# A Base-Free Neutral Phase-Transfer Reaction System

### Seiji Shirakawa, Lijia Wang, Rongjun He, Satoru Arimitsu, and Keiji Maruoka\*<sup>[a]</sup>

**Abstract:** Although phase-transfer reactions catalyzed by using quaternary ammonium salts are generally believed to require base additives, we discovered that, even without any base additives, conjugate additions of 3-substituted oxindoles to nitroolefins proceeded smoothly in the presence of lipophilic quaternary ammonium bromide under water–organic biphasic conditions. The mechanism of this novel base-free neutral phase-transfer reaction system is investigated and the assumed catalytic cycle is presented together with interesting effects of water and lipophilicity of the phase-transfer catalyst. The base-free neutral phase-transfer reaction system can be applied to highly

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enantioselective conjugate addition and aldol reactions under the influence of chiral bifunctional ammonium bromides as key catalysts. The structure of the chiral ammonium enolate intermediate is discussed based on the single-crystal X-ray structures of relevant ammonium salts and the importance of bifunctional design of catalyst is clearly explained in the model of intermediate.

### Introduction

Phase-transfer catalysis has long been recognized as a versatile methodology for organic synthesis that features simple experimental operation and mild reaction conditions.<sup>[1]</sup> In particular, during the last two decades, asymmetric phasetransfer catalysis based on the use of chiral quaternary ammonium salts has become a topic of great scientific interest.<sup>[2]</sup> Many studies have been undertaken to understand the reaction mechanism of these reactions and it was believed for a long period that base additives, such as alkali metals (Na, K, Cs) hydroxide, or carbonate, were essential to promote the phase-transfer reactions.<sup>[1,2]</sup> Although phase-transfer catalysis has made a significant contribution to practical organic synthesis, the drawback of this method from the point of view of atom economy<sup>[3]</sup> is that it often needs more than stoichiometric amounts of base additives. As a solution to this problem, we have recently developed a hitherto unknown base-free neutral phase-transfer reaction system in asymmetric conjugate addition reactions (Scheme 1).<sup>[4]</sup> The reaction was efficiently promoted by a chiral bifunctional phase-transfer catalyst of type (S)-1 under neutral conditions with high enantioselectivity. Surprisingly, however, tet-

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Scheme 1. Base-free neutral phase-transfer reaction.

rabutylammonium bromide as a representative achiral phase-transfer catalyst was less effective for the reaction under the same base-free reaction conditions (Scheme 1). Although some interesting observations have been reported in our preliminary study on the novel base-free reaction system,<sup>[4a]</sup> the mechanism for this very attractive and interesting reaction system is totally unclear. To obtain mechanistic insight into the base-free neutral phase-transfer reaction system, we are interested in the effect of water and catalyst structure on the efficiency of the reaction. Herein, we describe the full details of this base-free reaction system, including mechanistic insight into the interesting effects of water and lipophilicity of the catalyst.

### **Results and Discussion**

#### Effect of Lipophilicity of the Phase-Transfer Catalyst

We first investigated the effect of the alkyl chain length in tetraalkylammonium bromides in the conjugate addition of

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Table 1. Effect of alkyl chain-length of tetraalkylammonium bromides.<sup>[a]</sup>

	Ph NO2 Boc + Ph NO2	$\begin{array}{c} R_4 N^+ Br^- \qquad Ph \\ \hline (5 \text{ mol } \%) \\ \hline \\ H_2 O / toluene \\ (ratio = 2:1) \\ 0 \ ^\circ C, 2 \ h \end{array}$	Ph NO <sub>2</sub> N Boc <b>2a</b>
Entry	$R_4N^+Br^-$	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>
1	none	$\approx 0$	_
2	$Bu_4N^+Br^-$	trace	-
3	$Pen_4N^+Br^-$	trace	-
4	$Hex_4N^+Br^-$	84 (33) <sup>[d]</sup>	79:21 (75:25) <sup>[d</sup>
5	$Oct_4N^+Br^-$	>95 (>95) <sup>[d]</sup>	76:24 (80:20) <sup>[d</sup>
6	$\text{Dec}_4\text{N}^+\text{Br}^-$	>95 (>95) <sup>[d]</sup>	81:19 (82:18) <sup>[d</sup>
7	$(C_{12}H_{25})_4N^+Br^-$	>95 (>95) <sup>[d]</sup>	78:22 (81:19) <sup>[d</sup>
8	$(C_{16}H_{33})_4N^+Br^-$	49	81:19

[a] Reaction conditions: 3-phenyloxindole (0.10 mmol) and  $\beta$ -nitrostyrene (0.12 mmol) in the presence of tetraalkylammonium bromide (5 mol%) in H<sub>2</sub>O (2.0 mL)/toluene (1.0 mL). [b] Yield was determined by using <sup>1</sup>H NMR spectroscopy analysis based on 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by using <sup>1</sup>H NMR spectroscopy analysis. [d] Data in parenthesis were obtained by using 1 mol% of tetraalkylammonium bromide.

