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SPIRO CROWN ETHERS BEARING (*S*)-1,1'-SPIROBIINDANES AS CHIRAL BACKBONES

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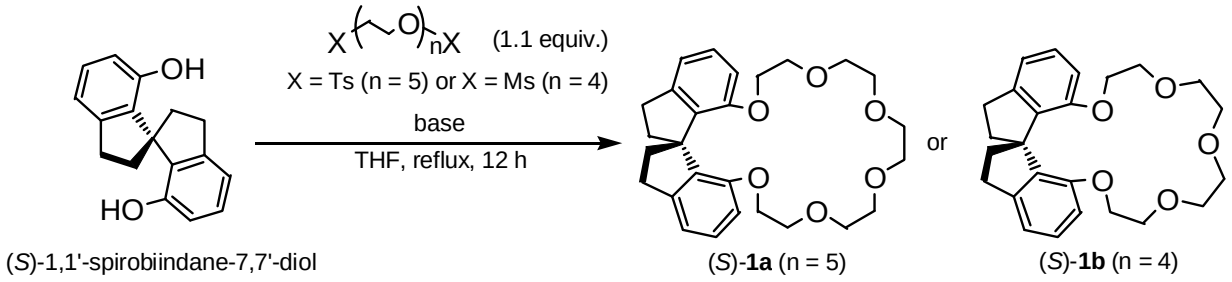
Abstract – The synthesis of spiro chiral crown ethers ((*S*)-**1a**) and ((*S*)-**1b**) has been achieved. The combination of (*S*)-**1a** and KOH promoted the asymmetric alkylation of glycine derivative (**2**) with moderate enantioselectivity.

Chiral phase transfer catalysis has been recognized as a practical methodology for asymmetric synthesis because of its mild reaction conditions and also because of environmental concerns.[1] The design of novel chiral phase transfer catalysts has been one of the most important challenges in the development of asymmetric reactions. Thus far, a large number of optically pure crown ethers derived from chiral natural products and chiral 1,1'-bi-2-naphthol derivatives have been prepared and applied in a variety of asymmetric reactions.[2] Previously, our group reported the design and synthesis of spiro compounds either as ligands or catalysts, which includes isoxazolines,[3a-e] isoxazoles,[3f] oxazolines,[3g] pyrazoles,[3h] pyridinium salts,[3i] and quinolinium salts.[3i] In continuation with our study, this paper deals with the synthesis of chiral spiro crown ethers ((*S*)-**1**) and preliminary studies on their application to asymmetric alkylation. The incorporation of crown ether units into a chiral rigid spiro skeleton would provide chiral phase transfer catalysts.[4]



(*S*)-1,1'-spirobiindane-7,7'-diol (*S*)-**1a** (n = 5) (*S*)-**1b** (n = 4)

Scheme 1. Synthesis of spiro crown ethers ((*S*)-**1**)

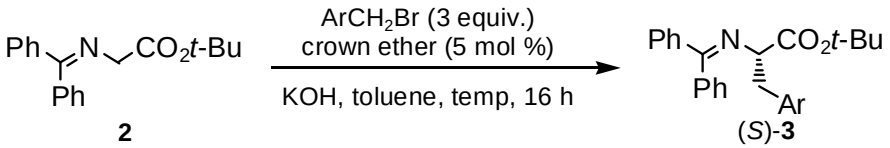
A diluted solution of (*S*)-1,1'-spirobiindane-7,7'-diol[5] and pentaethylene glycol bis(*p*-toluenesulfonate)[6]

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

in THF (0.075 M) was stirred under reflux condition for 12 h in the presence of *tert*-BuOK (2.1 equiv.). The desired chiral spiro crown ether ((*S*)-**1a**) was obtained in 66% yield with the recovery of (*S*)-spiro diol as a starting material in 21% yield. The spiro crown ether ((*S*)-**1b**) was also synthesized using a similar route for (*S*)-**1a**. These spiro crown ethers ((*S*)-**1a**) and ((*S*)-**1b**) are stable under both acidic and basic conditions.[7]

Next, the catalytic efficiency of chiral spiro crown ethers ((*S*)-**1a**) and ((*S*)-**1b**) as chiral phase transfer catalysts was evaluated in the alkylation of glycine derivative (**2**), which is used in numerous synthesis of optically active α-amino acids (Table 1).[1] Among the reaction conditions examined,[8] the combination of (*S*)-**1a** and excess amount of solid KOH (18 equiv.) in toluene promoted the reaction of **2** with benzyl bromide to afford the product ((*S*)-**3a**) in good yield with moderate enantioselectivity. The slow addition of **2** slightly improved the degree of chiral induction (Table 1, entry 2). A marginal effect on the enantioselectivity of the product with a decrease in the chemical yield was observed at low temperature (entry 4). The attempts to reduce catalyst loading (0.2 mol %) caused a decrease in enantioselectivity (entry 5). The use of bulky alkyl halides such as 9-bromomethylanthracene afforded the corresponding product with moderate enantioselectiveity. In order to rule out the possibility of kinetic resolution of product (**3**) in the presence of chiral crown ether, each racemic and enantiomerically enriched **3** (*R* form of 46% ee and/or *S* form of 94% ee) was stirred under the alkylation condition. However, racemic **3** was recovered in 96% yield. The enantiomerically enriched **3** also recovered without decreasing their ee values. These results suggested that the kinetic resolution did not occur in the reaction mixture.

