absorption in the membrane. The active Pyc site was reported to be an efficient catalyst for the ORR,[3b,7] and hence, the purging O_2 is essential for the formation of H_2O_2 during the reaction. The control experiment in pure H_2O_2 gave only about 47% conversion with poor selectivity (Table 1). However, the assistance of Pyc and $[Ru(bpy)_3]^{2+}$ in the SOR was supported by the indirect electrochemical studies mentioned earlier. The efficiency of the SOR was then evaluated by putting a 4.5×2 cm $|NPyc^{x-}Ru(bpy)|$ in a mixture of CH_3CN (30 mL), H_2O (40 mL), and 17 mM $RSCH_3$ (R = Ph, $PhCOCH_3$, and $PhOCH_3$) at pH 1, with constant purging of O_2 under illumination (500 W halogen lamp) for 3 h. The products were analyzed simply by evaporation of the solution of the separated reaction product in $CHCl_3$ with a rotary-vacuum system. All reactions gave a single product of sulfoxide (that is, no sulfone was observed on the TLC plate and was further confirmed by NMR and mass spectroscopic studies) in >90% yield. The high selectivity of the current approach was clearly demonstrated. Finally, three repeated experiments were performed with $PhSCH_3$ to test the recyclability of the $|NPyc^{x-}Ru(bpy)|$ system, and almost the same yield was observed.

In conclusion, we have demonstrated a clean and highly selective photochemical oxidation of sulfide to sulfoxide on a novel heterogeonous multicomponent nafion membrane containing a Pyc catalyst and a $[Ru(bpy)_3]^{2+}$ photosensitizer. The high sulfoxide selectivity, lack of pollution, ease of product separation, and recyclable nature of the muticomponent membrane has a clear advantage over classical approaches. Further investigations are currently underway to expand the scope of this reaction to sulfide compounds containing more complicated organic structures and to a macroscale synthesis.

Experimental Section

Photochemical experiments were carried out at pH 1 (adjusted with HCl) in a mixture of CH_3CN and H_2O (3:4, ca. 70 mL) in a closed round-bottomed flask sealed with a gasket-septum under constant purging of O_2 gas. Cyclic voltammetric (CV) experiments were performed using a CHI workstation with a three-electrode system of working (0.071 cm^2), reference (Ag/AgCl), and counter (Pt disc, 0.071 cm^2) electrodes between −0.4 to 1.4 V. A negative current in the cyclovoltammograms denotes an anodic response, while a positive current denotes a cathodic current. The oxidized product was separated into $CHCl_3$ and then analyzed by NMR spectroscopic (in $CDCl_3$) and mass spectrometric techniques after rotary-vacuum evaporation. The yield of the products was determined on the basis of the ratio between the molar weight of the reactant and the product.

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Stereoselective Alkylation

Highly Stereoselective N-Terminal Functionalization of Small Peptides by Chiral Phase-Transfer Catalysis**

*Takashi Ooi, Eiji Tayama, and Keiji Maruoka**

Peptide modification is an essential yet flexible synthetic concept for screening targets efficiently and optimizing lead structures in the application of naturally occurring peptides as pharmaceuticals.[1,2] The introduction of side chains directly to a peptide backbone is a powerful method for preparing nonnatural peptides. The achiral glycine subunit has generally been used for this purpose[3] and glycine enolates,[4–8] radicals,[9–11] and glycine cation equivalents[12,13] have been ex-

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ploited as reactive intermediates. However, controlling the stereochemical outcome of these processes in an absolute sense is difficult, especially in the modification of linear peptides, and hence the development of an efficient, practical, and general approach to establish sufficient stereoselectivity has been eagerly awaited.[7d,14] Although the stereoselective phase-transfer alkylation of Schiff-base-activated small peptides **2**, which involves chirality transfer between two adjoining amino acid residues, appears to be an attractive method,[6] it has never been developed to a useful level due to the lack of well-designed chiral catalysts.[15,16] Here we present the first solution to this problem, in which the optically pure, C_2-symmetric quaternary ammonium salt **1** is used as the catalyst (Scheme 1).[17] By fine-tuning the catalyst structure, a variety of new side chains can be attached to the growing peptide N terminus with remarkable stereoselectivity. This newly created chirality can be transferred efficiently to an adjacent amino acid residue, allowing the asymmetric construction of nonnatural oligopeptides.