3-phenyloxindole to  $\beta$ -nitrostyrene<sup>[5]</sup> under base-free neutral phase-transfer conditions (Table 1). In the absence of phase-transfer catalyst, the reaction did not occur under the neutral conditions (Table 1, entry 1). Tetrabutyl- and tetrapenty-lammonium bromides were examined as phase-transfer catalysts, and the reaction proceeded very sluggishly (Table 1, entries 2 and 3). On the other hand, tetrahexylammonium bromide promoted the reaction moderately and gave conjugate adduct **2a** in 84% yield at a 5 mol% catalyst loading (Table 1, entry 4) and in 33% yield at a 1 mol% catalyst loading (Table 1, entry 4 in parenthesis). Tetraoctyl-, tetra-(decyl)-, and tetradodecylammonium bromides worked as more efficient phase-transfer catalysts for this neutral reac-

### Abstract in Japanese:

第四級アンモニウム塩を触媒とした相間移動反応において、塩基の添加は反応を促進する上で必要不可欠であると長年考えられてきた。ところが我々は、塩基の添加を一切必要としない、中性条件下で進行する新たな相間移動反応系を見出す事に成功した。本中性反応系の反応機構に関する知見を得るため、触媒の脂溶性および反応溶媒としての水の効果を詳細に検討し、これらの結果を基に反応機構の考察を行った。また、本中性反応系を、キラル第四級アンモニウム塩を触媒として用いた不斉共役付加反応およびアルドール反応に適用し、高立体選択的に生成物を得る事に成功した。

tion system and the reactions using these catalysts gave product 2a in almost quantitative yields even at  $1 \mod \%$ catalyst loading (Table 1, entries 5–7). These results clearly indicate that high lipophilicity of the tetraalkylammonium salt is important to promote the reaction efficiently under neutral phase-transfer conditions. Tetraalkylammonium bromide with longer alkyl chains, such as tetrahexadecylammonium bromide, showed a decrease in catalytic efficiency that is probably due to the steric bulkiness of the catalyst (Table 1, entry 8).

Several chiral phase-transfer catalysts were employed in the conjugate addition under base-free neutral phase-transfer conditions (Scheme 2). Although binaphthyl-modified



Scheme 2. Effect of chiral phase-transfer catalysts.

lipophilic catalysts (S)-1a, (S)-1b, and (S)- $3^{[6]}$  promote the reaction efficiently, N-benzylcinchonidinium bromide  $4^{[2,7]}$  which is one of the most representative chiral phase-transfer catalysts, is less effective under the neutral conditions likely due to a lack of lipophilicity of the catalyst. It should be noted that hydroxy-protected catalyst (S)-1b and catalyst (S)-3 gave the product with only low enantioselectivities. These results clearly indicate that the bifunctional design of catalyst (S)-1a is essential to obtain high enantioselectivity in this reaction.<sup>[8,9]</sup>

### Effect of Water

With important information about an effective catalyst in hand, the solvent effect in this base-free neutral phase-transfer reaction system was examined (Table 2). Tetra-(decyl)ammonium bromide and chiral phase-transfer catalyst (S)-**1a** were used in the reaction with various solvent systems. The reactions in a biphasic solvent system (H<sub>2</sub>O/toluene 2:1) were efficiently promoted by tetra-

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Table 2. Effect of solvents.[a]



