

Chiral Camphor Derivatives as New Catalysts for Asymmetric Phase-Transfer Alkylation

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The synthesis of new chiral phase-transfer catalysts based on the optical camphor is described. The alkylation of the benzophenone imine of glycine *tert*-butyl ester with benzyl bromide in the presence of new chiral phase-transfer catalysts afforded the desired alkylation product in good yields and up to 39% *ee*.

Keywords Phase-transfer catalyst, asymmetric alkylation, chiral camphor derivatives

Introduction

Phase-transfer catalysis (PTC) plays an important role in the synthetic organic chemistry, and has many advantages over conventional, homogeneous procedure.¹ During the last decade, asymmetric synthesis using chiral PTC condition attracted an increasing attention, and impressive level of enantiocontrol has been achieved in the alkylation and other phase-transfer reactions.^{2,3} However, the number of chiral phase-transfer catalysts so far reported is limited, most of them are quaternary ammonium salts derived from *cinchona* alkaloids. Obviously, it is significant to develop a new type of chiral catalyst for expanding the applicability of asymmetric PTC reactions.

Camphor derivatives have been widely used as chiral auxiliary in the field of asymmetric synthesis.⁴ Compared to *cinchona* alkaloid derivatives, camphor deriva-

tives also have a rigid skeleton and are easier to be designed and tuned rationally for various reactions in the phase-transfer catalyzed condition. In this paper we wish to describe the synthesis of a new type of chiral phase-transfer catalysts based on camphor and their application in the asymmetric phase-transfer alkylation of benzophenone imine of glycine *tert*-butyl ester.

Results and discussion

Preparation of phase-transfer catalysts

The chiral quaternary ammonium salts **2** were synthesized in 66—95% yields by alkylation of amino alcohol **1** which was prepared by previous reported methods⁵ from commercially available (1*R*)-(–)-10-camphorsulfonic acid as shown in Scheme 1. The structure of **2b** was successfully determined by single-crystal X-ray diffraction analysis as shown in Fig. 1.⁶

Enantioselective phase-transfer catalyzed alkylation

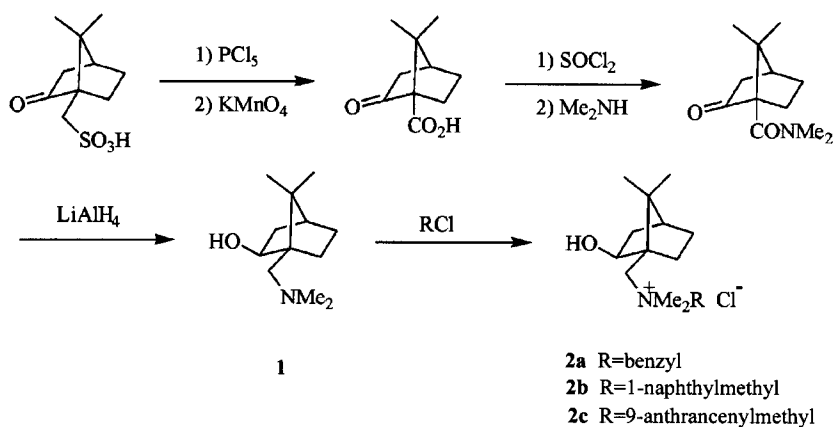
Phase-transfer catalyzed enantioselective alkylation of benzophenone imine of glycine *tert*-butyl ester, initiated by O'Donnell using *cinchona* alkaloid derivatives as the catalyst in 1989, is one of the most well-documented reaction in asymmetric PTC which provided a new

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Scheme 1



approach to the synthesis of α -amino acid derivatives.⁷ Significant improvements in the *cinchona* alkaloid catalysts for getting high level of enantiocontrol have been reported by Corey⁸ and Lygo groups.⁹ Recently, Maruoka developed a C_2 -symmetric chiral phase-transfer catalyst derived from optical binaphthol, which was shown to be effective in the chiral discrimination in this reaction.¹⁰ In order to evaluate the efficiency of catalysts **2** in asymmetric phase-transfer reaction, we initially investigated the alkylation of imine **3** with benzyl bromide. The preliminary results are summarized in Table 1.

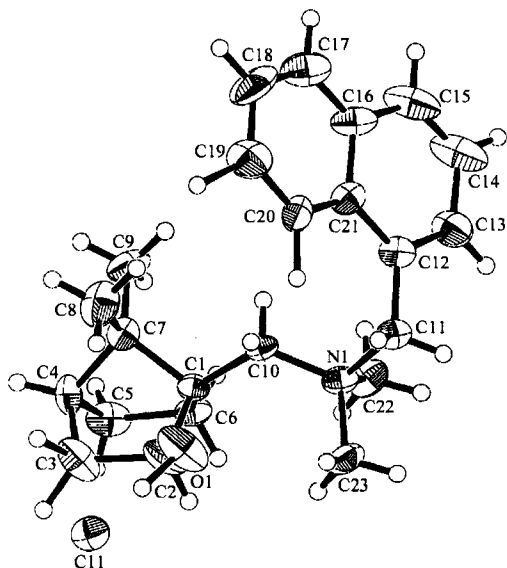


Fig. 1 ORTEP diagram of the catalyst **2b**.

