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Design of new polyamine-based chiral phase-transfer catalysts for the enantioselective synthesis of phenylalanine

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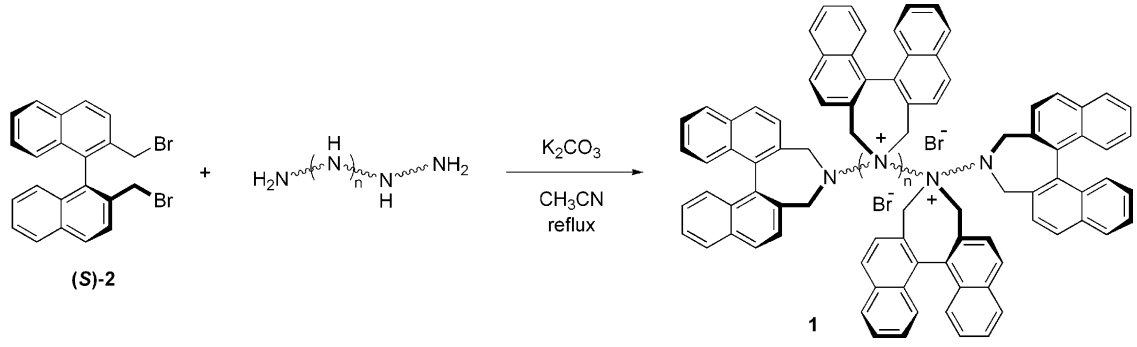
Abstract—Enantiomerically enriched phenylalanine was synthesized by asymmetric benzylation of a glycine Schiff base using polyamine-based chiral phase-transfer catalysts.

Catalytic asymmetric synthesis in the efficient production of enantiomerically enriched compounds is currently of considerable interest in organic synthesis, and as a result a number of chiral metal and nonmetal catalysts have been devised for reaching a useful as well as practical level of selectivity in recent years.[1] The development of efficient enantioselective processes utilizing new chiral catalysts, increasingly requires the rational design of such catalysts. Among these, the use of phase-transfer catalysis for the preparation of chiral, nonracemic organic compounds from prochiral substrates using enantiomerically pure quaternary ammonium salts has become a field of growing importance.[2] Currently, *cinchona*-alkaloid derived chiral phase-transfer catalysts[3] and C_2-symmetric binaphthyl-modified chiral spiro-type phase-transfer catalysts[4] are the best known in this area. In addition to these previous endeavors, we herein report the design of new chiral phase-transfer catalysts of type **1**, based on the use of commercially available polyamine frameworks with the expectation of the multiplier effect of chiral auxiliaries as illustrated in Scheme 1.

A variety of new chiral phase-transfer catalysts **3**–**10** containing several binaphthyl groups were easily prepared via treatment of the corresponding polyamines with dibromide (*S*)-**2**[4j] in refluxing acetonitrile in the presence of K_2CO_3 (Scheme 1, Fig. 1).[5] After simple aqueous work-up (aq $NaHCO_3$), these chiral phase-transfer catalysts were purified by chromatography on silica gel, and identified by mass spectrometric analysis (ESI). They fall into three categories: (i) mono-ammonium salts (*S*)-**3**–(*S*)-**6** derived from triamines, (ii) bis-ammonium salts (*S*)-**7** and (*S*)-**8**,



Scheme 1.

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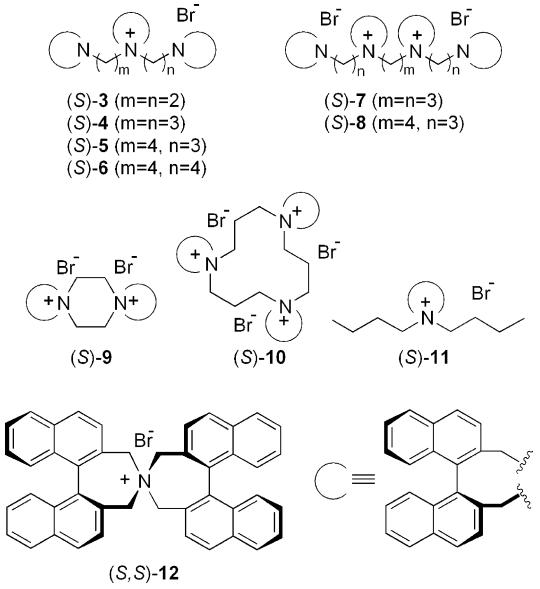

Figure 1.

and (iii) cyclic bis- and tris-ammonium salts (*S*)-**9** and (*S*)-**10**.

