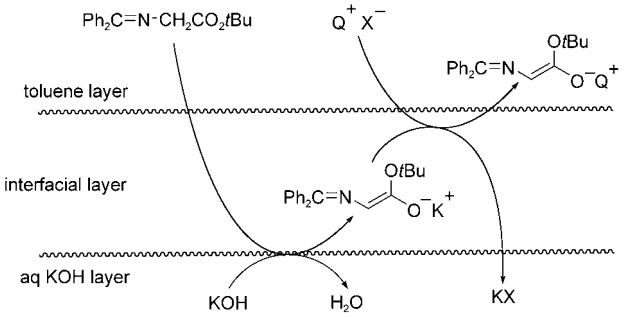
Asymmetric Synthesis

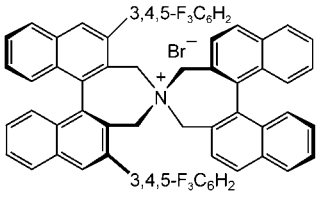
Powerful Chiral Phase-Transfer Catalysts for the Asymmetric Synthesis of α-Alkyl- and α,α-Dialkyl-α-amino Acids**

*Masanori Kitamura, Seiji Shirakawa, and Keiji Maruoka**

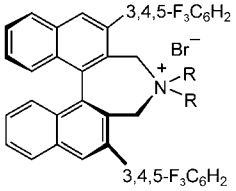
Phase-transfer catalysis (PTC) has been recognized as a convenient and highly useful tool in academia and industry because it offers several advantages for practical organic synthesis, such as operational simplicity, mild reaction conditions in aqueous media, environmental benefits, and suitability for large-scale reactions.[1,2] Also the development of efficient methods for the preparation of natural and non-natural α-alkyl- and α,α-dialkyl-α-amino acids, especially in their enantiomerically pure forms by asymmetric PTC, has become very important because of their high synthetic utility.[3,4] Accordingly, several phase-transfer catalysts have been developed that lead to products with excellent enantioselectivities in high yields.[4] However, despite numerous studies, truly efficient catalytic systems with high enantioselection at very low catalyst loading (e.g., <0.1 mol%) are still rare in asymmetric carbon–carbon bond formation, and major progress in terms of catalyst loading is still desirable for practical asymmetric synthesis. Since our recently developed, chiral spiro-type (*R*,*R*)- or (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **1** shows exceedingly high enantioselectivity in asymmetric alkylation of α-amino acid derivatives,[4d,e,m] our next target was the design of a very active catalyst. Considering the highly lipophilic nature of **1** and the generation of a metal enolate in an interfacial layer,[5] such lipophilic **1** (QX) must move to the interfacial layer to induce a facile exchange reaction with a metal enolate (Scheme 1). Based on this assumption, our strategy was to replace the rigid binaphthyl moiety in **1** by flexible straight-chain alkyl groups to furnish a new catalyst of type **2**, which substantially accelerates the enolate exchange with **2** because of the increasing polarity of the dialkylammonium moiety. Herein, we report that such a designer chiral quaternary ammonium salt **2** behaves as a very powerful chiral phase-transfer catalyst for the highly practical, enantioselective alkylation of protected-glycine and α-alkyl-α-amino acid derivatives.



Scheme 1. Proposed mechanism for the generation of chiral ammonium enolate.

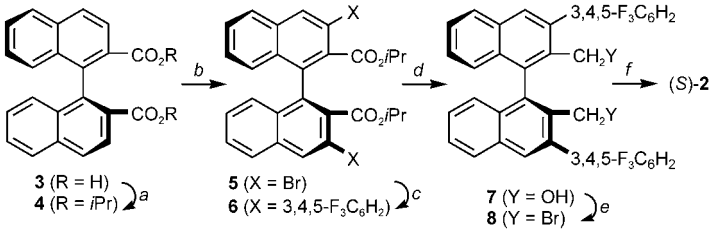


(*S*,*S*)-**1**



(*S*)-**2a** (R = Me)
(*S*)-**2b** (R = Et)
(*S*)-**2c** (R = Bu)
(*S*)-**2d** (R = $C_{10}H_{21}$)

The requisite catalyst (*S*)-**2** can be readily prepared from the commercially available (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (**3**)[6] in a six-step sequence as outlined in Scheme 2.[7]



Scheme 2. a) *i*PrBr (10 equiv), $Bu_4N{\cdot}HSO_4$ (20 mol%), $KF{\cdot}2H_2O$ (10 equiv), THF, reflux (95%); b) 1. $Mg(TMP)_2$ (4 equiv), THF, RT; 2. Br_2 (8 equiv), $-78\,^{\circ}C \rightarrow$RT (91%); c) $(3,4,5\text{-}F_3C_6H_2)B(OH)_2$ (2.4 equiv, $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), K_2CO_3 (3 equiv), DMF, 90 °C (94%); d) $LiAlH_4$ (3 equiv), THF, 0 °C→RT; e) PBr_3 (0.5 equiv), THF, 0 °C (90% from **6**); f) R_2NH (R = Me, Et, Bu, $C_{10}H_{21}$) (1.1 equiv), K_2CO_3 (2 equiv), CH_3CN, reflux (64–99%).