The reaction was carried out at -15°C using 10 mol% of catalysts **2**. When toluene was used as organic phase and 30% aq. KOH as aqueous phase, the alkyla-

tion product **4** could be isolated in 30% yield with 17% *ee*. The analysis of by-products showed that the hydrolysis of starting imine was the major reason for the low yield. Increasing the concentration of KOH to 50% led to the increase of the yield and the enantiomeric excess of alkylation product. Even higher enantioselectivity was obtained when solid KOH was used. The use of NaOH and CsOH decreased enantioselectivities of alkylation reaction although a high yield was given in the case of solid CsOH. Other organic solvents, instead of toluene, were also investigated. Lower enantioselectivities were obtained by using benzene. However, there was no asymmetric induction in the reaction with CH_2Cl_2 or CH_3CN as organic phase. Comparison of three catalysts **2a**—**c**, varied with the R group, showed that **2b** was the catalyst which gave the highest enantioselectivity.

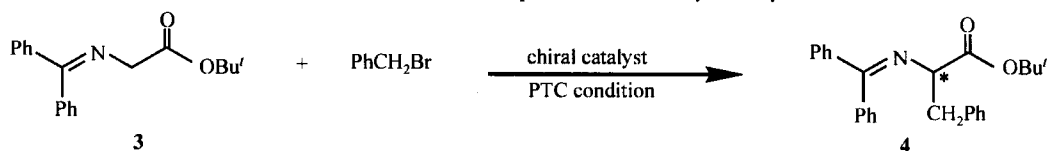
We are currently investigating the applications of the new chiral phase-transfer catalysts to other asymmetric phase-transfer reactions.

Experimental

Preparation of chiral quaternary ammonium salts

General procedure A mixture of (–)-*N,N*-dimethyl-10-amino-2-exo-borneol (0.392 g, 2 mmol)⁵ and benzyl chloride (1.0 g, 8 mmol) was heated at 80 – 85°C for 1.5 h. After cooling the mixture to room temperature, acetone (10 mL) was added. The precipitate formed was collected by filtration and washed with acetone. The crude product was recrystallized with

ethanol/acetone.

Table 1 Enantioselective phase-transfer catalyzed alkylation

Entry	Catalyst	Solvent ^a	Base	Time (h)	Yield (%) ^b	ee (%) ^c
1	2a	Toluene	30% aq. KOH	6	30	17
2	2a	Toluene	50% aq. KOH	2	67	26
3	2a	Toluene	solid KOH	3	61	30
4	2a	Toluene	solid CsOH	1	80	6
5	2a	Benzene	50% aq. NaOH	1.3	32	5
6	2a	Benzene	50% aq. KOH	2.5	50	21
7	2a	CH ₂ Cl ₂	50% aq. KOH	4	45	0
8	2a	CH ₃ CN	50% aq. KOH	2.5	76	0
9	2b	Toluene	50% aq. KOH	1	63	30
10	2b	Toluene	solid KOH	1.5	71	39
11	2b	Benzene	50% aq. KOH	2	80	20
12	2b	Benzene	solid KOH	2	79	20
13	2c	Toluene	50% KOH	1	67	23
14	2c	Toluene	solid KOH	1	72	29

^aOrganic solvent 3.0 mL, aq. base 0.67 mL. ^b Isolated yields. ^c Determined by HPLC (DAICEL CHIRALCEL OD-H column, *n*-hexane/2-propanol = 99:1, 1 mL/min).

2a White solid, yield 95%, mp 268–270°C. $[\alpha]_D^{20} + 15$ (*c* 1.0, EtOH). IR: 3300s, 2950s, 2870s, 1480s, 1455s, 1432s, 1390s, 1320m, 1260s, 1220s, 1070s, 1035m, 1005m, 940w, 860m, 810s, 780m, 730s, 705s, 630m. ¹H NMR (CDCl₃) δ: 0.89 (s, 3H), 1.09 (s, 3H), 1.16–1.21 (m, 1H), 1.40–1.45 (m, 1H), 1.69–1.70 (m, 1H), 1.76–1.93 (m, 4H), 3.26 (s, 3H), 3.31 (d, *J* = 13.6 Hz, 1H), 3.38 (s, 3H), 4.03 (d, *J* = 13.6 Hz, 1H), 4.10–4.14 (m, 1H), 4.91 (s, 2H), 5.58 (d, *J* = 2.82 Hz, 1H), 7.43–7.50 (m, 3H), 7.67 (d, *J* = 7.17 Hz, 2H). MS *m/z* (%): 288 (M – Cl, 1.04), 287 (M – 1 – Cl, 3.64), 274 (3.56), 273 (15.50), 198 (7.19), 197 (50.14), 195 (8.02), 179 (6.26), 134 (7.86), 91 (20.72), 58 (4.55), 57 (100). Anal. C₁₉H₃₀ClNO. Calcd: C, 70.45; H, 9.34; N, 4.33. Found: C, 70.30; H, 9.37; N, 4.21.