We also prepared the simple mono-ammonium salt (*S*)-**11** in order to examine the effect of the polyamine framework.

The chiral efficiency of polyamine-based phase-transfer catalysts (*S*)-**3**–(*S*)-**10** was examined by the asymmetric benzylation of glycine Schiff base **13** with the results summarized in Table 1. When **13** was treated with benzyl bromide in the presence of 3 mol% of chiral catalysts (*S*)-**3**–(*S*)-**10** in toluene/50% aqueous KOH (v/v 3:1) at 0 °C under an argon atmosphere, phenylalanine derivative **14** was obtained in moderate to good yields. As a controlled experiment, chiral quaternary ammonium catalyst (*S*)-**11** derived from dibutylamine gave **14** with an (*S*)-configuration in 60% yield with 20% ee (entry 10). Among the chiral mono-ammonium salts, (*S*)-**5** showed moderate enantioselectivity (50% ee) (entry 3) when compared to (*S*)-**3**, (*S*)-**4**, and (*S*)-**6** (entries 1, 2, and 4). Chiral bis-ammonium salt (*S*)-**8**, derived from spermine, exhibited higher enantioselectivity (63% ee) (entry 6). Interestingly, in the case of (*S*)-**7**, an opposite (*R*)-configuration was obtained (entry 5). While use of cyclic bis-ammonium salt (*S*)-**9** resulted in formation of nearly racemic product **14** (entry 8), the reaction with cyclic tris-ammonium salt (*S*)-**10** predominantly gave the opposite (*R*)-enantiomer (entry 9).

Based on the result that using bis-ammonium salt (*S*)-**8** provided the best result for asymmetric benzylation of **13**, we optimized the reaction conditions with (*S*)-**8**. Lowering the reaction temperature and using $CsOH{\cdot}H_2O$ instead of 50% aqueous KOH, the enantioselectivity was increased at the expense of the reaction rate, with **14** being obtained in 78% yield with 83% ee (entry 7).

We have previously shown that asymmetric benzylation of glycine Schiff base **13** with C_2-symmetric binaphthyl-modified chiral spiro-type phase-transfer catalyst (*S*,*S*)-**12** under identical reaction conditions gave (*R*)-**14** (entry 11).[4j] In contrast, the opposite (*S*)-configuration was obtained by using most of polyammonium catalysts with the (*S*)-binaphthyl moiety. Therefore, both enantiomers of **14** can be synthesized by using a single chiral source.

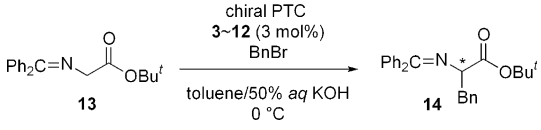

Table 1. Enantioselective benzylation of **13**[a]

Entry	Catalyst	Time (h)	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	**3**	11	51	0	—
2	**4**	2	64	32	*S*
3	**5**	6	76	50	*S*
4	**6**	10	81	7	*S*
5	**7**	4	87	27	*R*
6	**8**	3	76	63	*S*
7[e]	**8**	55	78	83	*S*
8[f]	**9**	2	49	4	*S*
9	**10**	50	46	31	*R*
10	**11**	5	60	20	*S*
11[e]	**12**	36	90	79	*R*

[a] Unless otherwise specified, the reaction was carried out with **13** (0.3 mmol) and 1.2 equiv of benzyl bromide in the presence of 3 mol% of **3**–**12** in 50% aqueous KOH/toluene (v/v 1:3) under the given reaction conditions under argon atmosphere.

[b] Yield of isolated product.

[c] Enantiopurity of **14** was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD) with hexane/2-propanol as solvent.

[d] Absolute configuration of **14** was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[4j]

[e] 5 equiv of $CsOH{\cdot}H_2O$ were used as a base and the reaction was performed at −40 °C.

[f] 5 equiv of KOH powder were used in the absence of H_2O.

In conclusion, novel polyammonium salts[6] containing several binaphthyl groups have been found to be good phase-transfer catalysts for the enantioselective synthesis of phenylalanine. The experimental findings show that the length of methylene chains in the catalysts has a distinct influence not only on the enantioselectivity, but also on the absolute configuration.