Entry	Catalyst	Solvent (ratio)	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup> (ee [%]) <sup>[d]</sup>
1	Dec <sub>4</sub> N+Br <sup>-</sup>	H <sub>2</sub> O/toluene (2:1)	>95	82:18
2	(S)- <b>1 a</b>	$H_2O$ /toluene (2:1)	96 <sup>[e]</sup>	91:9 (90)
3	Dec <sub>4</sub> N <sup>+</sup> Br <sup>-</sup>	$H_2O$ /toluene (10:1)	>95	79:21
4	(S)- <b>1 a</b>	$H_2O$ /toluene (10:1)	93 <sup>[e]</sup>	93:7 (90)
5	(S)- <b>1</b> a	H <sub>2</sub> O/anisole (10:1)	98 <sup>[e]</sup>	94:6 (92)
6	Dec <sub>4</sub> N+Br <sup>-</sup>	$H_2O$ /toluene (100:1)	>95	75:25
7	Dec <sub>4</sub> N <sup>+</sup> Br <sup>-</sup>	$H_2O$ /toluene (1:10)	39	78:22
8	$Dec_4N^+Br^-$	toluene	trace	-
9	(S)- <b>1 a</b>	toluene	trace	-
10	Dec <sub>4</sub> N <sup>+</sup> Br <sup>-</sup>	THF	trace	-
11	(S)- <b>1 a</b>	THF	trace	-
12	Dec <sub>4</sub> N <sup>+</sup> Br <sup>-</sup>	EtOH	trace	-
13	(S)- <b>1 a</b>	EtOH	trace	-

[a] Reaction conditions: 3-phenyloxindole (0.10 mmol) and β-nitrostyrene (0.12 mmol) in the presence of catalyst (1 mol%). [b] Yield was determined by using <sup>1</sup>H NMR spectroscopy analysis based on 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by using <sup>1</sup>H NMR spectroscopy or HPLC analysis. [d] Enantiomeric excess of the major diastereomer was determined by using chiral HPLC analysis. [e] Yield of isolated product.

(decyl)ammonium bromide and (S)-1a (Table 2, entries 1 and 2). Even in the water-rich solvent system (H<sub>2</sub>O/toluene 10:1-100:1), which might be favorable from an environmental point of view,<sup>[10]</sup> tetra(decyl)ammonium bromide and (S)-1a promoted the reaction efficiently to give conjugate adduct 2a in high yields (Table 2, entries 3-6). The reaction with (S)-1a under water-rich conditions gave high diastereoand enantioselectivity (90% ee; Table 2, entry 4), whereas carrying out the reaction in H<sub>2</sub>O/anisole (10:1) slightly improved the enantioselectivity (92% ee; Table 2, entry 5). Reduction of the amount of water (H<sub>2</sub>O/toluene 1:10) caused a decrease in of the reaction rate (Table 2, entry 7). The homogeneous reactions in toluene in the absence of water were also examined and very interestingly the reactions were completely shut off (Table 2, entries 8 and 9). Furthermore, homogeneous reactions in polar and protic solvents, such as THF and ethanol, were very sluggish (Table 2, entries 10-13). These results indicate that water-organic biphasic solvent systems, such as H2O/toluene, are essential for efficient promotion of the reaction under base-free neutral conditions.

The effect the pH of the aqueous solution in the enantioselective conjugate addition catalyzed by (S)-1a was carefully examined (Table 3). The reaction was efficiently promoted in buffer solutions at a nearly neutral pH range (pH 6.8-7.2; Table 3, entries 1-3). Even in slightly acidic buffer solution (pH 6.0) the reaction was promoted efficiently with high enantioselectivity (Table 3, entry 4). However, the reaction was completely shut off by further lowering pH (pH 5.0; Table 3, entry 5).

Table 3. Effect of pH value of the aqueous solution.<sup>[a]</sup>



[a] Reaction conditions: 3-phenyloxindole (0.05 mmol) and β-nitrostyrene (0.06 mmol) in the presence of (S)-1a (1 mol %) in H<sub>2</sub>O buffer (2.0 mL)/toluene (1.0 mL). [b] Yield of isolated product. [c] Determined by using HPLC analysis. [d] Enantiomeric excess of the major diastereomer was determined by using chiral HPLC analysis.

#### **Reaction Mechanism**

To obtain further information about the base-free neutral phase-transfer reaction system, deuteration experiments of 3-phenyloxindole were performed (Scheme 3). To promote this neutral reaction, ammonium enolate 6 should be formed as an intermediate under base-free phase-transfer conditions. Indeed, treatment of 3-phenyloxindole with (S)-**1a** or tetra(decyl)ammonium bromide in  $D_2O$ /toluene (2:1) at 5°C for 2 h gave rise to deuterated 3-phenyloxindole 5 in yields of 89 and 55%, respectively, which indicates the formation of ammonium enolate 6 with (S)-1a or tetra-(decyl)ammonium bromide in the biphasic solvent system. However, in the presence of tetrabutylammonium bromide or in the absence of catalyst, almost no deuteration product 5 was formed. These results completely agree with the results of conjugate addition in Table 1.

