Evaluation of the Efficiency of the Chiral Quaternary Ammonium Salt β-Np-NAS-Br in the Organic-Aqueous Phase-Transfer Alkylation of a Protected Glycine Derivative

Takashi Ooi, Yukitaka Uematsu, Keiji 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

Received: December 17, 2001; Accepted: February 24, 2002

Abstract: The inherent efficiency of the *N*-spiro C_2-symmetric chiral quaternary ammonium salt (*S*,*S*)-**3** [(*S*,*S*)-β-Np-NAS-Br] has been evaluated in the representative organic-aqueous liquid-liquid phase-transfer benzylation and allylation of glycine *tert*-butyl ester benzophenone Schiff base (**1**). This revealed the practical conditions for the asymmetric synthesis of both natural and unnatural α-amino acids, whose usefulness was demonstrated by the formal enantioselective synthesis of antibiotic L-azatyrosine.

Keywords: allylation; α-amino acids; antibiotics; L-azatyrosine; benzylation; chiral quaternary ammonium salt; organic catalysts

Asymmetric synthesis of both natural and unnatural α-amino acids has been an issue of enormous importance from synthetic as well as pharmaceutical viewpoints and numerous efforts have been made for the development of new methodologies over the last decades.[1] Among the number of well-elaborated procedures, catalytic enantioselective phase-transfer alkylation of a prochiral glycine Schiff base **1** using a chiral catalyst has appeared as a promising method,[2] which could meet the recent requirement for environmental consciousness. The use of *Cinchona* alkaloid-derived catalysts for this purpose, as initiated by O'Donnell,[3] has reached the level of sophistication especially after the recent progress mainly promoted by Corey[4] and Lygo[5]. Our contribution in this area allows the molecular design of the purely synthetic C_2-symmetric chiral quaternary ammonium salt **3** which efficiently catalyzes the alkylation of **1** under mild conditions.[6] During our continuing efforts on this project, we have been interested in the inherent efficiency of this catalyst and thus assessed the validity of this catalyst under typical phase-transfer conditions. In this paper, we report the results of this study, revealing the practical conditions for the asymmetric synthesis of α-amino acids.

For our purpose, we simply investigated the effect of catalyst loading on the chemical yield as well as enantioselectivity in the phase-transfer benzylation of **1**, where toluene-50% aqueous KOH system (volume ratio = 3:1) was employed with $[\mathbf{1}]_{org} = 0.17$ M at 0 °C under an argon atmosphere.[7] As revealed in Table 1, reaction with 0.5 mol % of (*S*,*S*)-**3** gave comparable results with the case of the previously reported 1 mol % recipe (entry 2) and a synthetically satisfactory chemical yield (83%) was still attained with 0.3 mol % of the catalyst (entry 3). Although further reduction of the catalyst loading diminished the chemical yield, the loss of enantiomeric excess was almost negligible, which probably stems from the extremely slow background reaction in this liquid-liquid phase-transfer system (entries 4 and 5). Based on these results, we further examined the reaction conditions with 0.2 mol % of (*S*,*S*)-**3** to induce higher catalytic efficiency, and the

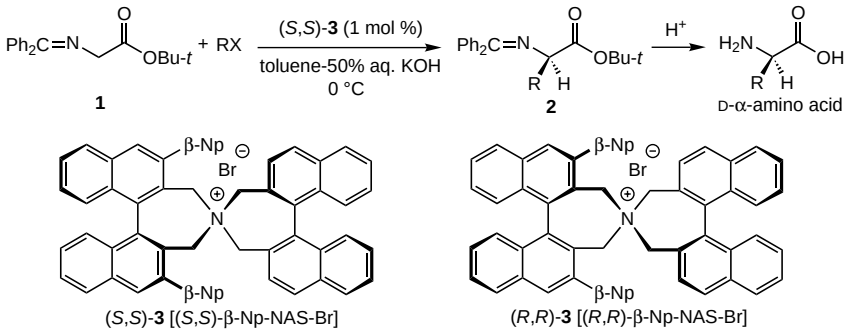
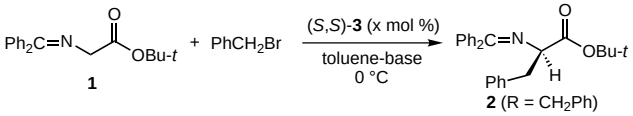


