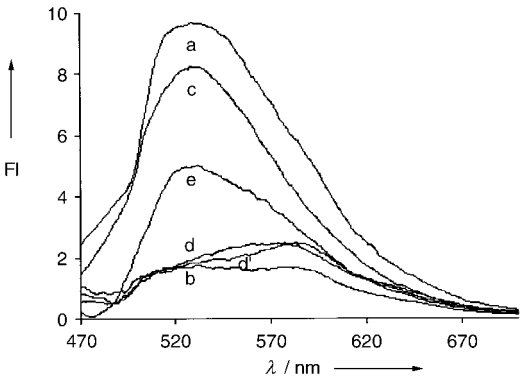

Figure 4. Fluorescence spectrum (FI = fluorescence intensity) of a solution (2.0×10^{-7} M, on a monomer unit basis) of a) polymer **1**, b) polymer **1**/**X1** duplex, c) polymer **1**/**X1**/**Y1** triplex, d) polymer **1**/**X1**/**Y2** mixture, d′) polymer **1**/**X1**/**Y2** (100 equivalents) mixture and e) polymer **1**/**X1**/**Y3** mixture at 55 °C, in 10 mM Tris buffer containing 0.1 M NaCl (pH 8).

or even 100 equivalents (Figure 4,d′) of the target oligonucleotide with two mismatches (**Y2**), the fluorescence intensity is not significantly modified. It is even possible to distinguish oligonucleotides with one mismatch (Figure 4,e). By measuring the fluorescence intensity at 530 nm (without recording the entire emission spectrum), it is possible to detect the presence of as few as 3×10^6 molecules of the perfect complementary oligonucleotide (20-mers) in a volume of 200 μL (this is a concentration of 2×10^{-14} M). Moreover, covalent attachment of the oligonucleotide to the fluorescent conjugated polymer, or use of an optimized fluorescence detection procedure based on a high-intensity blue diode (as the excitation source) and a nondispersive, interference filter-based system should yield even more sensitive and more specific detection capability. The electroactivity of these cationic polythiophene derivatives in aqueous solutions could also be exploited for the detection of DNA-hybridization events.

In conclusion, a novel methodology that allows simple optical (colorimetric or fluorometric) detection of nucleic acids has been developed. This rapid, selective, sensitive (as few as 3×10^6 molecules of oligonucleotide in 200 μL can be detected), and versatile method does not require any chemical reaction of the probes or the analytes and is based on conformational modifications of the conjugated backbone of cationic poly(3-alkoxy-4-methylthiophene)s, when mixed with single-stranded or double-stranded (hybridized) oligonucleotides. This procedure could provide inexpensive methodologies for the rapid detection and identification of nucleic acids.

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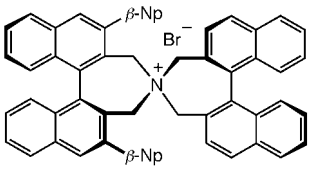
Conformationally Flexible, Chiral Quaternary Ammonium Bromides for Asymmetric Phase-Transfer Catalysis**

Takashi Ooi, Yukitaka Uematsu, Minoru Kameda, and Keiji Maruoka*

As clearly demonstrated by a number of notable recent successes, the use of phase-transfer catalysis for the preparation of chiral, nonracemic organic compounds from prochiral substrates using chiral catalysts such as optically pure quaternary ammonium salts has become a field of growing importance.[1, 2] We recently contributed to this area by introducing chiral C_2-symmetric quaternary ammonium bromides of type **1** which efficiently catalyze the phase-transfer



1 [(*S*,*S*)-β-Np-NAS-Br]

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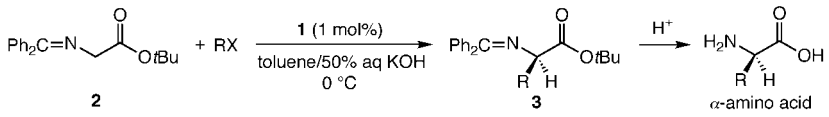
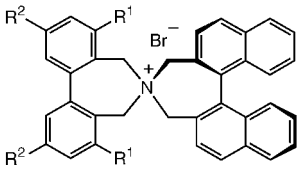


