognized as a versatile method for organic synthesis in the chemical community,¹ and asymmetric phase-transfer reactions catalyzed by chiral quaternary onium salts constitute a topic of great scientific interest, particularly in the last 20 years. Notable achievements have been made recently that have enabled an array of phase-transfer-catalyzed transformations in a highly enantioselective manner under mild conditions.² However, some reactions, such as the asymmetric desymmetrizations³ of cyclic ketones by using phase-transfer catalysis, remained challenging (Scheme 1). Although several approaches for the asymmetric desymmetrization of cyclohexanones have been reported, the enantioselectivities of the resulting chiral cyclic products were moderate at best (Scheme 1a and b).⁴ In this context, we are interested in the development of more efficient approaches for the asymmetric desymmetrization of cyclic ketones under phase-transfer conditions. Here we wish to report a valuable example on highly enantioselective desymmetrization of cyclopentanones catalyzed by chiral bifunctional quaternary ammonium bromides (Scheme 1c).⁵

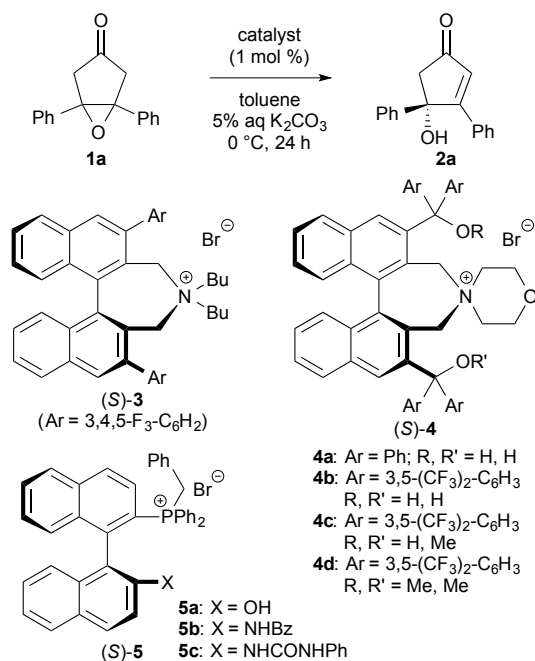


Scheme 1 Phase-transfer-catalyzed asymmetric desymmetrizations of cyclic ketones.

Results and discussion

We first examined the asymmetric desymmetrization of *meso*-epoxy ketone **1a**⁶ promoted by binaphthyl-modified chiral quaternary onium salts **3–5** as promising chiral phase-transfer catalysts (Table 1).² Attempted reaction of **1a** in aqueous K₂CO₃/toluene biphasic solution under the influence of chiral phase-transfer catalyst (*S*)-**3**⁷ at 0 °C for 24 h afforded the corresponding chiral cyclopentenone **2a** in high yield with low enantioselectivity (5% ee, entry 1). To improve the enantioselectivity of this reaction, we next examined the bifunctional catalysts (*S*)-**4a** and **4b**⁸ possessing hydroxy-groups (R, R' = H, H). Although the reaction with phenyl-substituted catalyst (*S*)-**4a** (Ar = Ph) showed poor selectivity (11% ee, entry 2), a dramatic improvement in enantioselectivity was attained by the use of 3,5-bis(trifluoromethyl)phenyl-substituted catalyst (*S*)-**4b** (Ar = 3,5-(CF₃)₂-C₆H₃), and product **2a** was obtained with high enantioselectivity (92% ee, entry 3). It should be noted that the use of mono- and di-hydroxy-protected catalysts (*S*)-**4c** (R, R' = H, Me) and **4d** (R, R' = Me, Me) caused decrease in enantioselectivities (65 and 3% ee, entries 4 and 5). These results clearly indicate that the two hydroxy-groups of catalyst (*S*)-**4b** are essential to obtain high enantioselectivity in this reaction. Although the role of hydroxy-groups in catalyst (*S*)-**4b** is not clear at this stage, one of the hydroxy-group may interact with the enolate anion⁹ derived from epoxy ketone **1**, and the other one may supply a proton in the epoxide-opening step (Fig. 1).⁵ Chiral bifunctional quaternary phosphonium bromides (*S*)-**5a–c**,¹⁰ which were developed recently by our group, did not give satisfactory results for this desymmetrization reaction (entries 6–8).¹¹

Table 1 Screening of chiral phase-transfer catalysts^a



Entry	Catalyst	Yield ^b (%)	ee ^c (%)
1	(<i>S</i>)- 3	99	-5
2	(<i>S</i>)- 4a	98	-11
3	(<i>S</i>)- 4b	99	92
4	(<i>S</i>)- 4c	99	65

5	(<i>S</i>)- 4d	94	3
6	(<i>S</i>)- 5a	94	-14
7	(<i>S</i>)- 5b	87	-8
8	(<i>S</i>)- 5c	98	10

^a Reaction conditions: **1a** (0.050 mmol), 5% aq K₂CO₃ (0.35 mL) in the presence of catalyst (1 mol %) in toluene (0.50 mL) at 0 °C for 24 h. ^b Yield of isolated product. ^c Determined by chiral HPLC analysis.

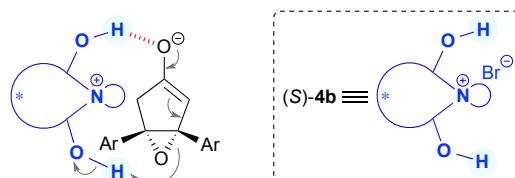
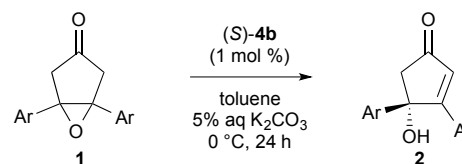


Fig. 1 Proposed working model of bifunctional catalyst (*S*)-**4b**.