Based on these interesting observations for the neutral phase-transfer reaction, the assumed catalytic cycle of the present reaction system is proposed as shown in Scheme 4. For the reaction to proceed, the combination of the H<sub>2</sub>O/toluene biphasic solvent system with lipophilic phase-transfer catalyst was indispensable. When the reaction is carried out under homogeneous conditions in toluene only, the reversible reaction between 3-phenyloxindole and ammonium bromide A does not favor the formation of ammonium enolate **B** due to the facile protonation of ammonium enolate **B** with in situ-generated HBr (Schemes 4 and 5). However,



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Scheme 3. Deuteration experiments

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Scheme 4. Assumed catalytic cycle.



Scheme 5. Formation of ammonium enolate.

when the reaction is performed in the H<sub>2</sub>O/toluene biphasic solvent system, hydrophilic HBr moves smoothly into the water phase, whereas lipophilic ammonium enolate B stays in the toluene phase. Consequently, protonation by contact of **B** and HBr was suppressed and the formation of ammonium enolate **B** is promoted (Schemes 4 and 5). This allows ammonium enolate **B** to react with  $\beta$ -nitrostyrene in the toluene phase to give conjugate adduct C (Scheme 4).

This explanation for the formation of ammonium enolate with release of HBr in the H<sub>2</sub>O/toluene biphasic system is strongly supported by the experimental and theoretical studies of the formation of ammonium phenoxides under neutral conditions by Ito, Odashima, Umezawa et al.<sup>[11]</sup> They found that lipophilic tetraalkylammonium chlorides, such as tridodecylmethylammonium chloride, react with phenols that have various substituents to form ammonium phenoxides under aqueous/organic biphasic conditions (Scheme 6). The formation of ammonium phenoxide with the release of HCl to the aqueous phase under neutral biphasic conditions was proved by analytical methods. In this study, various phenols, such as phenol and 4-nitrophenol, were examined for the formation of ammonium phenoxides and it was found that phenols with various  $pK_a$  values ( $pK_a$  in DMSO: phenol = 18.0, 4-nitrophenol = 10.8)<sup>[12]</sup> could form ammonium phenoxides. Although the  $pK_a$  value of *N-tert*-butoxycarbonyl-3phenyloxindole is unknown, it is expected to be lower than





that of phenol, based on the  $pK_a$  value of N-acetyloxindole  $(pK_a \text{ in DMSO} = 13.5)$ .<sup>[13]</sup> These results suggest that lipophilic tetraalkylammonium bromide can react with 3-phenyloxindole to form ammonium enolate with release of HBr to the aqueous phase under the neutral biphasic conditions, as shown in Schemes 4 and 5.<sup>[14]</sup>

This hypothesis is further supported by the conjugate addition of thiophenol (p $K_a$  in DMSO = 10.3)<sup>[15]</sup> to  $\beta$ -nitrostyrene under neutral phase-transfer conditions (Scheme 7). Al-



Scheme 7. Conjugate addition of thiophenol.

though the reactions with phenols did not give the conjugate adducts, probably due to the lack of nucleophilicity of ammonium phenoxides, the reaction with thiophenol as a related compound of phenols was efficiently promoted by tetra-(decyl)ammonium bromide in water-rich biphasic solvent.

We also examined the effect of the counterion of catalyst (S)-1a in an enantioselective conjugate addition under neutral conditions in a water-rich biphasic solvent (Scheme 8). The reactions with ammonium trifluoromethanesulfonate (X = OTf) and tetrafluoroborate  $(X = BF_4)$  analogues of (S)-1a gave product 2a in similar yields and stereoselectivities to ammonium bromide (S)-1a (X=Br). The reaction with



Scheme 8. Effect of counterion of catalyst (S)-1a.