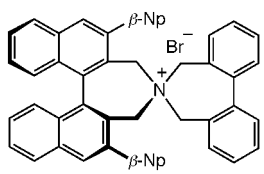
Scheme 1. Practical asymmetric synthesis of α-amino acids by the phase-transfer alkylation of the glycine Schiff base **2** catalyzed by the chiral C_2-symmetric quaternary ammonium bromide **1**.

alkylation of protected glycine derivative **2** with excellent enantioselectivities, providing a practical method for the asymmetric synthesis of both natural and unnatural α-amino acids (Scheme 1).[3, 4] Although the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of our catalysts and seems essential for attaining sufficient reactivity and enantioselectivity, it also imposes obvious limitations on the catalyst design due to the imperative use of the two chiral binaphthyl moieties and the difficulty of their fruitful modifications. Accordingly, a more simple yet flexible strategy for the molecular design of chiral catalysts is required to solve this intrinsic dilemma. Herein we disclose a new C_2-symmetric chiral quaternary ammonium bromide **4** that possesses an achiral, conformationally flexible biphenyl subunit, which exhibits high chiral efficiency by taking advantage of the considerable difference of activity between the diastereomeric homo- and heterochiral isomers through rapid conformational interconversion.

First, we assembled the quaternary ammonium bromide **4a** and evaluated its reactivity and selectivity using the phase-transfer catalytic benzylation of **2** as a benchmark reaction. Treatment of **2** with benzyl bromide (1.2 equiv) in 50% aqueous KOH/toluene (v/v 1:3) in the presence of 1 mol% of



4a : $R^1 = R^2 = H$
4b : $R^1 = \beta$-Np, $R^2 = H$
4c : R^1 = 3,5-diphenylphenyl, $R^2 = H$
4d : R^1 = 3,5-diphenylphenyl, $R^2 = Ph$



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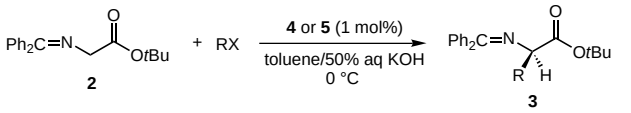
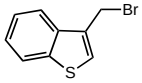
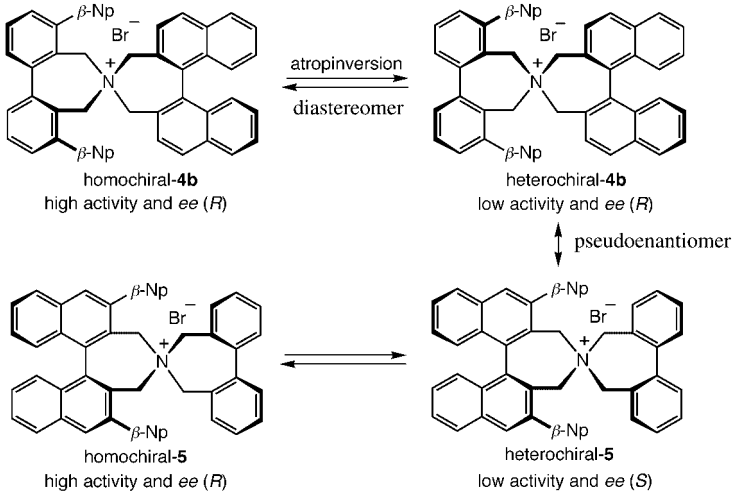
4a at 0 °C for 36 h under an argon atmosphere resulted in formation of **3** ($R = CH_2Ph$) in 62% yield.[5] Fortunately, appreciable enantioselectivity (64% *ee*) was attained and the absolute configuration was assigned to be *R* as shown in Table 1 (entry 1). Based on this result, we next examined the catalyst **4b**, which has a β-naphthyl group at the 3,3′-position of the flexible biphenyl moiety, and found, as hoped, that both chemical yield and the enantioselectivity were improved to 85%, 87% *ee* (*R*) (Table 1, entry 2). The reaction was also smoothly catalyzed by the chiral ammonium bromide **5**, which has β-naphthyl (β-Np) substituents on the chiral binaphthyl framework, giving **3** ($R = CH_2Ph$) in 87%, 83% *ee* with the same *R* configuration (Table 1, entry 3). Here, we assumed that the origin of the observed chiral efficiency could be ascribable to the considerable difference of catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral-**4** or -**5** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce **3** ($R = CH_2Ph$) with high enantiomeric excess, whereas heterochiral-**4** or -**5** displays low reactivity and stereoselectivity (Scheme 2).[6, 7] To gain supportive evidence of this, we prepared the heterochiral quaternary ammonium

