Phase-Transfer Catalysis

Dramatic Rate Enhancement of Asymmetric Phase-Transfer-Catalyzed Alkylations**

*Seiji Shirakawa, Kenichiro Yamamoto, Masanori Kitamura, Takashi Ooi, and Keiji Maruoka**

The synthesis of optically active organic molecules from prochiral substrates by using chiral catalysts under phase-transfer conditions is one of the most exciting topics in practical organic synthesis because of its operational simplicity, mild reaction conditions, and environmental consciousness.[1] Hence, numerous efforts have been devoted to the elaboration of effective chiral quaternary ammonium salts,

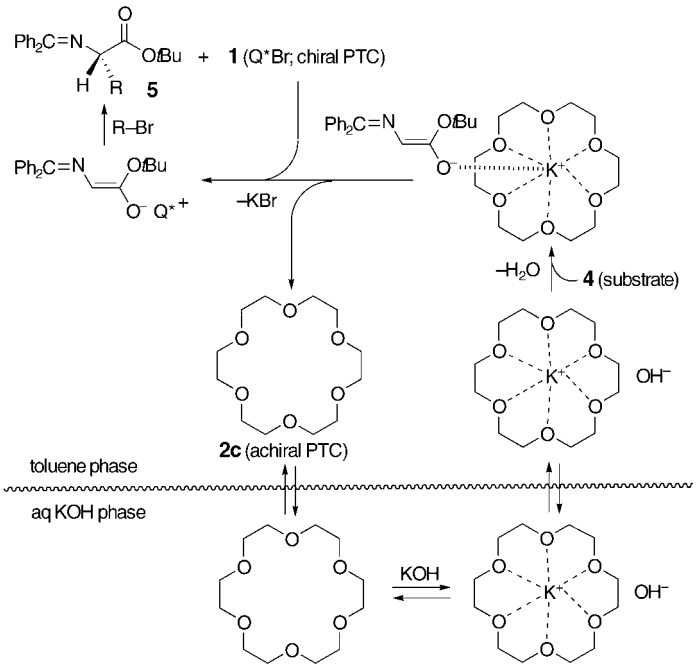
[*] Dr. S. Shirakawa, K. Yamamoto, Dr. M. Kitamura, Dr. T. Ooi, Prof. K. Maruoka
Department of Chemistry
Graduate School of Science
Kyoto University
Sakyo, Kyoto, 606-8502 (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

[**] This work was partially supported by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. S.S. and M.K. are grateful to the Japanese Society for the Promotion of Science for Young Scientists for research fellowships.

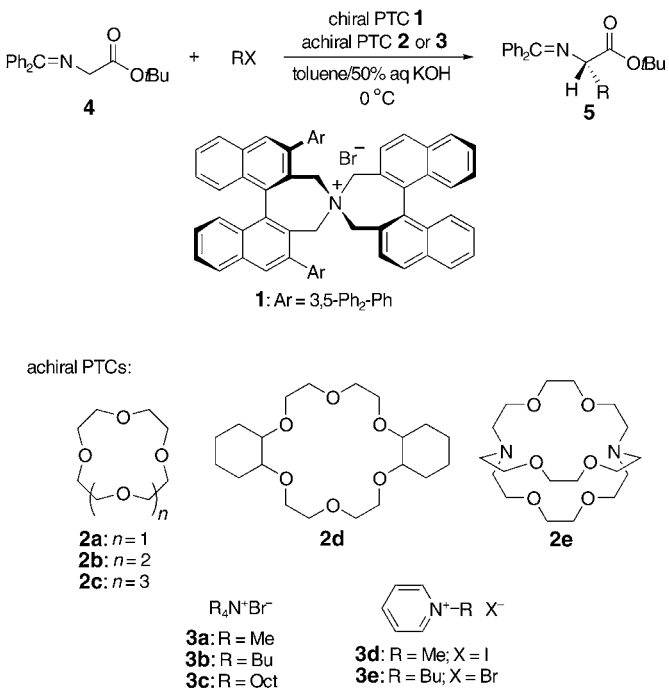
 DOI: 10.1002/ange.200462035

and considerable progress has recently made it possible to successfully perform various asymmetric bond-forming reactions under mild phase-transfer conditions.[2] However, one intrinsic yet critical problem associated with this type of reaction is insufficient catalytic efficiency, which often necessitates the use of a relatively large amount of catalyst (1–10 mol%). As part of our program for the truly practical asymmetric synthesis of α-amino acids utilizing designed C_2-symmetric chiral quaternary ammonium bromide **1**,[3] we required a new approach to fully induce its potential catalytic activity in the asymmetric phase-transfer alkylation of the *tert*-butyl glycinate Schiff base **4** to adequately reduce the catalyst loading. Our strategy to this end is the development of a dual mode of phase-transfer catalysis (Scheme 1).

