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Substituent effect of binaphthyl-modified spiro-type chiral phase-transfer catalysts

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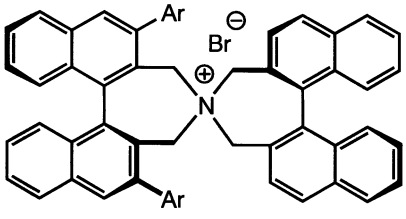
Abstract—Binaphthyl-modified spiro-type phase-transfer catalysts possessing 4,4′-diaryl substituents are shown to exhibit high asymmetric induction in asymmetric benzylation of benzophenone imine glycine *tert*-butyl ester under phase-transfer conditions.

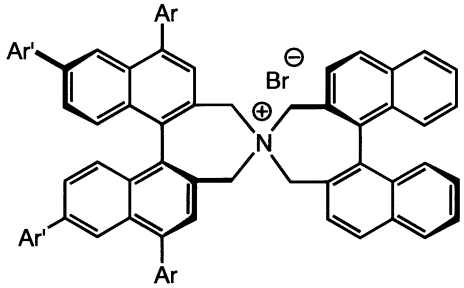
We recently communicated the design of new binaphthyl-modified spiro-type phase-transfer catalysts of type **1**, and their application to the highly practical asymmetric synthesis of various α-alkyl- and α,α-dialkyl-α-amino acids.[1,2] In the series of this work, introduction of 3,3′-diaryl substituents to the parent symmetrical ammonium bromide **1a** is found to be crucially important for obtaining higher enantioselectivity. Indeed, asymmetric benzylation of benzophenone imine glycine *tert*-butyl ester in toluene/50% *aqueous* KOH with 1 mol% of catalysts **1a**–**c** at 0°C gave rise to phenylalanine derivative in 79, 89 and 98% ee's, respectively.[2a,j] During the course of this study, we have been interested in the possibility of examining the effect of adjacent 4,4′-substituents of the catalyst rather than 3,3′-substituents in the asymmetric phase-transfer alkylations. Here we wish to report that even 4,4′-diaryl substituents of the catalysts of type **2** exhibited a meaningful effect on such asymmetric phase-transfer alkylations.

We first prepared (*S*,*S*)-4,4′,6,6′-tetraphenylbinaphthyl derivative **2a** from a synthetic point of view rather than (*S*,*S*)-4,4′-diphenylbinaphthyl derivative **2b**. The reaction sequences for the synthesis of **2a** starting from the known (*S*)-4,4′,6,6′-tetraphenylbinaphthol (**3**)[3] are shown in Scheme 1. Thus, (*S*)-4,4′,6,6′-tetraphenylbinaphthol (**3**) is transformed with Tf_2O and NEt_3 to the corresponding (*S*)-bis-triflate **4** which is then susceptible to the Ni-catalyzed cross-coupling with MeMgI and catalytic $NiCl_2$(dppp) to furnish (*S*)-bis-methyl derivative **5**. Radical bromination of **5** is effected with NBS and catalytic AIBN as radical initiator to afford (*S*)-dibromide **6**. Treatment of **6** with cyclic *secondary* amine **7**[4] as a right-hand side molecule gives the desired spiro-type (*S*,*S*)-ammonium bromide **2a**.

The chiral efficiency of the spiro-type phase-transfer catalyst **2a** was examined by carrying out asymmetric alkylation of benzophenone imine glycine *tert*-butyl



1a (Ar = H)
1b (Ar = Ph)
1c (Ar =3,5-diphenylphenyl)



2a (Ar = Ar' = Ph)
2b (Ar = Ph; Ar' = H))
2c (Ar = Ar' = 3,5-diphenylphenyl)

Keywords: asymmetric alkylation; phase-transfer catalyst; binaphthol; glycine ester.
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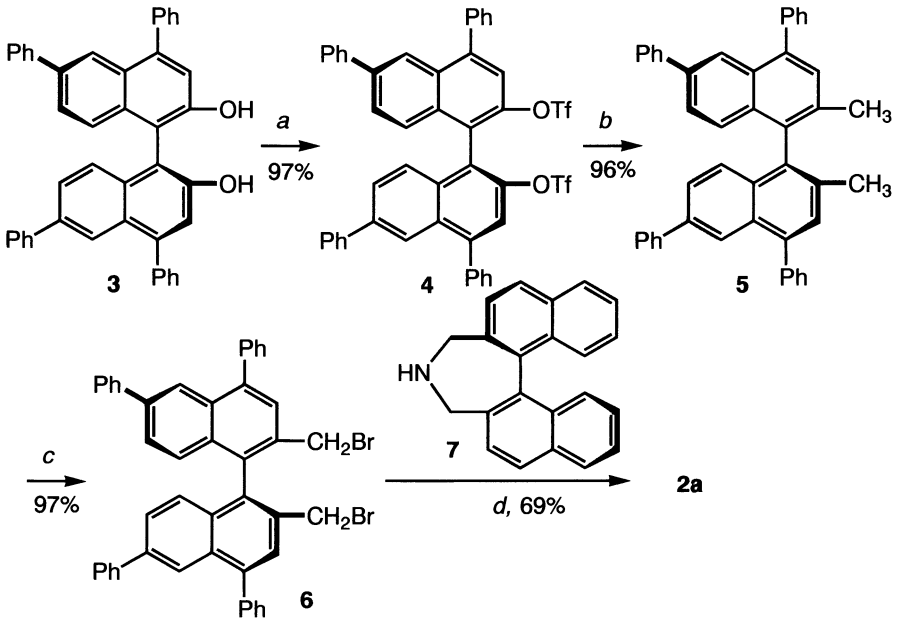
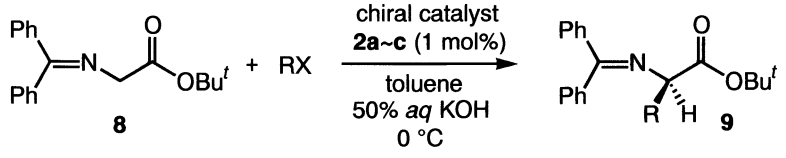