With an effective desymmetrization catalyst in hand, we next studied the substrate generality of this reaction using various *meso*-epoxy ketones **1** (Table 2). The introduction of electron-donating and electron-withdrawing substituents on the aryl groups in **1** uniformly gave the products **2b–e** in high yields and enantioselectivities (90–93% ee, entries 1–4). Sterically hindered aryl group-substituted ketones **1f** and **1g** could also be used in this reaction, thus providing the products **2f** and **2g** with high enantioselectivities (90–96% ee, entries 5 and 6). Unfortunately, alkyl-substituted epoxy ketones **1** gave low enantioselectivities.¹²

Table 2 Asymmetric desymmetrization of epoxy ketones **1**^a

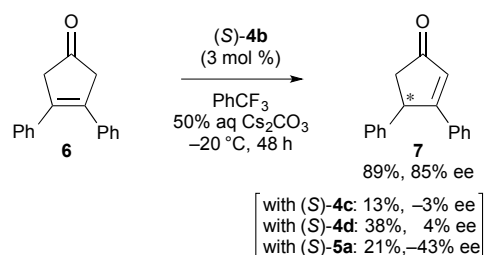


Entry	Ar	Yield ^b (%)	ee ^c (%)
1	4-Me-C ₆ H ₄ (1b)	99 (2b)	90
2	3-Me-C ₆ H ₄ (1c)	95 (2c)	91
3	4-F-C ₆ H ₄ (1d)	96 (2d)	93
4 ^d	4-Cl-C ₆ H ₄ (1e)	93 (2e)	90
5	4-Ph-C ₆ H ₄ (1f)	93 (2f)	96
6	2-naphthyl (1g)	90 (2g)	90

^a Reaction conditions: **1** (0.050 mmol), 5% aq K₂CO₃ (0.35 mL) in the presence of (*S*)-**4b** (1 mol %) in toluene (0.50 mL) at 0 °C for 24 h. ^b Yield of isolated product. ^c Determined by chiral HPLC analysis. ^d Reaction was performed with 3 mol % of (*S*)-**4b**.

To expand the synthetic utility of chiral bifunctional quaternary ammonium bromide (*S*)-**4b** catalyzed asymmetric desymmetrization, we examined the asymmetric isomerization¹³ of cyclic ketone **6** (Scheme 2). Although adjustment of the optimal reaction conditions was required, the reaction in aqueous Cs₂CO₃/trifluoromethylbenzene biphasic solution under the influence of (*S*)-**4b** at -20 °C for 48 h afforded the corresponding chiral cyclopentenone **7** in good

yield and enantioselectivity. The reaction with other catalysts (*S*)-**4c**, **4d**, and **5a** gave product **7** with low to moderate yields and enantioselectivities.



Scheme 2 Asymmetric isomerization of cyclic ketone **6**.

Conclusions

In summary, we have successfully achieved highly enantioselective desymmetrization of cyclic ketones under phase-transfer conditions. The desymmetrization of epoxy ketones **1** and ketone **6** was efficiently promoted by chiral phase-transfer catalysts. The bifunctional design of chiral quaternary ammonium bromide catalysts was essential to achieve high enantioselectivities. Further studies will be directed toward expansion of the reaction scope.

Experimental

General procedure for the catalytic asymmetric desymmetrization of epoxy ketones **1** (Table 2)

To a solution of epoxy ketone **1** (0.050 mmol) and chiral phase-transfer catalyst (*S*)-**4b** (1 mol %, 0.00050 mmol) in toluene (0.50 mL) was added 5% aqueous K_2CO_3 (0.35 mL) at 0 °C. The reaction mixture was vigorously stirred for 24 h at 0 °C. The resulting mixture was quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate as eluent) to give product **2**. The enantiomeric excess of the product **2** was determined by chiral HPLC analysis.

Procedure for the catalytic asymmetric isomerization of ketone **6** (Scheme 2)

To a solution of ketone **6** (0.050 mmol) and chiral phase-transfer catalyst (*S*)-**4b** (3 mol %, 0.0015 mmol) in trifluoromethylbenzene (0.50 mL) was added 50% aqueous Cs_2CO_3 (0.50 mL) at -20 °C. The reaction mixture was vigorously stirred for 48 h at -20 °C. The resulting mixture was quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate 10:1–3:1 as eluent) to give product **7**. The enantiomeric excess of the product **7** was determined by chiral HPLC analysis.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS and MEXT (Japan). S.B.J.K. thanks JSPS for a postdoctoral fellowship.

Notes and references

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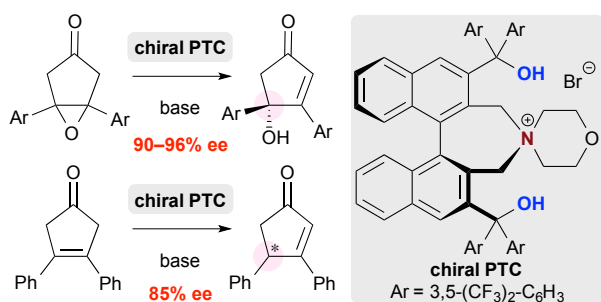
† This paper is dedicated to Professor Ei-ichi Negishi for his 80th Birthday.

‡ Electronic Supplementary Information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/b000000x/

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- 11 The reaction of **1a** in the absence of phase-transfer catalyst gave product **2a** in very low yield (<5%).
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Graphical abstract



Highly enantioselective phase-transfer-catalyzed epoxide-opening reaction and isomerization of cyclopentanones were achieved.