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TETRAHEDRON: *ASYMMETRY*

Symmetrical 4,4′,6,6′-tetraarylbinaphthyl-substituted ammonium bromide as a new, chiral phase-transfer catalyst

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Abstract—Binaphthyl-modified spiro-type symmetrical phase-transfer catalysts possessing 4,4′,6,6′-tetraaryl substituents are shown to exhibit high asymmetric induction in asymmetric alkylation of benzophenone imine glycine *tert*-butyl ester under ordinary phase-transfer conditions.

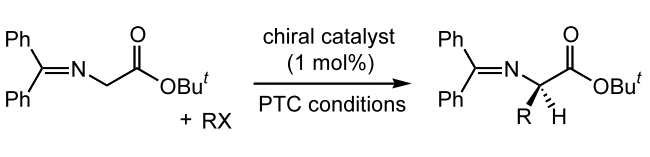
1. Introduction

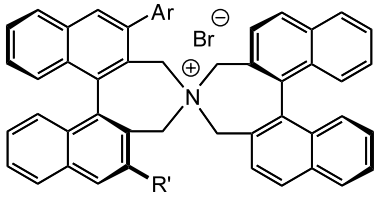
We recently reported the design of binaphthyl-modified, spiro-type chiral ammonium salts of type **1** and their application to the catalytic asymmetric synthesis of various α-alkyl- and α,α-dialkyl-α-amino acids in addition to β-hydroxy-α-amino acids.[1,2] In this part of the study, introduction of 3,3′-diaryl substituents to the parent symmetrical ammonium bromide **1a** was found to be highly effective for obtaining higher enantioselectivity. For example, in a typical asymmetric benzylation of benzophenone imine glycine *tert*-butyl ester, 1 mol% of unsymmetrical catalyst **1b** and **1c** afforded 89% ee (81% yield) and 96% ee (95% yield), respectively, compared to the lower enantioselectivity (79% ee) by using the parent symmetrical **1a**.[2a] From the viewpoint of catalyst design, such an unsymmetrical catalyst **1** requires the independent synthesis of both right-hand and left-hand sides of the molecules as illustrated in Scheme 1. Obviously, preparation of symmetrical ammonium salts of type **2** has a distinct advantage over unsymmetrical **1** (Ar≠H), because synthesis of only one side of the symmetrical catalyst **2** is required. Unfortunately, however, attempted synthesis of symmetrical bis(3,3′-diphenylbinaphthyl-modified) ammnonium salt was found to be totally unsuccessful due to the steric repulsion of such tetraphenyl substituents. Accordingly, we prepared symmetrical 4,4′-diaryl-substituted ammonium salts **3** by mixing 2 equiv. of dibromide **4** and ammonia, and evaluated their chiral efficiency in the asymmetric alkylation of glycine derivative.[3]

2. Results

The requisite catalysts **3a** and **3b** can be prepared as outlined in Schemes 2 and 3. Thus, the known (*S*)-4,4′,6,6′-tetraphenylbinaphthol **5**[4] is transformed with Tf_2O and Et_3N to the corresponding (*S*)-bis-triflate **6** which is susceptible to the Ni-catalyzed cross coupling with MeMgI and catalytic $NiCl_2$(dppp) to furnish (*S*)-bis-methyl derivative **7**. Radical bromination of **7** is effected with NBS and catalytic AIBN as a radical initiator to afford (*S*)-dibromide **4a**. Treatment of **4a** (2 equiv.) with aqueous ammonia in CH_3CN directly gives the desired spiro-type (*S*,*S*)-ammonium bromide **3a**.

We also prepared (*S*)-4,4′-diphenylbinaphthyl derivative **3b** in order to examine the substituent effects of 6,6′-diphenyl moieties (Scheme 3). The known (*S*)-4,4′-





1a (Ar= H), **b** (Ar= Ph), **c** (Ar= β-Np)