Acknowledgements

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References and notes

1. For reviews, see: (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; 2nd ed.; Wiley–VCH: New York, 2000; (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Phaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; (c) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994; (d) Dalko, P. I.; Moison, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3727.
2. For reviews, see: (a) Shioiri, T. In *Handbook of Phase Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; Chapter 14; (b) Ebrahim, S.; Wills, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3163; (c) Esikova, I. A.; Nahreini, T. S.; O'Donnell, M. J. Phase-Transfer Catalysis. In *ACS Symp. Ser. 659*; American Chemical Society: Washington, DC, 1997; Chapter 7; (d) Shioiri, T.; Ando, A.; Masui, M.; Miura, T.; Tatematsu, T.; Bohsako, A.; Higashiyama, M.; Asakura, C. Phase-Transfer Catalysis. In *ACS Symp. Ser. 629*; American Chemical Society: Washington, DC, 1997; Chapter 11; (e) O'Donnell, M. J. Catalytic asymmetric synthesis. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; 2nd ed.; Wiley–VCH: New York, 2000; Chapter 10; (f) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3; (g) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
3. For representative examples: (a) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507; (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; (c) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Chem. Commun.* **1999**, 49; (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671; (e) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097; (f) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245.
4. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519; (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228; (c) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett.* **2001**, 1185; (d) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716; (e) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551; (f) Maruoka, K. *J. Fluorine Chem.* **2001**, *112*, 95; (g) Ooi, T.; Uematsu, Y.; Maruoka, K. *Adv. Synth. Catal.* **2002**, *344*, 288; (h) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542; (i) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 579; (j) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139; (k) Hashimoto, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3313; (l) Hashimoto, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1599.
5. Synthesis of chiral bis-ammonium salt (*S*)-**8**: To a mixture of (*S*)-**2** (440 mg, 1.0 mmol) and K_2CO_3 (249 mg, 1.8 mmol) in acetonitrile (4 mL) was added spermine (40.5 mg, 0.20 mmol) at room temperature. The mixture was heated at reflux with stirring for 5 h, and then poured into water. After extraction with CH_2Cl_2, the organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel ($MeOH/CH_2Cl_2$=1:18 as eluent) afforded chiral bis-ammonium salt (*S*)-**8** (182 mg, 0.12 mmol, 61% yield): IR(film): 3400, 2960, 2360, 2200, 1466, 1363 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ 1.77 (br s, 4H, $CH_2CH_2CH_2CH_2$), 2.21 (br s, 4H, $CH_2CH_2CH_2CH_2$), 2.76 (br m, 4H, $NCH_2CH_2CH_2$), 3.13 (d, J = 12.0 Hz, 4H, $ArCH_2N$), 3.22 (br m, 2H, $NCH_2CH_2CH_2$), 3.37 (br m, 2H, $NCH_2CH_2CH_2$), 3.52 (d, J = 13.2 Hz, 2H, $ArCH_2N$), 3.63 (d, J = 12.4 Hz, 2H, $ArCH_2N$), 3.84 (d, J = 12.0 Hz, 4H, $ArCH_2N$), 3.93 (br m, 2H, $NCH_2CH_2CH_2$), 4.53 (br m, 2H, $NCH_2CH_2CH_2$), 4.90 (d, J = 12.8 Hz, 2H, $ArCH_2N$), 5.04 (d, J = 12.0 Hz, 2H, $ArCH_2N$), 7.17–7.44 (m, 20H, ArH), 7.52–7.59 (m, 6H, ArH), 7.73 (d, J = 8.4 Hz, 4H, ArH), 7.91 (d, J = 8.4 Hz, 12H, ArH), 7.98 (d, J = 8.4 Hz, 2H, ArH), 8.01 (d, J = 8.4 Hz, 2H, ArH), 8.19 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.1, 20.1, 21.7, 29.7, 50.6, 57.4, 58.7, 63.1, 63.2, 125.2, 125.5, 126.3, 126.6, 126.7, 126.8, 126.9, 127.2, 127.5, 128.1, 128.2, 128.3, 128.4, 128.5, 129.8, 130.1, 130.8, 131.0, 131.1, 133.0, 134.0, 134.1, 134.7, 136.0, 136.4; HRMS (ESI-TOF): m/z 658.3359 ($[M-2Br]^{2+}/2$. $C_{98}H_{84}N_4$ requires 658.3348).
6. Recently bis- or tris-ammonium salts as phase-transfer catalysts have been reported: (a) Park, H.; Jeong, B.; Yoo, M.; Park, M.; Huh, H.; Jew, S. *Tetrahedron Lett.* **2001**, *42*, 4645; (b) Jew, S.; Jeong, B.; Yoo, M.; Huh, H.; Park, H. *Chem. Commun.* **2001**, 1244; (c) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539.