We initially examined the alkylation of the dipeptide Gly-L-Phe derivative **2a** as a representative system and evaluated the critical importance of the chiral phase-transfer catalyst in obtaining high stereoselectivity (Table 1). When a mixture of **2a** and tetrabutylammonium bromide (2 mol%) as a typical achiral ammonium salt in toluene was treated with 50% KOH aqueous solution and benzyl bromide (1.1 equiv) at 0°C for 4 h, the corresponding benzylation product **3a** was obtained in 85% yield. The diastereomer ratio (D,L-**3a**:L,L-**3a**) was determined to be 54:46 (8% diastereomeric excess (*de*)) by chiral HPLC analysis (entry 1 in Table 1). In contrast, the reaction with the chiral quaternary ammonium bromide (*S*,*S*)-**1a** as the catalyst under similar conditions gave rise to **3a** with a D,L:L,L ratio of 77.5:22.5 (55% *de*, 88% yield, entry 2). Here, use of enantiomeric (*R*,*R*)-**1a** led to the preferential formation of L,L-**3a** in 20% *de* (entry 3), indicating that (*R*,*R*)-**1a** is a mismatched catalyst for this diastereofacial differentiation of **2a**. Significantly, the stereoselectivity was increased dramatically when the aryl substituent (Ar) on the 3- and 3′-positions of the catalyst was changed. Almost complete diastereocontrol was achieved with the catalyst (*S*,*S*)-**1d**, which has 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl groups (97% *de*, entries 4–6).[18] It is worthy of comment that neither racemization of the preexisting chiral center nor N-alkylation was observed under the present biphasic conditions.

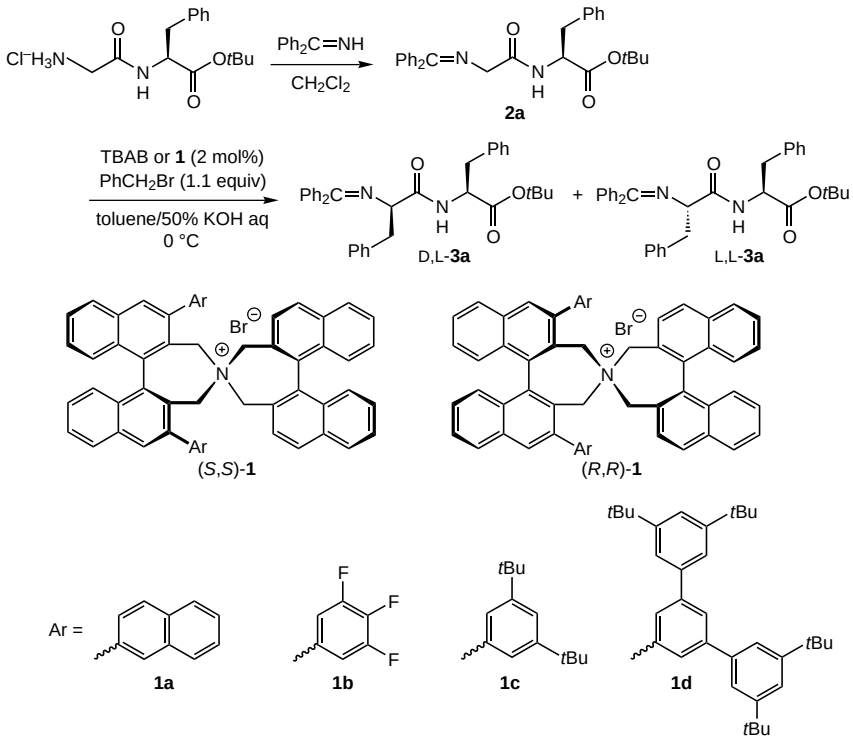
Table 1: Effect of the chiral C_2-symmetric quaternary ammonium salts on the diastereoselectivity of the phase-transfer benzylation of **2a**.[a]

Entry	Catalyst	Reaction time [h]	Yield [%][b]	*de* [%][c]
1	TBAB	4	85	8
2	(*S*,*S*)-**1a**	4	88	55
3	(*R*,*R*)-**1a**	6	83	20
4	(*S*,*S*)-**1b**	8	43	81
5	(*S*,*S*)-**1c**	4	98	86
6	(*S*,*S*)-**1d**	6	97	97

[a] The reactions were carried out with 1.1 equivalents $PhCH_2Br$ in the presence of 2 mol% TBAB or **1** in 50% aqueous KOH/toluene (volume ratio = 1:3) at 0°C under argon. [b] Yield of isolated product. [c] The diastereomeric excess of **3a** (R = CH_2Ph) was determined by ^1H NMR spectroscopy and by HPLC analysis with a chiral column (Daicel Chiralcel OD) and hexane/2-propanol as solvent. The absolute configuration of **3a** was determined by comparison of the ^1H NMR spectrum and the HPLC retention time with those of the independently synthesized authentic sample.