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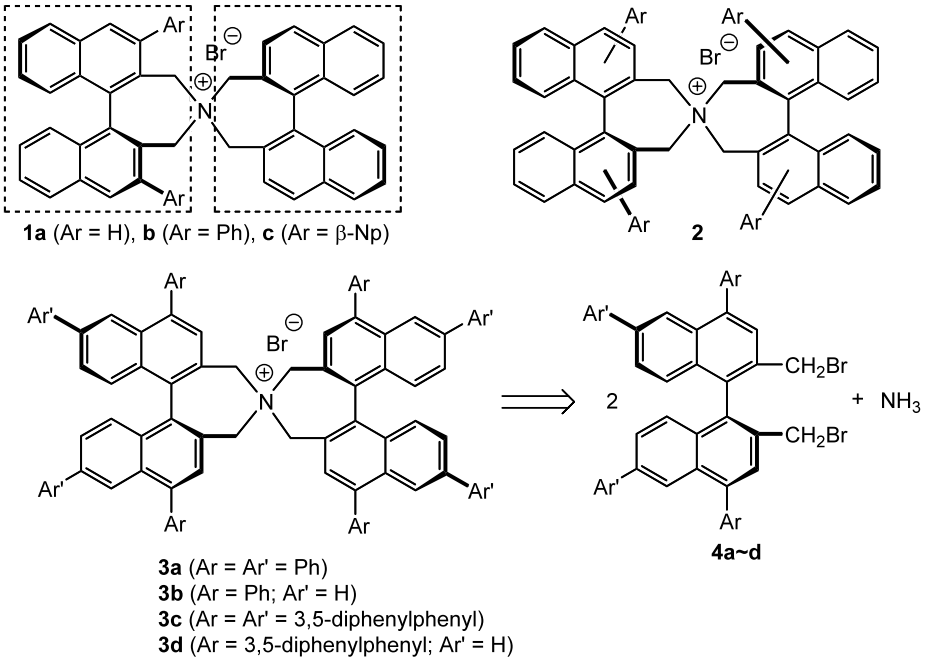
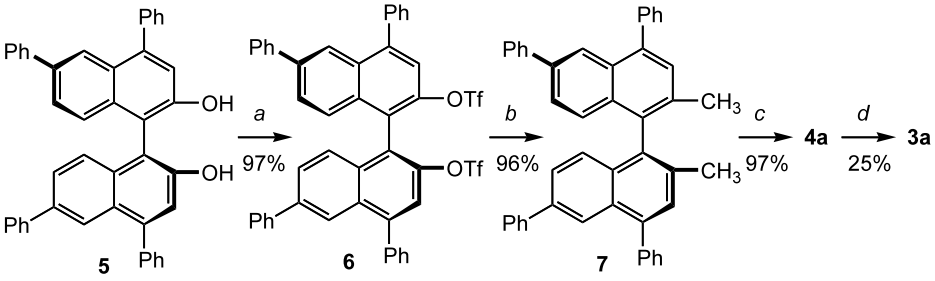
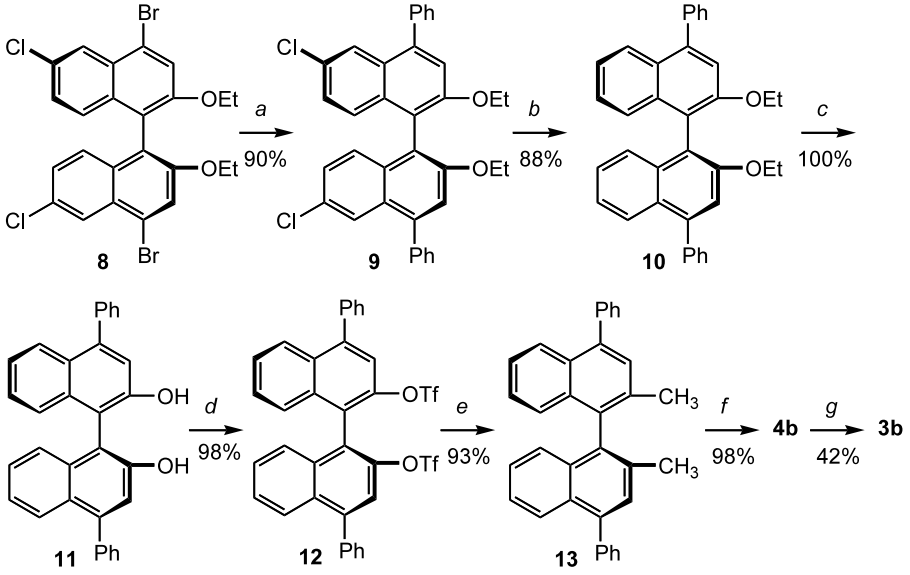