Table 1. Asymmetric alkylation of **2** with $ArCH_2Br$ using spiro crown ethers ((*S*)-**1**)



entry	$ArCH_2Br$	crown ether	KOH (equiv.)	temp (°C)		yield (%) [a]	ee (%) [b]
1	$PhCH_2Br$	(*S*)-**1a**	3	0	(*S*)-**3a**	60	41
2	$PhCH_2Br$	(*S*)-**1a**	18	0	(*S*)-**3a**	79	50 (63[c])
3	$PhCH_2Br$	(*S*)-**1a**	18 [d]	0	(*S*)-**3a**	57	39
4	$PhCH_2Br$	(*S*)-**1a**	3	-20	(*S*)-**3a**	42	42
5	$PhCH_2Br$	(*S*)-**1a** [e]	18	0	(*S*)-**3a**	81	36
6	9-bromomethylanthracene	(*S*)-**1a** [f]	18	0	(*S*)-**3b**	55	53
7	$PhCH_2Br$	(*S*)-**1b**	3	0	(*S*)-**3a**	20	14

a) Isolated yield
b) Determined by HPLC (DAICEL CHIRALCEL OD, hexane/*i*-PrOH = 99/1)
c) Slow addition of **2** was performed overnight.
d) 50% aq. KOH was used.
e) 0.2 mol % of (*S*)-**1a** was used.
f) 10 mol % of (*S*)-**1a** was used.

The spiro crown ether ((*S*)-**1a**) was quantitatively recovered by a simple column chromatographic purification after the completion of the reaction.

In conclusion, the synthesis of spiro crown ethers ((*S*)-**1**) which act as a chiral phase transfer catalyst has been described. In a preliminary study, the combination of (*S*)-**1a** and KOH promoted the asymmetric alkylation reaction of glycine derivative (**2**) with moderate enantioselectivity. Further studies for the development of a new asymmetric reaction using spiro crown ethers are under way.

EXPERIMENTAL

General procedures

^{1}H- and ^{13}C-NMR spectra were recorded with JEOL JNM-EX 270 FT NMR (^{1}H-NMR-270 MHz, ^{13}C-NMR-67.7 MHz). All signals were expressed as ppm down field from tetramethylsilane which was used as an internal standard. IR spectral data were obtained on a Shimadzu FTIR 8300. The optical rotations were measured with a JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/VIS detector) using a mixture of hexane and *i*-PrOH as the eluent. MS spectra were obtained on a JEOL JMS-700 (for FAB-MS) and JMS-T100LC (for ESI-MS). The melting points were measured with a Yanaco Micro Melting Point Apparatus Model MP-S9. Column chromatography was performed using Kanto Silica Gel 60 (40-100 μm). Anhydrous THF and toluene were purchased from Kanto Chemicals, Tokyo.

(*S*)-1,16-[7,7'-(1,1'-Spirobiindano)]-1,4,7,10,13,16-hexaoxahexadecane ((*S*)-1a): To a stirred solution of (*S*)-1,1'-spirobiindane-7,7'-diol (76 mg, 0.30 mmol) in anhydrous THF (4.0 mL) was added *tert*-BuOK (70.7 mg, 0.63 mmol) at 0 ^{o}C under argon atmosphere. This mixture was allowed to stir at rt for 20 min. The reaction mixture was then cooled to 0 ^{o}C and pentaethylene glycol bis(*p*-toluenesulfonate) (180 mg, 0.33 mmol) was added in one portion. The reaction mixture was stirred under reflux condition for 12 h. The reaction mixture was then cooled to rt and poured into ice-cold water and acidified using 1N HCl. After stirring for 10 min, the pH was adjusted to 7 by using sat. aq. sodium hydrogen carbonate followed by extraction with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to yield (*S*)-**1a** (90 mg, 66%) as a white solid. mp: 72 ^{o}C ($CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.06-2.26 (m, 4H), 2.89-2.94 (m, 4H), 3.13-3.26 (m, 4H), 3.40-3.59 (m, 12H), 3.78-3.83 (m, 2H), 3.94-3.99 (m, 2H), 6.60 (d, *J* = 7.82 Hz, 2H), 6.75 (d, *J* = 7.28 Hz, 2H), 7.01 (t, *J* = 7.68 Hz, 2H); ^{13}C-NMR ($CDCl_3$): δ 31.5, 38.4, 59.2, 67.8, 69.3, 70.5, 70.7, 70.8, 109.7, 116.8, 127.3, 137.2, 145.0, 155.3; IR (neat): 3007, 2932, 2870, 1603, 1586, 1474, 1458, 1349, 1304, 1264, 1131, 1089, 1006, 947, 773, 748, 515, 507 cm^{-1}; MS (ESI-HRMS) calcd for $C_{27}H_{34}O_6Na$ [M+Na^{+}]: 477.2248, Found: 477.2250; $[\alpha]_D^{27}$ -56.9^{o} (c 1.47, $CHCl_3$).

