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DEVELOPMENT OF NOVEL OPTICALLY ACTIVE TWO-CANTER PHASE-TRANSFER CATALYSTS FOR ENANTIOSELECTIVE SYNTHESIS OF α-AMINO ACID

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ABSTRACT

New optically active bis-quaternary ammonium salts were synthesized and applied to catalytic asymmtric alkylation of tert-butyl glycinate benzophenone Schiff base to provide a chiral α-amino acid derivative with 54% ee.

Stereoselective synthesis of both nature and non-natural α-amino acids is an important subject in the field of synthetic and bioorganic chemistry. Asymmetric alkylation of glycine ester benzophenone Schiff base using chiral phase-transfer catalyst is a powerful method for this purpose (figure 1) [1]. Recently, Maruoka developed a series of chiral spiro ammonium salts **1** as efficient phase-transfer catalysts for this asymmetric alkylation (figure 2) [2]. However, a large number of reaction steps were required for the synthesis of catalysts **1**. In this paper, we desribe the design and concise synthesis of novel optically active bis-quaternary ammonium salts **2** (figure 2) and their application to catalytic asymmetric alkylation to provide α-amino acid derivatives.

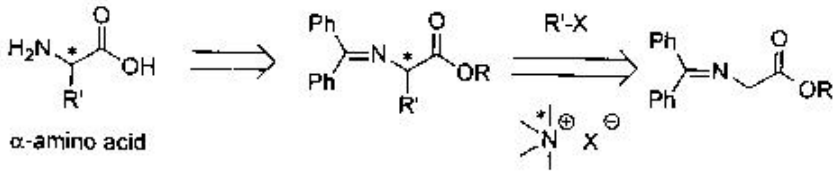


Figure 1: Approach to the synthesis of chiral α-amono acids

Synthesis of (*S*,*S*,*S*)-**2** was started from commercially available (*S*)-BINOL as shown in scheme 1 [3 - 7]. (*S*)-BINOL was converted to (*S*)-2,2'-bis(bromomethyl)-1,1'-binaphthyl[(*S*)-**3**] according to known procedure [8]. Azidation of (*S*)-**3** with sodium azide and following Pb-catalyzed hydrogenation provided (*S*)-2,2'-bis(aminomethyl)-1,1'-binaphthyl [(*S*)-**5**] with quantitative yield. The reaction of (*S*)-**5** with 2 equivalent of (*S*)-**3** gave (*S*,*S*,*S*)-**6** with 64% yield, and then treatment of (*S*,*S*,*S*)-**6** with benzyl bromide afforded desired bis-quanternary ammonium salts (*S*,*S*,*S*)-**2** with 83% yield. (*S*,*S*,*S*)-**2** was also synthesized with (*S*)-**5** and (*R*)-**3** by the same procedure.

Next, we applied new phase-transfer catalysts **2** to asymmetric alkylation of **7** (table 1). The reaction of **7** with 1.2 equivalent of

benzyl bromide in the presence of 2 mol% of (*S*,*S*,*S*)-**2** under basic conditions afforded 55% yield of desired alkylated product **8** with 42% ee (entry 2) whereas the use of (*S*,*S*,*S*)-**2** showed poor asymmetric induction (entry 1). The reaction under lower temperature increased enantioselectivity to 54% ee (entry 3).

In conclusion, we have developed new optically active bis-quaternary ammonium salts **2**. Asymmetric benzylation of **7** using (*S*,*S*,*S*)-**2** as a phase-transfer catalyst provided α-amino acid derivatives **8** with 54% ee. Further improvement of catalysts structure as well as optimization of the reaction conditions are undergoing.