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ammonium hydroxide (X=OH), which has a basic property and could easily deprotonate an acidic hydrogen,<sup>[1]</sup> also gave similar results. These results suggest that reactions with catalysts that have different counterions proceed through the same intermediate to produce conjugate adduct **2a** in high enantioselectivity. However, exchanging the counterion for bulky hydrophobic anions, such as 3,5-bis(trifluoromethyl)phenyltrifluoroborate (X=BF<sub>3</sub>Ar) and tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (X=BAr<sub>4</sub>), caused a significant decrease in reactivity. These results also support the proposed reaction mechanism, which requires a hydrophilic HX to move to the aqueous phase for efficient formation of an ammonium enolate (Schemes 4 and 5).

### Catalytic Enantioselective Conjugate Additions of 3-Substituted Oxindoles to Nitroolefins

With the assumed reaction mechanism in hand, we further studied the generality of the asymmetric conjugate addition of various 3-substituted oxindoles to  $\beta$ -nitrostyrene under neutral conditions in water-rich biphasic solvent in the presence of chiral bifunctional phase-transfer catalyst (*S*)-1a (Scheme 9). The introduction of electron-donating and electron-withdrawing substituents on both the oxindole core and the 3-aryl group uniformly gave good diastereoselectivities with high enantioselectivities (85–95% *ee*, 2a–j). 3-Hetero-aryl-substituted oxindole could also be applied to this reaction and gave conjugate adduct 2k with high enantioselectivity (90% *ee*). Unfortunately, 3-alkyloxindoles, such as 3-methyloxindole, gave low reactivity and selectivity (21).

Various types of nitroolefins were found to be employable for the reaction (Table 4). The reactions of nitroolefins that have aromatic, heteroaromatic, and alkyl groups gave corresponding products 2 in good-to-high enantioselectivities. In

Table 4. Enantioselective conjugate additions of 3-phenyloxindole to nitroolefins.  $^{\left[ a\right] }$ 



Entry	R	Yield [%] <sup>[b]</sup>	d.r. <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	o-MeO-C <sub>6</sub> H <sub>4</sub>	91 ( <b>2m</b> )	65:35	91
2 <sup>[e]</sup>	<i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub>	93 ( <b>2n</b> )	92:8	85
3 <sup>[e]</sup>	o-F-C <sub>6</sub> H <sub>4</sub>	99 ( <b>2</b> o)	84:16	94
4 <sup>[e]</sup>	2-thienyl	93 ( <b>2p</b> )	90:10	90
5	2-furyl	91 ( <b>2q</b> )	75:25	80
6 <sup>[f]</sup>	PhCH <sub>2</sub> CH <sub>2</sub>	95 ( <b>2r</b> )	13:87	91
7 <sup>[f]</sup>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	98 ( <b>2s</b> )	45:55	94/84
8 <sup>[g]</sup>	Н	81 (2t)	_	51

[a] Reaction conditions: 3-phenyloxindole (0.05 mmol) and  $\beta$ -nitrostyrene (0.06 mmol) in the presence of (S)-**1a** (1 mol %) in H<sub>2</sub>O (2.0 mL)/toluene (0.2 mL). [b] Yield of isolated products. [c] Determined by using HPLC analysis. [d] Enantiomeric excess of the major diastereomer was determined by using chiral HPLC analysis. [e] Reaction was performed in H<sub>2</sub>O (2.0 mL)/anisole (0.2 mL). [f] Reaction was performed for 12 h. [g] Nitroethene was added over 7 h.



Scheme 9. Enantioselective conjugate addition of 3-substituted oxindoles to  $\beta$ -nitrostyrene.

the case of 1-nitro-1-pentene, high enantioselectivities were observed for both diastereomers in spite of the low diastereoselectivity (Table 4, entry 7). The reaction with nitroe-thene gave product 2t in moderate enantioselectivity (Table 4, entry 8).

To obtain insight into the enantiofacial recognition of 3substituted oxindoles by bifunctional catalysts of type (S)-1, X-ray diffraction analysis of (S)-1c (Ar = Ph) was performed (Figure 1, left).<sup>[16]</sup> Importantly, the hydrogen-bonding interaction between the hydroxy group and bromide anion is clearly observed in the crystal structure of (S)-1c. Based on the X-ray structure of (S)-1c, a plausible structure for the ammonium enolate intermediate is proposed to account for the absolute configuration of conjugate adducts 2 (Figure 1, right). In the generation of ammonium enolate derived from 3-aryloxindole and catalyst (S)-1a under neutral conditions, the enolate anion could be stabilized by both ionic interaction with the ammonium cation and hydrogen bonding between the enolate oxygen and one hydroxy group in catalyst (S)-1a. The binaphthyl unit of catalyst (S)-1a completely