Owing to the highly lipophilic nature of **1**, the reaction would proceed through the interfacial mechanism initiated by the direct interfacial deprotonation of **4** by an alkaline metal hydroxide such as potassium hydroxide.[4] On the basis of this plausible mechanistic profile, we envisioned that the addition of an achiral cocatalyst which is capable of extracting KOH into the organic phase would substantially accelerate the otherwise slow deprotonation process. This process should result in a significant rate enhancement without diminishing the enantioselectivity if the subsequent enolate exchange with **1** is extremely fast. Verification of this hypothesis is illustrated by the novel binary phase-transfer catalyst systems with the chiral phase-transfer catalyst **1** and the crown ether **2** as an ideal achiral cocatalyst, taking advantage of its well-known ability of extracting metal cations (Scheme 2). This conceptually new approach allowed the reaction to be implemented with as low as 0.05 mol% each of **1** and **2** to give the corresponding alkylation product **5** in excellent yield and enantioselectivity.



Scheme 2. Proposed mechanism of the binary phase-transfer system. Q*Br = chiral PTC **1**.



Scheme 1. Catalytic asymmetric alkylation of **4** with binary phase-transfer system. PTC = phase-transfer catalyst.

First, we investigated the effect of achiral phase-transfer catalysts as additives on the chemical yield and enantioselectivity in the phase-transfer benzylation of benzophenone derivative **4** under the influence of the chiral phase-transfer catalyst **1**. Thus, treatment of the protected glycine derivative **4** with benzyl bromide (1.2 equiv) and 50% aqueous KOH/toluene (volume ratio 2:3) with 0.10 mol% of chiral catalyst **1** at 0°C for 3 h resulted in the formation of phenylalanine derivative **5** (R = CH_2Ph) in only 8% yield with 94% *ee* (entry 1 in Table 1). In marked contrast, however, addition of 18-crown-6 **2c** (0.10 mol%) as the achiral phase-transfer catalyst under similar conditions gave rise to **5** in 98% yield with 98% *ee* (entry 4 in Table 1). Without the chiral phase-transfer catalyst **1**, 18-crown-6 (0.10 mol%) did not show any acceleration effect (entry 5 in Table 1) which suggests a low reactivity of the potassium enolate/18-crown-6 complex. Analogues of 18-crown-6, **2d** and **2e**, showed similar reactivity and enantioselectivity (entries 6 and 7 in Table 1).

Other examples including various achiral phase-transfer catalysts are also included in Table 1. Several characteristic features of the present benzylation follow: 1) 18-Crown-6 and its analogues **2c–e** as additives led to high chemical yields with high enantioselectivities compared to when other crown ethers **2a–b** of smaller cavity sizes were used (entries 2–3 in Table 1).[5] 2) Tetrabutyl- and tetraoctylammonium bromide **3b–c** as achiral phase-transfer catalysts gave relatively high yields with high enantioselectivities (entries 9 and 11 in Table 1). As tetrabutylammonium bromide itself gave a similarly high chemical yield (84%) in the phase-transfer-catalyzed benzylation of **4** (entry 10 in Table 1), the chiral

Table 1: Catalytic enantioselective phase-transfer benzylation of **4** with chiral and achiral phase-transfer catalysts (PTCs).[a]

Entry	Chiral PTC	Achiral PTC	Yield[b] [%]	*ee*[c] [%] (config)[d]
1	**1**	none	8	94 (*S*)
2	**1**	**2a**	16	96 (*S*)
3	**1**	**2b**	29	96 (*S*)
4	**1**	**2c**	98	98 (*S*)
5	none	**2c**	3	
6	**1**	**2d**	92	97 (*S*)
7	**1**	**2e**	96	96 (*S*)
8	**1**	**3a**	17	97 (*S*)
9	**1**	**3b**	80	96 (*S*)
10	none	**3b**	84	
11	**1**	**3c**	90	96 (*S*)
12	**1**	**3d**	9	91 (*S*)
13	**1**	**3e**	13	91 (*S*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of $PhCH_2Br$ in the presence of 0.1 mol% of **1** and 0.1 mol% of **2** or **3** in 50% aq KOH/toluene (v/v 2:3) at 0°C for 3 h under argon atmosphere. [b] Isolated yield. [c] Enatiopurity of **5** was determined by HPLC analysis of the alkylated imine by using a chiral column (DAICEL Chiralcel OD or OD-H) with hexane/propan-2-ol (v/v 100:1) as solvent. [d] The absolute configuration of **5** was determined by comparison of the HPLC retention time with that of the authentic sample independently synthesized by the reported procedure.[3a]