(*S*)-1,13-[7,7'-(1,1'-Spirobiindano)]-1,4,7,10,13-pentaoxatridecane ((*S*)-1b): To a stirred solution of (*S*)-1,1'-spirobiindane-7,7'-diol (25.3 mg, 0.10 mmol) in anhydrous THF (2.0 mL) was added 60% NaH (10 mg, 0.25 mmol) at 0 °C under argon atmosphere. This mixture was allowed to stir at rt for 10 min. The reaction mixture was then cooled to 0 °C and tetraethylene glycol bis(methanesulfonate)[9] (43.4 mg, 0.11 mmol) was added in one portion. The reaction mixture was stirred under reflux condition for 12 h. The reaction mixture was then cooled to rt and poured into ice-cold water and acidified using 1N HCl. After stirring for 10 min, the pH was adjusted to 7 by using sat. aq. sodium hydrogen carbonate followed by extraction with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give (*S*)-**1b** (20 mg, 49%) as a white solid and recover the (*S*)-spiro diol as a starting material in 40% yield. mp: 70 °C ($CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.15-2.34 (m, 4H), 2.96-3.02 (m, 4H), 3.22-3.33 (m, 6H), 3.45-3.54 (m, 6H), 3.82-3.88 (m, 2H), 4.13-4.15 (m, 2H), 6.75 (d, *J* = 8.09 Hz, 2H), 6.82 (d, *J* = 7.28 Hz, 2H), 7.09 (t, *J* = 7.82 Hz, 2H); ^{13}C-NMR ($CDCl_3$): δ 31.5, 38.4, 59.9, 67.4, 70.3, 71.4, 71.4, 109.9, 116.7, 127.3, 137.2, 145.0, 155.5; IR (neat): 3016, 2931, 2857, 1719, 1586, 1475, 1302, 1262, 1217, 1090, 941, 771, 668, 514, 502 cm^{-1}; MS (ESI-HRMS) calcd for $C_{25}H_{30}O_5Na$ [M+Na^+]: 433.1985, Found: 433.2006; $[\alpha]_D^{27}$ -52.1° (c 0.28, $CHCl_3$).

General procedure for catalytic asymmetric alkylation reaction using chiral spiro crown ethers: To a mixture of **2** (75 mg, 0.254 mmol), solid KOH (253 mg, 4.57 mmol) and chiral crown ether ((*S*)-**1b**) (5.8 mg, 5 mol %) in anhydrous toluene (0.68 mL) was added benzyl bromide (0.090 mL, 0.762 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 16 h. The mixture was the poured into water and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane/ether=10/1) to give the product (**3a**) (77 mg, 79% yield, 50% ee) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD, hexane/*i*-PrOH = 99/1, 0.5 mL/min, 14.1 min(*R*) and 23.8 min (*S*)).

(**3b**)[10]**:** (DAICEL CHIRALCEL OD, hexane/*i*-PrOH = 99/1, 0.5 mL/min, 22.3 min (*S*) and 29.4 min (*R*)).

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7. Acidic conditions: 5N HCl-THF solution (1/1) at rt for 24 h. Basic conditions: 50% aq. KOH-THF solution (1/1) at rt for 24 h.
8. Results of the reaction using the combination of (*S*)-**1a** and other bases in toluene: 40% aq. NaOH (22 h, 51%, 2% ee), 50% aq. RbOH (168 h, 39%, 39% ee), 50% aq. CsOH (40 h, no reaction). Results of the reaction using the combination of (*S*)-**1a** and 18 equiv. of solid KOH in various solvents for 16 h: THF (59%, 10% ee), CH_2Cl_2 (58%, 27% ee), Et_2O (11%, 29% ee), *t*-BuOMe

(52%, 29% ee), *o*-xylene (62%, 46% ee), *m*-xylene (68%, 38% ee), mesitylene (23%, 30% ee), cyclohexane (48%, 36% ee), hexane (35%, 32% ee).

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