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Figure 1. X-ray crystal structure of (S)-1c and plausible structure of ammonium enolate intermediate. Ellipsoids were drawn at the 50% probability level.

shields the lower face of the enolate, which allows the nitroolefin to approach from the upper face and leads to conjugate adduct 2 with the observed absolute configuration.<sup>[17]</sup>

### Other Asymmetric Reactions under Base-Free Neutral Phase-Transfer Conditions

This attractive base-free neutral phase-transfer reaction system was applied to other asymmetric conjugate additions by using carbon and heteroatom nucleophiles (Scheme 10). Highly enantioselective conjugate additions<sup>[18]</sup> were achieved by using bifunctional phase-transfer catalysts of type



Scheme 10. Asymmetric reactions under base-free neutral phase-transfer conditions.

(*S*)-**1**.<sup>[4b,c]</sup> Furthermore, the neutral reaction system could be applied to the hitherto difficult direct aldol reaction<sup>[19]</sup> of  $\alpha$ -substituted nitroacetates with aqueous formaldehyde to obtain  $\alpha$ -alkyl serine derivatives in high enantioselectivity.<sup>[4d,20]</sup> It should be noted that these reactions do not work well under ordinary phase-transfer conditions with aqueous base solutions, such as aqueous KOH, K<sub>2</sub>CO<sub>3</sub>, and PhCO<sub>2</sub>K, and under homogeneous reaction conditions without aqueous solution.<sup>[4b-d]</sup> Thus, these highly enantioselective reactions were only achieved when the reaction was performed under base-free neutral phase-transfer conditions.

Herein, we attempted X-ray diffraction analysis of ammonium nitronate and ammonium amide to gain insight into the structure of intermediate and succeeded in obtaining single-crystal X-ray structures of ammonium nitronate (S)-**1f** and ammonium amide (S)-**1g** (Figure 2).<sup>[21]</sup> Very impor-



Figure 2. X-ray crystal structures of ammonium nitronate (S)-**1 f** and ammonium amide (S)-**1 g**.

tantly, the hydrogen-bonding interactions between the hydroxy group in the binaphthyl unit and the anionic oxygen are clearly observed in the crystal structures. These X-ray structures of (S)-**1f** and (S)-**1g** strongly support the plausible structure of the ammonium enolate intermediate in Figure 1.

### Conclusion

In summary, a mechanism for the novel base-free neutral phase-transfer reaction system based on some interesting observations was presented in this study. The aqueous–organic biphasic reaction system with lipophilic tetraalkylammonium bromide was essential to promote neutral phasetransfer reactions. The base-free neutral phase-transfer reaction system could be applied to several asymmetric reactions under the influence of chiral bifunctional tetraalkylammoni-

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um bromides. The role of hydroxy groups in the bifunctional catalysts was clearly shown based on the single-crystal X-ray structures of ammonium salts. Further application of the base-free neutral phase-transfer reaction system to other asymmetric reactions by using a chiral bifunctional ammonium salt is currently underway in our group.

### **Experimental Section**

Typical Procedure for Enantioselective Conjugate Addition of 3-Aryloxindoles to Nitroolefins

Water (2.0 mL) was added to a mixture of 3-phenyloxindole (0.050 mmol), trans- $\beta$ -nitrostyrene (0.060 mmol), and (S)-1a (0.00050 mmol, 1 mol%) in toluene (0.20 mL) at 0°C, and the mixture was vigorously stirred at 0°C for 2 h. The resulting mixture was diluted with water (3.0 mL) and extracted with Et<sub>2</sub>O (5.0 mL×3). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Purification of the residue by using column chromatography on silica gel (neutral) with hexane/EtOAc (10:1) as the eluent gave 2a. The diastereomeric and enantiomeric ratios of the product were determined by using chiral HPLC analysis.

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# **FULL PAPER**



**In and out of phase**: The mechanism of a novel base-free neutral phasetransfer reaction system was investigated (see scheme). The aqueousorganic biphasic reaction system with lipophilic tetraalkylammonium bromide was essential to promote the neutral phase-transfer reactions. The basefree reaction system could be applied to several asymmetric reactions.

### **Phase-Transfer Catalysis**

Seiji Shirakawa, Lijia Wang, Rongjun He, Satoru Arimitsu, Keiji Maruoka\*\_\_\_\_\_

A Base-Free Neutral Phase-Transfer Reaction System