Table 2: Catalytic enantioselective phase-transfer alkylation of **4** with chiral PTC **1** and achiral 18-crown-6 **2c**.[a]

Entry	RX	**1** [mol%]	**2c** [mol%]	*t* [h]	Yield[b] [%]	*ee* [%][c] (config)[d]
1	$PhCH_2Br$	0.1	none	3	8	94 (*S*)
2		0.1	0.1	3	98	98 (*S*)
3		0.05	none	3	4	92 (*S*)
4		0.05	0.05	3	90	98 (*S*)
5		0.05	none	5	2	93 (*S*)
6		0.05	0.05	5	97	91 (*S*)
7		0.2	0.1	1.5	93	91 (*S*)
8		0.1	none	2	13	86 (*S*)
9		0.1	0.1	2	87	85 (*S*)
10	EtI	1.0	none	5	9	96 (*S*)[e]
11		1.0	0.5	5	70	95 (*S*)[e]
12		0.5	0.5	20	63	94 (*S*)[e]
13		0.5	0.5	3	86	91 (*S*)[e,f]

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of RX in 50% aq KOH/toluene (v/v 2:3) under the given reaction conditions under argon. [b] Isolated yield. [c] The enantiopurity of **5** was determined by HPLC analysis of the alkylated imine by using a chiral column (DAICEL Chiralcel OD or OD-H) with hexane/propan-2-ol as solvent. [d] The absolute configuration of **5** was determined by comparison of the HPLC retention time with that of the authentic sample independently synthesized by the reported procedure.[3a] [e] 5.0 equiv of EtI employed. [f] Reaction under ultrasonic irradiation.

catalyst **1** must induce extremely facile enolate exchange with tetrabutylammonium enolate.[6] However, polar tetramethylammonium bromide **3a** and pyridinium salts **3d–e** were not effective for the system (entries 8, 12, and 13 in Table 1). 3) The enantioselectivity of **5** was lowered by increasing or decreasing the amount of achiral catalyst **2** or **3**.

We further found that the amounts of chiral catalyst **1** and 18-crown-6 **2c** as achiral catalyst could both be reduced to 0.05 mol% without losses in yields or enantioselectivity of the products as shown in Table 2 (entry 4). The present catalytic system is also applicable to other alkyl halides, and some selected results are summarized in Table 2. By the addition of a catalytic amount of 18-crown-6 **2c**, the reaction rate is dramatically accelerated (6.7–49-times faster than in the absence of **2c** under the same reaction conditions). The satisfactory yield and enantioselectivity of product **5** results by the use of only 0.05–0.10 mol% of chiral catalyst **1** and **2c**, except when less-reactive alkyl halides such as EtI are used. Combination of ultrasonic irradiation with this catalytic system further accelerated the rate of the alkylation (entry 13 in Table 2).[7]

In conclusion, we have demonstrated a dramatic rate enhancement by combination of an achiral phase-transfer catalyst with a chiral phase-transfer catalyst. The present catalyst system provides powerful options in asymmetric reactions for practical organic synthesis.

Experimental Section

General procedure for catalytic enantioselective alkylation of **4** with catalyst **1** and **2c**: Benzyl bromide (0.36 mmol) was added dropwise to a mixture of **4** (0.30 mmol), chiral catalyst **1** (0.15 μmol, 0.05 mol%), and 18-crown-6 **2c** (0.15 μmol, 0.05 mol%) in toluene (3.0 mL) and 50% aqueous KOH solution (2.0 mL) at 0°C. The reaction mixture was then stirred vigorously at 0°C for 3 h and then poured into water and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (1:10 ether/hexane) gave the corresponding benzylation product **5** (104 mg, 0.27 mmol, 90% yield, 98% *ee*). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD, 100:1 hexane/propan-2-ol, flow rate: 0.5 mL min^{-1}, retention times: 14.8 min (*R*) and 28.2 min (*S*)). The absolute configuration was determined by comparison of the HPLC retention time with that of the authentic sample independently synthesized by the reported procedure.[3a]