Scheme 1. *Reagents and conditions*: (a) Tf_2O (3 equiv.), Et_3N (3 equiv.), CH_2Cl_2, −78°C to rt; (b) MeMgI (4 equiv.), $NiCl_2(dppp)_2$ (5 mol%), ether reflux; (c) NBS (2.2 equiv.), AIBN (10 mol%), benzene reflux; (d) K_2CO_3 (3 equiv.), MeCN, 50°C.

ester (**8**). For example, reaction of **8** with benzyl bromide in toluene/50% *aqueous* KOH under the influence of 1 mol% of catalyst **2a** at 0°C for 7 h gave rise to benzylation product **9** (R = CH_2Ph) in 90% yield with 91% ee. The absolute configuration of **9** (R = CH_2Ph) was determined to be *R* by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[2] The observed enantioselectivity is rather surprising compared to that (89% ee) using 3,3′-diphenyl-substituted **1b** under similar reaction conditions. Other selected examples are listed in Table 1. With several other alkyl halides, good to high enantioselectivity is observable in the catalytic enantioselective phase transfer alkylation of glycine derivative **8**.

The (*S*,*S*)-4,4′-diphenylbinaphthyl derivative **2b** was found to exhibit similar reactivity and a little bit lower selectivity compared to **2a** in the asymmetric alkylation of glycine derivative **8** (entry 2 versus 1). We also prepared sterically more hindered (*S*,*S*)-4,4′,6,6′-tetrakis(3,5-diphenylphenyl)-binaphthyl analogue **2c** and applied it to the asymmetric alkylation of glycine derivative **8** to furnish the alkylation product **9** with slightly higher enantioselectivity and shorter reaction time (entries 3, 5, 8 and 10). However, the observed enantioselectivity is not as appealing as that with 3,3′-bis(3,5-diphenylphenyl) analogue **1c** (e.g. 98% ee in the asymmetric benzylation of **8** with **1c** under similar phase transfer conditions).

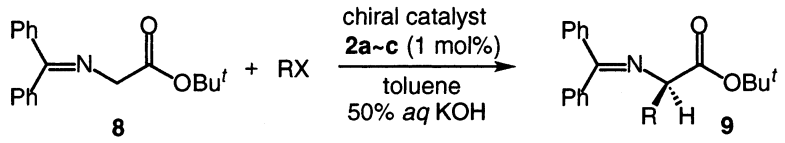


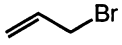
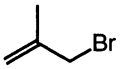
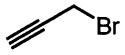
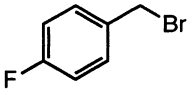
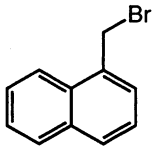
We also prepared (*S*,*S*)-4,4′-diphenylbinaphthyl derivative **2b** in order to examine the substituent effect of 6,6′-diphenyl moieties (Scheme 2). The known (*S*)-4,4′-dibromo-6,6′-dichlorobinaphthyl ether **10**[5] is selectively converted to (*S*)-4,4′-diphenyl-6-6′-dichlorobinaphthyl ether **11** by Suzuki–Miyaura coupling with $PhB(OH)_2$, *aqueous* K_2CO_3 and *catalytic* $Pd(PPh_3)_4$, and 6,6′-dichloro groups are then removed by catalytic hydrogenation with Pd/C and ammonium formate to furnish (*S*)-4,4′-diphenylbinaphthyl ether **12a** which is cleaved with BBr_3 to furnish (*S*)-4,4′-diphenylbinaphthol (**12b**) in 79% overall yield. Transformation of **12b** to **2b** via **12c**, **13**, and **14** was accomplished in a similar manner as described in Scheme 1.