2b White solid, yield 88%, mp 220–222°C. $[\alpha]_D^{20} + 5$ (*c* 1.0, EtOH). IR: 3530m, 3380s, 3250s, 3050w, 3020w, 2950s, 2930s, 2880m, 1650w, 1515w, 1475m, 1450m, 1435w, 1390w, 1360w, 1080s, 1048w, 890s, 830s, 810m, 780s, 600m. ¹H NMR (CDCl₃) δ: 0.75 (s, 3H), 1.05 (s, 3H),

1.15–1.20 (m, 1H), 1.39–1.43 (m, 1H), 1.69 (t, *J* = 4.03 Hz, 1H), 1.73–1.79 (m, 1H), 1.83–1.94 (m, 3H), 3.25 (s, 3H), 3.30 (d, *J* = 13.5 Hz, 1H), 3.53 (s, 3H), 4.13–4.15 (m, 1H), 4.25 (d, *J* = 13.5 Hz, 1H), 5.11 (d, *J* = 4.3 Hz, 1H), 5.41–5.47 (m, 2H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 8.46 (d, *J* = 8.6 Hz, 1H). MS *m/z* (%): 338 (M – Cl, 0.73), 337 (M – 1 – Cl, 1.89), 198 (27.31), 197 (9.31), 176 (20.78), 142 (12.64), 141 (90.8), 139 (14.21), 115 (20.08), 57 (100). Anal. C₂₃H₃₂ClNO. Calcd: C, 73.87; H, 8.62; N, 3.75; Found: C, 73.89; H, 8.77; N, 3.79.

2c White solid, 66% yield, mp 190–192°C. $[\alpha]_D^{20} + 35.4$ (*c* 0.42, EtOH). IR: 3220s, 3070w, 3040w, 2980w, 2950m, 2900m, 1480m, 1470m, 1450w, 1080m, 975w, 900w, 845w, 825m, 740m. ¹H NMR (CDCl₃) δ: 0.62 (s, 3H), 0.95 (s, 3H), 1.11–1.13 (m, 1H), 1.29–1.35 (m, 1H), 1.61–1.73 (m, 5H), 3.09 (s, 3H), 3.15 (d, *J* = 13.6 Hz, 1H), 3.56 (s, 3H), 4.10–4.12 (m,

1H), 4.29 (d, $J = 13.6$ Hz, 1H), 5.34 (s, 1H), 5.96 (d, $J = 4.1$ Hz, 1H), 6.09 (d, $J = 4.1$ Hz, 1H), 7.45—7.51 (m, 1H), 7.63—7.73 (m, 2H), 8.00 (d, $J = 8.3$ Hz, 2H), 8.55 (s, 1H), 8.62 (d, $J = 9.0$ Hz, 1H), 8.82 (d, $J = 9.0$ Hz, 1H). MS m/z (%): 388 (M - Cl, 1.98), 387 (M - 1 - Cl, 4.79), 226 (13.54), 199 (9.71), 198 (68.00), 197 (13.20), 192 (19.24), 191 (95.74), 190 (10.55), 189 (23.37), 57 (100). Anal. $C_{27}H_{34}ClNO$. Calcd: C, 76.48; H, 8.08; N, 3.30. Found: C, 76.40; H, 8.04; N, 3.41.

Enantioselective phase-transfer catalyzed alkylation of imine **3**

General procedure A mixture of imine **3** (100 mg, 0.34 mmol), benzyl bromide (290 mg, 1.70 mmol), catalyst **2b** (13 mg, 10 mol%), 50% aq. KOH (0.67 mL) and toluene (3.0 mL) was stirred vigorously at $-15^{\circ}C$ for 1.5 h. The mixture was then poured into water (10 mL) and extracted with diethyl ether. The organic extracts were washed with brine and dried over Na_2SO_4 . Evaporation of solvents and purification of the residue with flash column chromatography on silica gel with petroleum ether/ethyl acetate (95:5) gave product **4** as a colorless oil (92 mg, 71%). The enantiomeric excess (39% ee) was determined by chiral HPLC (DAICEL CHIRALCEL OD-H, $\lambda = 254$ nm, n -hexane/2-propanol = 99:1, 1 mL/min, $t_R = 6.518$ min, $t_S = 9.245$ min).

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- Crystal structure data of **2b**: $C_{23}H_{32}ClNO$, $M_w = 374.95$, colorless prismatic crystal, $0.20 \times 0.20 \times 0.30$ mm, primitive triclinic, $P1$, $a = 9.408(3) \times 10^{-1}$ nm, $b = 15.670(4) \times 10^{-1}$ nm, $c = 9.143(2) \times 10^{-1}$ nm, $\alpha = 94.06(2)^{\circ}$, $\beta = 114.02(2)^{\circ}$, $\gamma = 77.80(2)^{\circ}$, $V = 1203.1(6) \times 10^{-3}$ nm³. $T = 293$ K, $Z = 1$, $D_{\text{calcd}} = 1.18$ g/cm³, $R = 0.058$.
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