In a similar manner a variety of alkyl halides can be employed as the electrophile in this alkylation (Table 2, entries 1–5), where excellent stereoselectivities were uniformly observed. The efficiency of the transmission of stereochemical information was not affected by the side-chain structure of the preexisting amino acid residues, as clearly demonstrated in the phase-transfer benzylation of various dipeptides derived from natural α-amino acids (Table 2, entries 6–9). Interestingly, sterically less demanding (*S*,*S*)-**1c** was found to be a suitable catalyst for the substrate with the L-proline *tert*-butyl ester moiety (entry 10).

We further examined the stereoselective alkylation of the dipeptide L-Ala-L-Phe derivative **4**, which would enable the asymmetric construction of noncoded α,α-dialkyl-α-amino acid residues at the peptide terminal (Scheme 2).[19] Thus, reaction of a mixture of **4**, benzyl bromide (1.1 equiv), and the catalyst (*S*,*S*)-**1d** (2 mol%) in toluene with $CsOH\cdot H_2O$ (5 equiv) as a solid base at 0°C for 1 h



Scheme 1. Catalytic asymmetric alkylation of Schiff-base-activated dipeptide **2a** under phase-transfer conditions. TBAB = tetrabutylammonium bromide.

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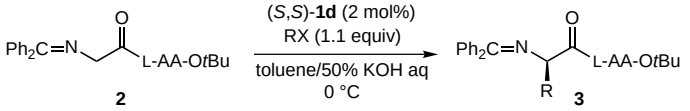
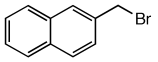
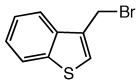
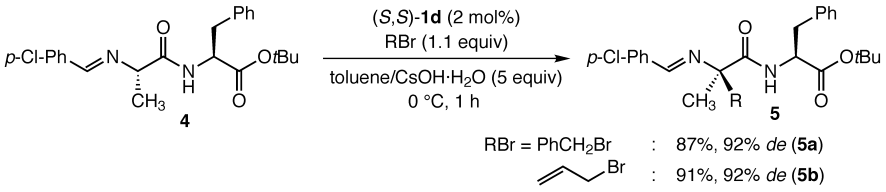
Table 2: Stereoselective N-terminal alkylation of dipeptides by chiral phase-transfer catalysis.[a]

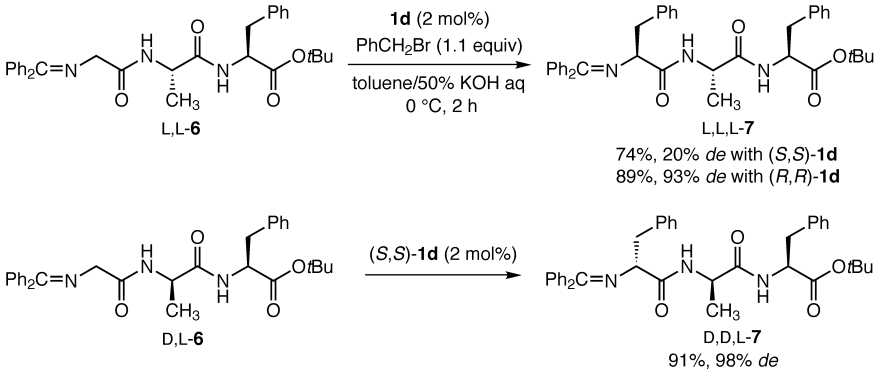


Entry	AA	RX	Reaction time [h]	Yield [%][b]	*de* [%][c]
1	Phe (**2a**)		6	89	98
2			6	80	96
3[d]		CH_3CH_2I	12	90	98
4			8	92	96
5[d]			6	95	91
6	Leu	$PhCH_2Br$	6	91	96
7	Val		12	85	93
8	Tyr(Bn)		8	90	98
9	Ala		6	92	93
10	Pro		8	80	90[e]