Table 1. Effect of the catalyst loading and base on the reactivity and selectivity.[a]



Entry	Catalyst loading [x, mol %]	Base	Reaction time [h]	Yield [%][b]	% ee[c] (configuration)[d]
1	1.0	50% aq. KOH	1.5	93	96 (*R*)
2	0.5	50% aq. KOH	2.5	92	96 (*R*)
3	0.3	50% aq. KOH	3.5	83	96 (*R*)
4	0.2	50% aq. KOH	3.5	76	96 (*R*)
5	0.1	50% aq. KOH	4.0	54	95 (*R*)
6[e]	0.2	50% aq. KOH	4.0	51	96 (*R*)
7[e]	0.2	50% aq. KOH	4.0	73	95 (*R*)
8	0.2	KOH powder (1.2 eq.)	26	72	95 (*R*)
9	0.2	KOH powder (2.5 eq.)	9.0	86	92 (*R*)
10	0.2	KOH powder (5.0 eq.)	10	78	88 (*R*)
11	0.2	KOH powder (10 eq.)	10	76	82 (*R*)

[a] Unless otherwise specified, the reaction of glycine Schiff base **1** was carried out with 1.2 equivalents of $PhCH_2Br$ in the presence of catalytic (*S*,*S*)-**3** in toluene ($[\mathbf{1}]_{org} = 0.17$ M) with the appropriate base under the given reaction conditions under an argon atmosphere.

[b] Isolated yield.

[c] Enantiopurity of **2** (R = CH_2Ph) was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD) with hexane-isopropanol as solvent.

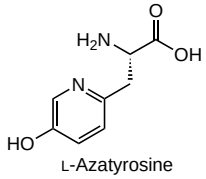
[d] Absolute configuration of **2** was determined as previously reported.[6a]

[e] $[\mathbf{1}]_{org} = 0.10$ M (entry 6) and 0.25 M (entry 7), respectively.

representative results are also included in Table 1. An attempted reaction under more dilute conditions proceeded very sluggishly (entry 6) and the reaction system seemed to become saturated in both catalyst and substrate for $[\mathbf{1}]_{org} = 0.25$ M, leading to the slight decrease of chemical yield and enantioselectivity (entry 7).

We subsequently tested a solid base[8] and found that the use of 2.5 equivalents of KOH powder in toluene at 0 °C resulted in formation of **2** (R = CH_2Ph) in 86% yield, though the enantiomeric excess was decreased to 92% ee (entry 9). Here, enantioselectivity recovered to 95% ee with a reduced amount of KOH powder (1.2 equivalents) at the sacrifice of the chemical yield (72%) (entry 8) and addition of excess base did not afford a beneficial effect in terms of both reactivity and selectivity (entries 10 and 11). Consequently, it would be suggested that the practical procedure for the phase-transfer alkylation of **2** requires 0.3 ~ 0.5 mol % of the catalyst and a substrate concentration in the organic phase of 0.17 M with 50% aqueous KOH as a base.

The applicability of these conditions to other alkyl halides has also been demonstrated, which indicates that the satisfactory product yield and enantioselectivity can be achieved with 0.3 ~ 0.5 mol % of (*S*,*S*)-**3** (Table 2). The usefulness of this practical procedure can be emphasized by the asymmetric synthesis of protected L-azatyrosine.[9] L-Azatyrosine is an antibiotic isolated from *Streptomyces chibaensis*[10] and was reported to inhibit chemical carcinogen-induced tumor growth in mice harboring normal human c-Ha Ras genes.[11] We chose the 2-(bromomethyl)-5-hydroxypyridine derivative **4** as a requisite electrophile in our alkylation according to the Myers' report[9d] and prepared it from commercially available 5-hydroxy-2-methylpyridine. The reaction of **1** with **4** under the optimized conditions using 0.5 mol % of (*R*,*R*)-**3** gave rise to the desired alkylation product **5** in 81% yield with 78% ee and, fortunately, the enantioselectivity was greatly improved to 92% ee by employing the catalyst possessing a 3,5-diphenylphenyl substituent [(*R*,*R*)-3,5-Ph_2-Ph-NAS-Br] as illustrated in Scheme 1.