Received: September 18, 2004
Published online: December 13, 2004

Keywords: alkylation · amino acids · crown compounds · enantioselectivity · phase-transfer catalysis

[1] Reviews: a) M. J. O'Donnell in *Catalytic Asymmetric Synthesis, 2nd ed.*, (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, chap. 10; b) T. Shioiri in *Handbook of Phase-Transfer Catalysis* (Eds.: Y. Sasson, R. Neumann), Blackie Academic & Professional, London, **1997**, chap. 14; c) M. J. O'Donnell in *Phases—The Sachem Phase-Transfer Catalysis Review* **1998**, *4*, 5; M. J. O'Donnell in *Phases—The Sachem Phase-Transfer Catalysis Review* **1999**, *5*, 5; d) T. Shioiri, S. Arai in *Stimulating Concepts in Chemistry* (Eds.: F. Vogtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**, p. 123; e) M. J. O'Donnell, *Aldrichimica Acta* **2001**, *34*, 3; f) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013; g) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506; h) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518; i) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526.

[2] Representative examples: a) M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353; b) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414; c) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595; d) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 3329; e) H.-G. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-K. Park, Y.-J. Lee, M.-J. Kim, S.-S. Jew, *Angew. Chem.* **2002**, *114*, 3162; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036; f) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem.* **2002**, *114*, 2956; *Angew. Chem. Int. Ed.* **2002**, *41*, 2832; g) T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Oshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 9539; h) S. Arai, R. Tsuji, A. Nisida, *Tetrahedron Lett.* **2002**, *43*, 9535; i) S.-S. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park, H.-G. Park, *Org. Lett.* **2002**, *4*, 4245; j) N. Mase, T. Ohno, N. Hoshikawa, K. Ohishi, H. Morimoto, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2003**, *44*, 4073; k) B. Lygo, B. Allbutt, S. R. James, *Tetrahedron Lett.* **2003**, *44*, 5629.

[3] a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519; b) T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228; c) T. Ooi, M. Takeuchi, D. Ohara, K. Maruoka, *Synlett* **2001**, 1185; d) T. Ooi, M. Takeuchi, K. Maruoka, *Synthesis* **2001**, 1716; e) K. Maruoka, *J. Fluorine Chem.* **2001**, *112*, 95; f) T. Ooi, Y. Uematsu, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 1621; *Angew. Chem. Int. Ed.* **2002**, *41*, 1551; g) T. Ooi, Y. Uematsu, K. Maruoka. *Adv. Synth. Catal.* **2002**, *344*, 288; h) T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 4724; *Angew. Chem. Int. Ed.* **2002**, *41*, 4542; i) T. Ooi, E. Tayama, K. Maruoka, *Angew. Chem.* **2003**, *115*, 599; *Angew. Chem. Int. Ed.* **2003**, *42*, 579; j) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 5139; k) T. Ooi, M. Kameda, M. Taniguchi, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 9685; l) K. Maruoka, E. Tayama, T. Ooi, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5824.

[4] For a discussion of mechanisms in normal chiral phase-transfer catalyst systems, see: a) K. B. Lipkowitz, M. W. Cavanaugh, B. Baker, M. J. O'Donnell, *J. Org. Chem.* **1991**, *56*, 5181; b) M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507.

[5] 18-Crown-6 derivatives are known to make the most-stable host–guest complex with potassium ions and hence they accelerate the phase-transfer reaction with potassium hydroxide compared with other crown ethers that have a different ring size. For reviews, see: a) E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis, 3rd ed.*, VCH, Weinheim, **1993**; b) C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, New York, **1994**; c) *Handbook of Phase-Transfer Catalysis* (Eds.: Y. Sasson, R. Neumann), Blackie Academic & Professional, London, **1997**; d) *Phase-Transfer Catalysis, ACS Symposium Series 659* (Ed.: M. E. Halpern), American Chemical Society, Washington DC, **1997**.

[6] A similar acceleration effect with some loss of enantioselectivity was observed by adding tetrahexylammonium bromide (1 mol%) in the phase-transfer catalyzed asymmetric cyclopropanation reaction. See: S. Arai, K. Nakayama, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 4215.

[7] T. Ooi, E. Tayama, K. Doda, M. Takeuchi, K. Maruoka, *Synlett* **2002**, 1500.