Thus, (*S*)-dicarboxylic acid **3** was transformed with *i*PrBr, catalytic $Bu_4N{\cdot}HSO_4$, and $KF{\cdot}2H_2O$ to the corresponding diisopropyl ester **4** in 95% yield. Treatment of **4** with freshly prepared $Mg(TMP)_2$ (TMP = 2,2,6,6-tetramethylpiperidide) in THF and subsequent additon of bromine gave rise to (*S*)-3,3′-dibromo-1,1′-binaphthyl-2,2′-dicarboxylic ester **5** in 91% yield. Suzuki–Miyaura cross coupling of **5** with 3,4,5-trifluorophenylboronic acid in the presence of catalytic $Pd(OAc)_2$, PPh_3, and K_2CO_3 in *N*,*N*-dimethylformamide (DMF) afforded (*S*)-3,3′-bis(3,4,5-trifluorophenyl)-1,1′-binaphthyl-2,2′-dicarboxylic ester (**6**) in 94% yield. Reduction of **6** with

[*] M. Kitamura, S. Shirakawa, 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

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$LiAlH_4$ in THF and subsequent treatment of the resulting crude alcohol **7** with PBr_3 in THF furnished (*S*)-dibromide **8** in 90% yield. Reaction of **8** with R_2NH (R = Me, Et, Bu, $C_{10}H_{21}$) and K_2CO_3 in acetonitrile led to the formation of the catalyst (*S*)-**2** in yields of 64–99%. The overall yields of (*S*)-**2** from the starting (*S*)-dicarboxylic acid **3** were 47–72%. The structure of (*S*)-**2c** as a PF_6^- salt determined by X-ray crystallographic analysis is shown in Figure 1.[8]

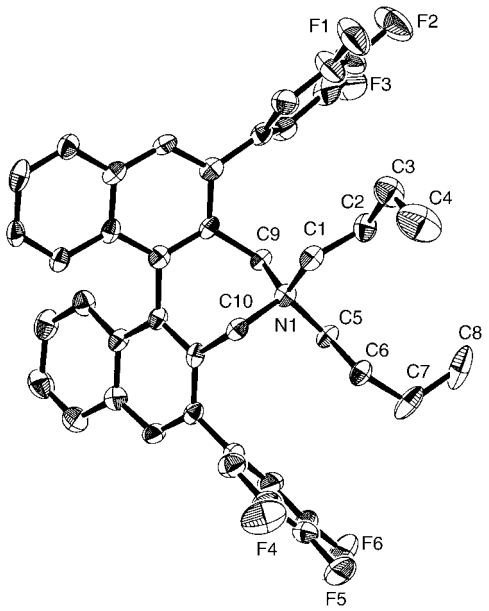
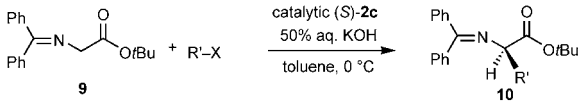


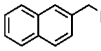
Figure 1. ORTEP drawing of (*S*)-**2c** as a PF_6^- salt. PF_6^-, solvent, and hydrogen atoms have been omitted for clarity.

The chiral efficiency of the phase-transfer catalyst (*S*)-**2** was examined by carrying out asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**9**; Table 1). (*S*)-**2a** gave a rather disappointing result in terms of reactivity, the higher homolog (*S*)-**2b** was however found to be a very active phase-transfer catalyst. Indeed, reaction of **9** with benzyl bromide (1.2 equiv) and 50% aqueous KOH in toluene was effected in the presence of only 0.05 mol% of catalyst (*S*)-**2b** under argon atmosphere at 0°C for 3 hours to furnish the benzylation product **10** (R′ = CH_2Ph) in 81% yield with excellent enantioselectivity (97% *ee*) (entry 2). Further acceleration of the reaction was observed by using 0.05 mol% of catalyst (*S*)-**2c** (98% yield with 99% *ee* at 0°C for 2 hours) (entry 3).[9] Even 0.01 mol% of catalyst (*S*)-**2c** still gave high enantioselectivity (98% *ee* at 0°C for 9 hours) (entry 4).