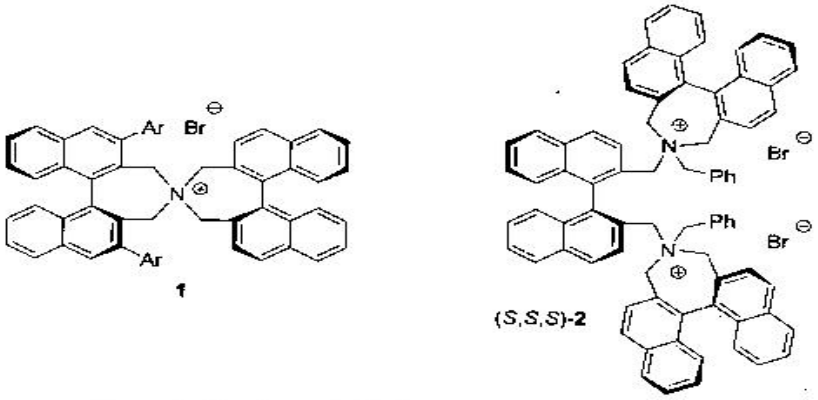
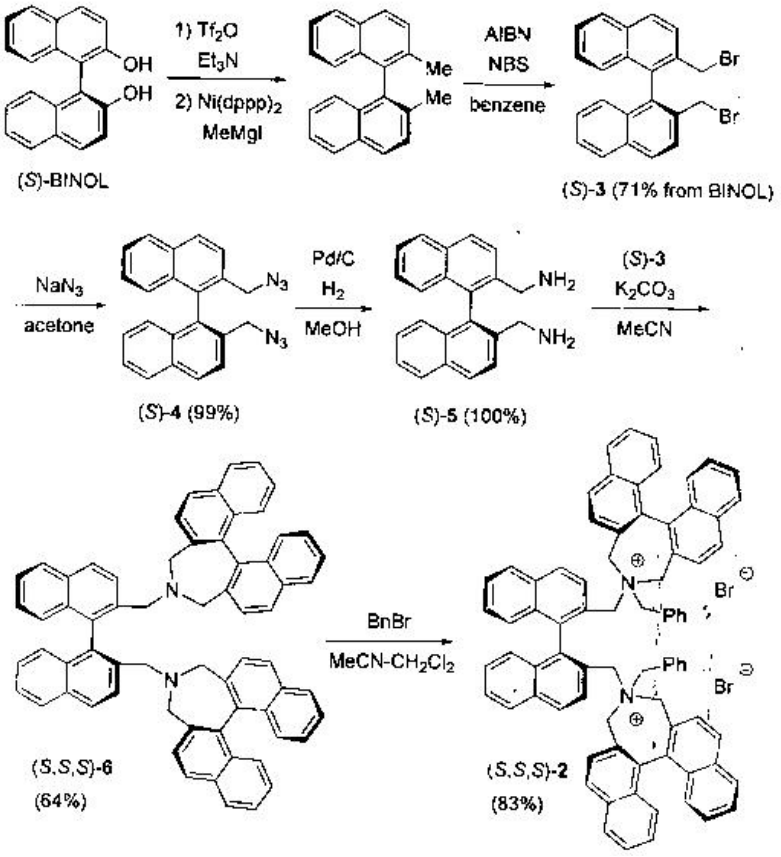
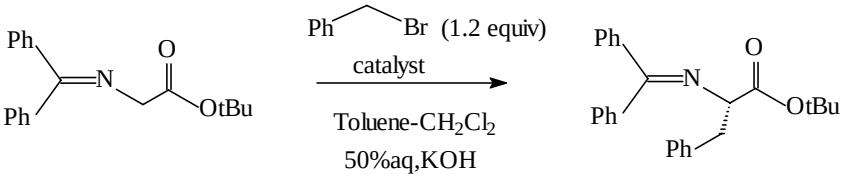


Figure 2: Structure of chiral quaternary ammonium salts



Scheme 1: Synthesis of bis-quaternary ammonium salts (*S*,*S*,*S*)-**2**

Table 1: Asymetric alkylation with phase-transfer catalyst **2** [a]



Entry	Catalyst (mol%)	Temp., °C	Time, h	%Yield[b]	%ee[c](config.)
1	(*S*,*R*,*R*)-**1**(2)	0	0.5	47	2(S)
2	(*S*,*S*,*S*)-**1**(2)				
3	(*S*,*S*,*S*)-**1**(10)	S20	3	45	54

(a) All reactions were carried out with 1.2 equiv. of benzyl bromide
(b) Isolated yield
(c) Determined by HPLC analysis.

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REFERENCES AND NOTES

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2. T. Ooi, M. Kameda, K. Maruoka. J. Am. Chem. Soc., 121, 6519 (1999).
3. (*S*)-**3**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ8.03 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.50 (ddd, J = 8.1, 6,9, 1.2 Hz, 2H), 7.28 (ddd, J = 8.4, 6.9, 1.1 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 4.26 (s, 4H), pp.
4. (*S*)-**4**: ^{1}H-NMR (300 MHz, $CDCl_3$), δ8.06 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 8.7 HZ, 2H), 7.51 (dd, J = 8.1, 8.3 Hz, 2H), 7.29 (dd, J = 7.5, 7.7 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 4.08 (s, 4H), ppm.
5. (*S*)-**5**: ^{1}H-NMR (300 MHz, $CDCl_3$), δ 8.00 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H), 7.7 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 7.5, 6.0 Hz, 2H), 7.23 (dd, J = 7.5, 7.8 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 3.56 (d, J = 13.8 Hz, 2H), 3.48 (d, J = 13.8 Hz, 2H) ppm.
6. (*S*,*S*,*S*)-**6**: ^{1}H-NMR (300 MHz, $CDCl_3$), δ 8.06 (m, 6H), 7.84 (d, J = 8.4 Hz, 4H), 7.62 (d, J = 8.4 Hz, 4H), 7.42 — 7.09 (m, 22H), 6.83 (m, J = 8.1 Hz, 4H), 3.34 (d, J = 12.3 Hz, 4H), 3,23 (s, 4H), 2.94 (d, J = 12.0 Hz, 4 H), ppm.
7. (*S*,*S*,*S*)-**2**: ^{1}H-NMR (300 MHz, $CDCl_3$), δ 8.36 (d, J = 8.4 Hz, 4H), 8.17 (d, J = 8.4 Hz, 4H), 8.11 (d, J = 8.1 Hz, 4H), 7.93 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.67 — 7.79 (m, 30H), 5.76 (d, J = 13.6 Hz, 2H), 5.20 (d, J = 13.2 Hz, 2H), 4.68 (d, J = 12.9 Hz, 2H), 4.52 (d, J = 12.9 Hz, 4H), 4.29 (d, J = 13.2 Hz, 2H), 3.93 (d, J = 12.3 Hz, 4H) ppm.
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