Table 1. Catalytic enantioselective phase-transfer alkylation with conformationally interconvertible catalyst.[a]



Entry	RX	Catalyst	Reaction time [h]	Yield[b] [%]	*ee*[c] [%]	Config.[d]
1	$PhCH_2Br$	**4a**	36	62	64	*R*
2	$PhCH_2Br$	**4b**	18	85	87	*R*
3	$PhCH_2Br$	**5**	8.5	87	83	*R*
4	$PhCH_2Br$	**4c**	27	95	92	*R*
5	$PhCH_2Br$	**4d**	48	81	95	*R*
6	$PhCH_2Br$	**4d**	16	87	94	*R*[e]
7	$CH_2{=}CHCH_2Br$	**4d**	16	85	93	*R*[e]
8	EtI	**4d**	15	61	93	*R*[e,f]
9		**4d**	19	91	93	*R*[e]

[a] Unless otherwise specified, the reaction was carried out with **2** (0.5 mmol) and 1.2 equiv of RX in the presence of 1 mol% of **4** or **5** in 50% aqueous KOH/toluene (v/v 1:3) under the given reaction conditions under argon atmosphere. [b] Yield of isolated product. [c] Enantiopurity of **3** was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD for entries 1–8 and Chiralpak AD for entry 9) with hexane/2-propanol as solvent. [d] Absolute configuration of **3** was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[1b] [e] Three equivalents of $CsOH \cdot H_2O$ in water (29.2 μL) were used as a base and the reaction was performed at −15 °C. [f] Five equivalents of alkyl halide were used.



Scheme 2. Expected conformational interconversion of **4b** and **5**.

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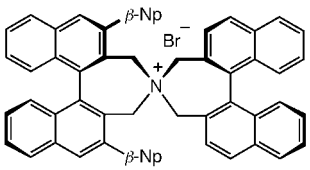
bromide **6** and found that the alkylation of **2** with benzyl bromide (1.2 equiv) and 1 mol% of **6** under similar conditions proceeded slowly, and, after 60 h, gave rise to the corresponding benzylation product **3** (R = CH_2Ph) in 47% yield with low enantiomeric excess (11% *ee*, *R*).[3a] We also confirmed that



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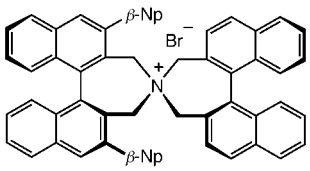

***ent*-6**

ent-**6** exerted comparable catalytic activity as **6** in the phase-transfer benzylation of **2** with the opposite sense of asymmetric induction (51%, 11% *ee*, *S*). Furthermore, the benzylation of **2** with 0.5 mol% each of **1** and **6** under otherwise similar phase-transfer conditions at 0 °C for 13 h afforded **3** (R = CH_2Ph) in 88% yield with 94% *ee* (*R*), and the use of 0.5 mol% each of **1** and *ent*-**6** as catalyst, though a mismatched combination in terms of the enantioselectivity, resulted in the formation of **3** (R = CH_2Ph) in 92% yield with 93% *ee* (*R*) after 8.5 h at 0 °C. On the basis of this information, the slight decrease of the enantiomeric excess observed in the reaction with **5** compared to that with **4b** can be accounted for by the intervention of heterochiral-**5** (Scheme 2), which is considered to be a pseudoenantiomer of heterochiral-**4b**, having led to the production of **3** (R = CH_2Ph) with the opposite *S* configuration.