Other selected examples are also listed in Table 1. There are several characteristic features of these alkylation reactions: 1) In contrast to the existing chiral phase-transfer catalysts, catalyst (*S*)-**2c** exhibited a high catalytic performance (0.01–0.1 mol%) and demonstrated the remarkable efficiency and practicality of the present approach towards the enantioselective synthesis of α-alkyl-α-amino acids. 2) The didecyl analogue (*S*)-**2d** exhibited a little less reactivity to (*S*)-**2c** without decreasing enantioselectivity (entries 5 and 6). 3) Not only benzylation and allylation, but also alkylation of **9** with a simple alkyl halide, such as ethyl iodide, proceeded smoothly under mild conditions to furnish the corresponding α-alkyl-α-amino acids in high yield and excellent enantioselectivity (entry 13).

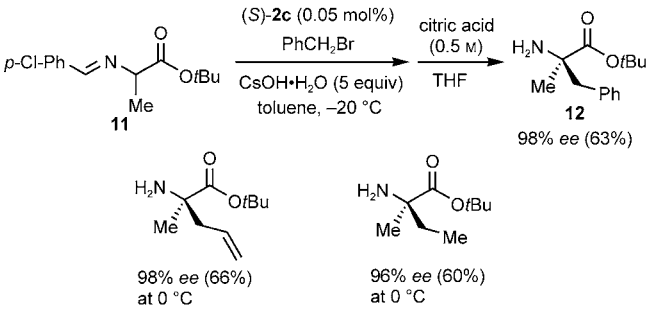
Table 1: Catalytic enantioselective phase-transfer alkylation of glycine derivative **9**.[a]



Entry	Catalyst [mol%]	R′-X	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%] (Config)[c]
1	(*S*)-**2a** (0.05)	$PhCH_2Br$	0	4	7	33 (*R*)
2	(*S*)-**2b** (0.05)		0	3	81	97 (*R*)
3	(*S*)-**2c** (0.05)		0	2	98	99 (*R*)
4[d]	(*S*)-**2c** (0.05)		0	12	97	99 (*R*)
5	(*S*)-**2c** (0.01)		0	9	92	98 (*R*)
6	(*S*)-**2d** (0.05)		0	4	94	99 (*R*)
7	(*S*)-**2d** (0.01)		0	24	79	98 (*R*)
8	(*S*)-**2c** (0.05)	$CH_2{=}CHCH_2Br$	0	3	87	98 (*R*)
9	(*S*)-**2d** (0.05)		0	5	75	97 (*R*)
10	(*S*)-**2c** (0.05)	$HC{\equiv}CCH_2Br$	0	4	88	98 (*R*)
11	(*S*)-**2d** (0.05)		0	6	83	98 (*R*)
12	(*S*)-**2c** (0.05)		0	64	81	97 (*R*)
13	(*S*)-**2c** (0.1)	CH_3CH_2I[e,f]	−20	1	67	99 (*R*)

[a] Unless otherwise specified, the reaction of **9** (0.3 mmol) was carried out with 1.2 equivalents of R′X in the presence of catalytic (*S*)-**2** in 50% aqueous KOH/toluene (volume ratio = 1:1) under the given reaction conditions. [b] Yield of isolated product. [c] Enantiopurity of **10** was determined by HPLC analysis using a column with a chiral stationary phase (DAICEL Chiralcel OD) with hexane/isopropanol as the solvent. [d] Reaction scale = 3 mmol. [e] Use of 5 equivalents of alkyl halide and $CsOH{\cdot}H_2O$ as base. [f] Attempted reaction of **9** with EtI in the presence of (*S*)-**2c** (0.05 mol%) in 50% aqueous KOH/toluene at 0°C for 72 hours gave **10** (R′ = Et) in 12% yield with 91% *ee*.

In conclusion, we successfully designed very powerful chiral phase-transfer catalysts of type **2** to realize a general



Scheme 3. Asymmetric alkylation of Schiff base **11** by using (S)-**2c** as catalyst.

and useful procedure for highly practical enantioselective synthesis of α-alkyl- and α,α-dialkyl-α-amino acids.

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[8] Crystallographic data for (*S*)-**2c** as a PF_6^- salt: $0.4\times0.3\times0.2$ mm^3, monoclinic, *C*2, $a=18.70(1)$, $b=13.80(1)$, $c=18.176(9)$ Å, $\beta=106.79(5)°$, $V=4488(4)$ Å^3, $\rho_{calcd}=1.403$ g cm^{-3}, $Z=4$, $2\theta_{max}=54.7°$, $\mu=0.1383$ mm^{-1}, $Mo_{K\alpha}$, $\lambda=0.7107$ Å, $T=-150$ °C. A total of 20154 reflections were measured. $R=0.068$, and $Rw=0.081$ for 11668 observed reflections with $I>3.0\sigma(I)$. CCDC-250335 [(*S*)-**2c** as a PF_6^- salt] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Attempted asymmetric benzylation of **9** with 50% aqueous KOH in toluene in the presence of 0.05 mol% of catalyst (*S*,*S*)-**1** under argon atmosphere at 0 °C for 24 hours resulted in formation of **10** ($R' = CH_2Ph$) in only 22% yield with 85% *ee*.