Although elucidation of the effect of 4,4′-diaryl substituents in chiral phase transfer catalyst **2** must await further research, the new finding described herein further expands the potential in the design of new chiral phase transfer catalysts.

A typical experimental procedure is as follows (entry 1 in Table 1): To a mixture of benzophenone imine glycine *tert*-butyl ester (**8**) (148 mg, 0.5 mmol) and chiral catalyst **2a** (4.8 mg, 0.005 mmol) in toluene (3.0 mL)–50% KOH aqueous solution (1.0 mL) was added benzyl bromide (72.1 μL, 0.6 mmol) dropwise at 0°C. The reaction mixture was stirred vigorously at the same temperature for 7 h. The mixture was then poured into

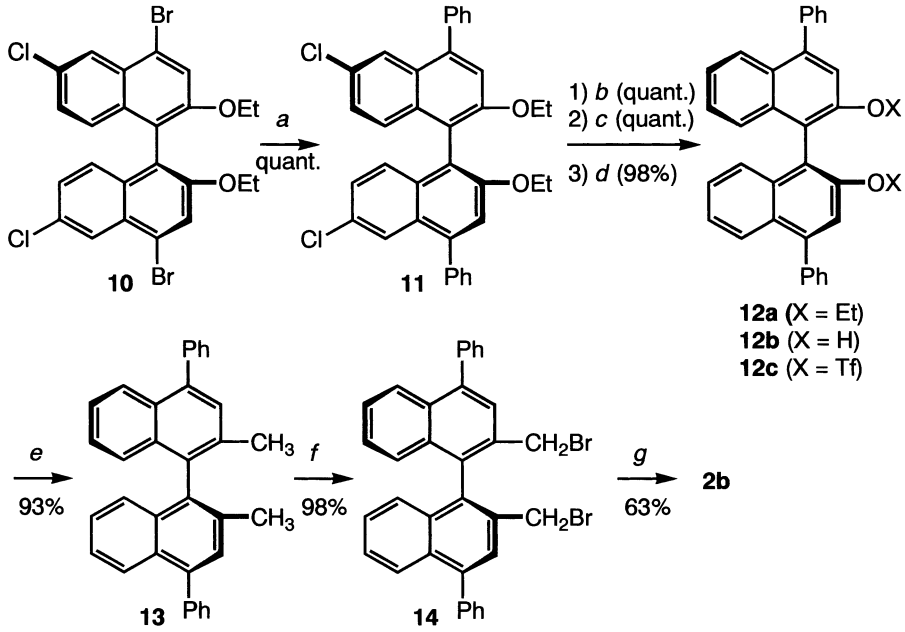
Table 1. Catalytic enantioselective phase transfer alkylation[a]



entry	catalyst	RX	condition (°C, h)	% yield [b]	% ee [c] (config) [d]
1	**2a**	$PhCH_2Br$	0, 7	90	91 (*R*)
2	**2b**		0, 4	92	87 (*R*)
3	**2c**		0, 3	88	96 (*R*)
4	**2a**		0, 8	83	84 (*R*)
5	**2c**		0, 3	92	88 (*R*)
6	**2a**		0, 6	82	74 (*R*)
7	**2a**		0, 5	86	86 (*R*)
8	**2c**		0, 4	92	88 (*R*)
9	**2a**		0, 7	88	88 (*R*)
10	**2c**		0, 2	93	92 (*R*)
11	**2a**		0, 4	88	91 (*R*)
12	**2a**	CH_3CH_2I [e]	0, 24	18	71 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of RX in the presence of 1 mol% of **2** in 50% aqueous KOH/toluene (volume ratio = 1:3) under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity of **9** was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD) with hexane-isopropanol as solvent. [d] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[2] [e] Use of 5 equiv of alkyl halide.

water and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:10 as eluant) gave the alkylation product **9** (R = CH_2Ph) (173.5 mg, 0.45 mmol, 90% yield) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD, hex-



Scheme 2. *Reagents and conditions*: (a) $PhB(OH)_2$ (2.4 equiv.), $Pd(PPh_3)_4$ (3 mol%), aq. K_2CO_3 (2 M), THF reflux; (b) HCO_2NH_4 (16 equiv.), Pd/C (5 mol%), $MeOCH_2CH_2OH$, 60°C; (c) BBr_3 (2 equiv.), CH_2Cl_2, −78°C to rt; (d) Tf_2O (3 equiv.), Et_3N (3 equiv.), CH_2Cl_2, −78°C to rt; (e) MeMgI (9 equiv.), $NiCl_2$(dppp) (5 mol%), ether reflux; (f) NBS (2.2 equiv.), AIBN (10 mol%), benzene reflux; (g) **7**, K_2CO_3 (3 equiv.), MeCN, rt.

ane:isopropanol = 100:1, flow rate = 0.5 mL/min, retention time; 14.8 min (*R*) and 28.2 min (*S*)).

Acknowledgements

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