The unique phenomenon discussed above provides a new, yet powerful strategy in the molecular design of chiral catalysts; that is, the requisite chirality can be served by the simple binaphthyl moiety and an additional structural requirement for fine-tuning of reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure (Figure 1); this certainly obviates the use of two chiral units and should be greatly appreciated in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. For instance, quaternary ammonium bromides possessing a sterically demanding substituent such as **4c** can be easily prepared, and the benzylation of **2** with **4c** as a phase-transfer catalyst gave **3** (R = CH_2Ph) in 95% yield with 92% *ee* (Table 1, entry 4). Moreover, the enantioselectivity was enhanced to 95% *ee* when **4d** was used as a catalyst (Table 1, entry 5) and, interestingly, use of aqueous CsOH as a base at a lower reaction temperature led to an increase of reactivity with similar enantioselectivity (Table 1, entry 6).[8] The generality of the present system was demonstrated with other representative alkyl halides (Table 1, entries 7–9).

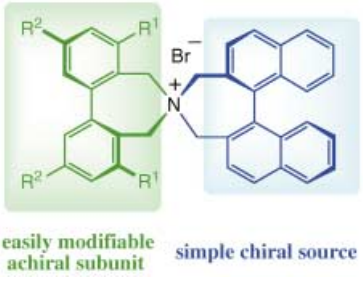

Figure 1. New strategy for the molecular design of chiral phase-transfer catalysts.

To obtain spectroscopic evidence for the expected conformational interconversion, the dynamic structural behavior of **4c** in solution was analyzed by a variable-temperature ^1H NMR study. Figure 2 shows the temperature dependence of the ^1H NMR signals (benzylic protons) of the quaternary ammonium bromide **4c** in [D_2]dichloromethane at low temperature. The peak broadening at 283–263 K and sharpening to two sets of four benzylic signals (nearly 1:1 ratio) at 243 K clearly indicates that there is a rapid equilibrium between two diastereomeric, homochiral and heterochiral conformations that arises from rotation about the biphenyl axis. The composition of the conformational structures depends on temperature and the existence ratio of the homochiral isomer was found to increase as the temperature lowered.[8] This observation is a result of the positive enthalpy ($\Delta H^\circ = 5.74$ kcal mol^{-1}) and the identical-signed large entropy ($\Delta S^\circ = 23.1$ cal mol^{-1} K^{-1}) for the conversion from homochiral to heterochiral conformation.[9, 10]

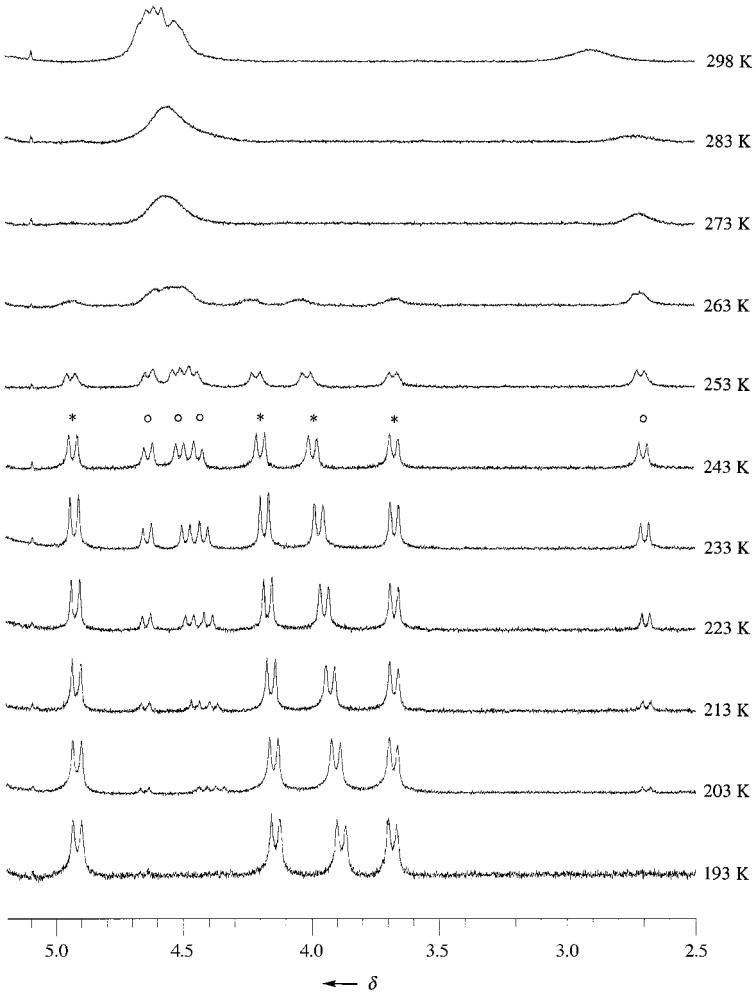

Figure 2. The temperature dependence of the ^1H NMR signals of the benzylic protons of homochiral (∗) and heterochiral (○) conformers of **4c**.[10]