[a] Unless otherwise specified, the reactions were carried out with 1.1 equivalents RX in the presence of 2 mol% (*S*,*S*)-**1d** in 50% aqueous KOH/toluene (volume ratio = 1:3) under the given reaction conditions. [b] Yield of isolated product. [c] Diastereomeric excess of **3** was determined by ^{1}H NMR spectroscopy and HPLC analysis of the alkylated peptide with a chiral column (Daicel Chiralpak AD (entries 1, 3, and 8–10) and Chiralcel OD (entries 2, 4, and 5–7)) and hexane/2-propanol or hexane/ethanol as solvent. [d] A saturated solution of CsOH was used as the aqueous base. [e] With (*S*,*S*)-**1c** as catalyst.



Scheme 2. Asymmetric construction of terminal α,α-dialkyl-α-amino acid residues.



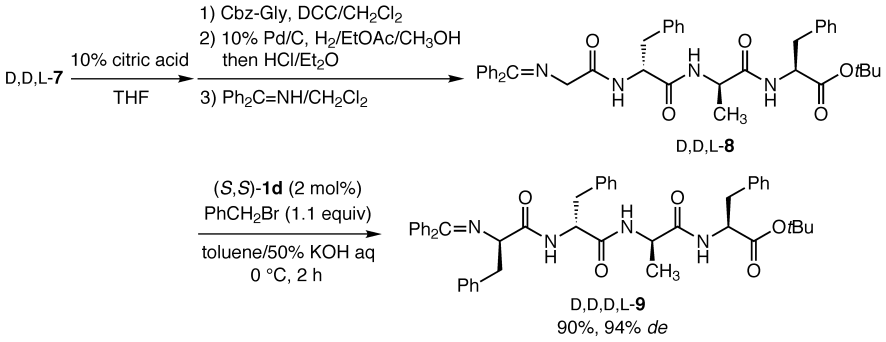
Scheme 3. Reversal of stereochemical preference in the asymmetric phase-transfer catalytic alkylation of tripeptide derivative **6**.

afforded **5a** in 87% yield and 92% *de*. The reaction with allyl bromide under similar conditions also proceeded smoothly with high diastereoselectivity (**5b**; 91% yield, 92% *de*).

Encouraged by the results, we extended the chiral phase-transfer catalysis with (*S*,*S*)-**1d** to the stereoselective N-terminal alkylation of Gly-Ala-Phe derivative **6**, that is, asymmetric synthesis of tripeptides (Scheme 3). To our surprise, the benzylation of L,L-**6** with (*S*,*S*)-**1d** under the optimized biphasic conditions resulted in poor diastereoselectivity (20% *de*) with L,L,L-**7** as the major product; however, the selectivity was enhanced to 93% *de* (89% yield) by the use of (*R*,*R*)-**1d** as a catalyst. The observed stereochemical relationship was totally opposite to that in the reactions of dipeptides. This interesting fact was further supported by the benzylation of D,L-**6**, where (*S*,*S*)-**1d** turned out to be a matched catalyst leading to almost exclusive formation of D,D,L-**7** under similar conditions (Scheme 3).

Furthermore, we found that this tendency for stereochemical communication was consistent in the phase-transfer alkylation of D,D,L-**8**, which can be readily prepared from D,D,L-**7** by means of hydrolysis and successive introduction of a new glycine subunit by well-established methods. The corresponding protected tetrapeptide D,D,D,L-**9** was obtained in 90% yield with excellent stereochemical control (94% *de*) as illustrated in Scheme 4. We also confirmed that similar alkylation of L,L,L-**8** with (*R*,*R*)-**1d** as the catalyst furnished L,L,L,L-**9** in 87% yield and 92% *de*, suggesting that (*R*,*R*)-**1d** is suitable for the stereoselective N-terminal alkylation of naturally occurring polypeptides.

Our approach based on the use of chiral quaternary ammonium salts enables the asymmetric phase-transfer catalytic alkylation of peptides. This provides a general procedure not only for the highly stereoselective N-terminal functionalization of peptides but also



Scheme 4. Asymmetric synthesis of tetrapeptides by chiral phase-transfer catalysis of (*S*,*S*)-**1d**. Cbz = benzyloxycarbonyl, DCC = 1,3-dicyclohexylcarbodiimide.

for the sequential asymmetric construction of nonnatural oligopeptides, which play a vital role in the development of peptide-based drugs.

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