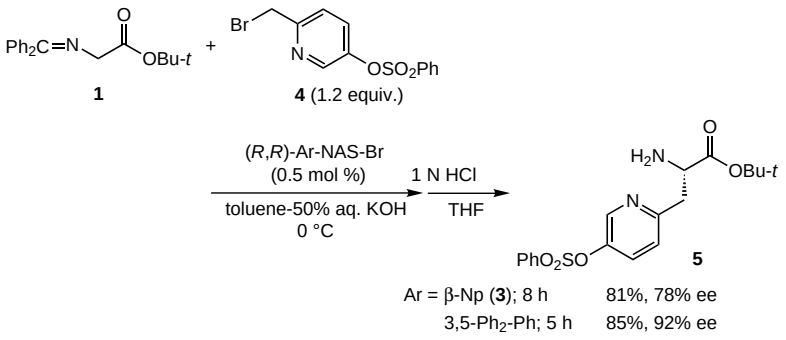


L-Azatyrosine

Experimental Section

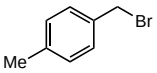
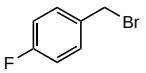
Protected L-Azatyrosine 5

A 25-mL two-necked flask containing a Teflon-coated magnetic stirring bar and a mixture of glycine *tert*-butyl ester benzophenone Schiff base (**1**; 295 mg, 1 mmol), **4** (394 mg, 1.2 mmol), and (*R*,*R*)-3,5-Ph_2-Ph-NAS-Br (5.4 mg, 0.005 mmol) in toluene (6 mL) under an argon atmosphere was



Scheme 1.

Table 2. Practical catalytic enantioselective phase-transfer alkylation of glycine Schiff base **1**.[a]

Entry	RX	Catalyst loading [mol %]	Conditions [°C, h]	Yield [%][b]	% ee[c] (configuration)[d]
1		0.5	0, 2.5	80	92 (*R*)
2		0.3	0, 3	81	90 (*R*)
3		0.3	0, 3	86	95 (*R*)
4		0.3	0, 3	84	94 (*R*)

[a] Unless otherwise specified, the reaction of **1** was carried out with 1.2 equivalents of RX in the presence of catalytic (*S*,*S*)-**3** in 50% aqueous KOH/toluene (volume ratio = 1:3, $[\mathbf{1}]_{org} = 0.17$ M) under the given reaction conditions under an argon atmosphere.

[b] Isolated yield.

[c] Enantiopurity of **2** was determined by HPLC analysis of the corresponding amino ester or its *N*-benzoate using a chiral column [DAICEL Chiralcel OD (entries 1 and 2) and Chiralpak AD (entries 3 and 4)] with hexane-isopropanol as solvent.

[d] Absolute configuration was determined as previously reported.[6a]

immersed in an ice-water bath. After 5 min of gentle stirring, 50% KOH aqueous solution (2 mL) was added and the reaction mixture was stirred vigorously (900 ~ 950 rpm) for 5 h. The resulting mixture was then poured into water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (10 mL) and 1 N HCl (5 mL) was added. This solution was stirred at room temperature for 2 h. After removal of THF under vacuum, the aqueous solution was washed with ether (10 mL × 3), then neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL × 3). The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residual oil by column chromatography on silica gel (CH_2Cl_2/methanol = 15:1 as eluant) gave the corresponding amino ester **5** as a colorless oil; yield: 322 mg (0.85 mmol, 85%); 92% ee. The enantiomeric excess was determined by chiral HPLC analysis [DAICEL CHIRALPAK AD, hexane/isopropanol = 2:1, flow rate = 0.5 mL/min, retention time; 17.5 min (*R*) and 20.7 min (*S*)]. $[\alpha]_D^{25.7}$: −2.67 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (1H, d, *J* = 2.8 Hz, Py), 7.85 (2H, m, Ph), 7.70 (1H, m, Ph), 7.55 (2H, m, Ph), 7.36 (1H, dd, *J* = 2.8, 8.8 Hz, Py), 7.17 (1H, d, *J* = 8.8 Hz, Py), 3.80 (1H, dd, *J* = 5.2, 7.6 Hz, CHC = O), 3.19 (1H, dd, *J* = 5.2, 14.4 Hz, PyCH), 3.01 (1H, dd, *J* = 7.6, 14.4 Hz, PyCH); IR (liquid film): ν = 2978, 2933, 1728, 1588, 1479, 1450, 1379, 1205, 1178, 1094, 1024, 868, 847, 750, 689 cm^{-1}.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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