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In conclusion, we have described a new and simple strategy for the molecular design of chiral phase-transfer catalysts by introducing a conformationally flexible, chiral C_2-symmetric quaternary ammonium bromide **4** and uncovering its characteristic feature. The representative phase-transfer alkylation of **2** was smoothly catalyzed by **4** in a highly enantioselective manner, which stems from the high chiral efficiency of a homochiral isomer rapidly equilibrating with a heterochiral one as verified by a variable-temperature ^{1}H NMR study. Our approach conceptually parallels the successful utilization of a flexible ligand to magnify the effect of the other chiral ligand through a coordinative interaction with the metal center,[7] and should eventually offer a new dimension for asymmetric phase-transfer catalysis based on the design of the catalyst.

Experimental Section

Phase-transfer benzylation of **2** with catalyst **4d** (entry 6 in Table 1): Water (29.2 μL) was introduced to a 10-mL two-neck flask containing a Teflon-coated magnetic stirring bar and $CsOH \cdot H_2O$ (265 mg, 1.5 mmol) and the mixture was stirred under an argon atmosphere. Then, **4d** (5.8 mg, 0.005 mmol) and a solution of glycine *tert*-butyl ester benzophenone Schiff base **2** (148 mg, 0.5 mmol) in toluene (3 mL) were added and the mixture was cooled to $-15\,^\circ C$. After 10 min of gentle stirring, benzyl bromide (73.6 μL, 0.6 mmol) was added dropwise and the reaction mixture was stirred vigorously for 16 h. The resulting mixture was poured into brine (25 mL) and extracted with CH_2Cl_2 (6 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated. The residual oil was purified by column chromatography on silica gel (diethyl ether/hexane = 1:20 to 1:10 as eluant) to give the corresponding benzylation product **3** (R = CH_2Ph) (168 mg, 0.436 mmol; 87 % yield, 94 % *ee*) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol = 100:1, flow rate = 0.5 mL min^{-1}, retention time; 13.7 min (*R*) and 24.6 min (*S*)).

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[4] The catalyst **1** as well as the one with a 3,4,5-trifluorophenyl group at the 3,3′-position are going to be commercially available from Aldrich Chemical Co. Ltd. as (*S*,*S*)-β-naphthyl-NAS-bromide (**1**) [54,839-1] and (*S*,*S*)-3,4,5-trifluorophenyl-NAS-bromide [54,838-3].

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[8] Although the benzylation of **2** with **4d** and aqueous CsOH at 0 °C proceeded faster to give **3** (R = CH_2Ph) in 84 % yield after 6 h, the enantioselectivity was found to be 83 % *ee* probably because of the background alkylation of the more nucleophilic cesium enolate. This observation led us to conduct the reaction at lower temperature, taking advantage of not only the simple temperature effect but also the increase of the existence ratio of homochiral isomer.

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[10] The ^{1}H NMR assignment of the homo- and heterochiral **4c** was conducted based on the ^{1}H NMR spectra of conformationally rigid, diastereomeric **1** and **6**.

A Model System Mimicking Glycosphingolipid Clusters to Quantify Carbohydrate Self-Interactions by Surface Plasmon Resonance**

María J. Hernáiz, Jesús M. de la Fuente, África G. Barrientos, and Soledad Penadés*

Dedicated to Professor Julio D. Martin on the occasion of his 60th birthday

Cell surface carbohydrates play a role in cell–cell adhesion and communication.[1, 2] Several models for cell interactions based on carbohydrates have been proposed. In most of them, the carbohydrate binds to selectins, galectins, and other

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