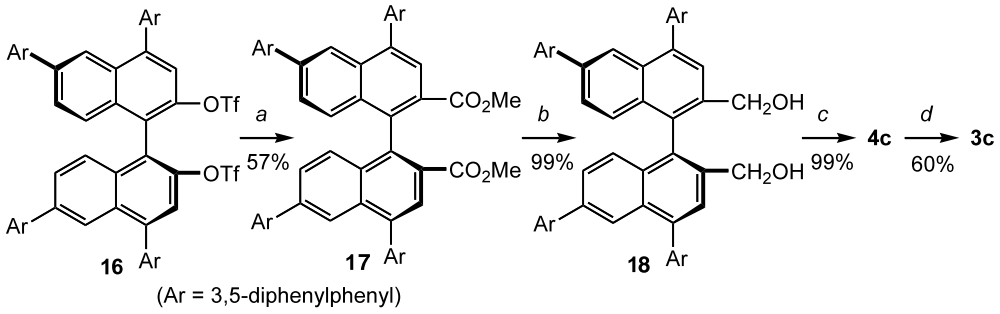
Scheme 1.



Scheme 2. *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) (5 mol%), ether reflux; (c) NBS (2.2 equiv.), AIBN (10 mol%), benzene reflux; (d) 28% aq. NH_3 (4 equiv.), CH_3CN.

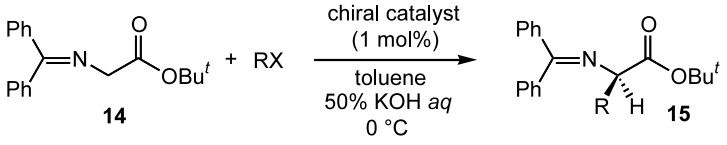


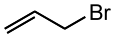
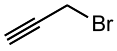
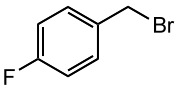
Scheme 3. *Reagents and conditions*: (a) $PhB(OH)_2$ (2.4 equiv.), $Pd(PPh_3)_4$ (3 mol%), aq. K_2CO_3 (2 M), THF reflux; (b) HCO_2NH_4 (16 equiv.), Pd/C (5 mol%), $MeOCH_2CH_2OH$, 60°C; (c) BBr_3 (2 equiv.), CH_2Cl_2, 0°C; (d) Tf_2O (3 equiv.), Et_3N (3 equiv.), CH_2Cl_2, −78°C to rt; (e) MeMgI (4 equiv.), $NiCl_2$(dppp) (5 mol%), ether reflux; (f) NBS (2.2 equiv.), AIBN (10 mol%), benzene reflux; (g) 28% aq. NH_3 (4 equiv.), CH_3CN.



Scheme 4. *Reagents and conditions*: (a) $Pd(OAc)_2$ (15 mol%), dppp (16.5 mol%), *i*-Pr_2NEt (5 equiv.), CO, MeOH/DMSO, 80°C; (b) $LiAlH_4$ (2 equiv.), THF, 0°C; (c) BBr_3 (2 equiv.), CH_2Cl_2, 0°C; (d) 28% aq. NH_3 (4 equiv.), CH_3CN.

Table 1. Catalytic enantioselective phase-transfer alkylation[a]



Entry	Catalyst	RX	Conditions (°C, h)	Yield (%)[b]	% ee[c] (config.)[d]
1	**3a**	$PhCH_2Br$	0, 3.5	85	92 (*R*)
2	**3b**		0, 3.5	82	90 (*R*)
3	**3c**		0, 24	87	97 (*R*)
4	**3d**		0, 6	86	96 (*R*)
5	**3a**		0, 1	81	91 (*R*)
6	**3b**		0, 2	83	87 (*R*)
7	**3c**		0, 20	76	93 (*R*)
8	**3d**		0, 5	91	92 (*R*)
9	**3a**		0, 2	90	94 (*R*)
10	**3b**		0, 4	92	94 (*R*)
11	**3c**		0, 20	83	94 (*R*)
12	**3d**		0, 7	56	95 (*R*)
13	**3a**		0, 3	88	90 (*R*)
14	**3c**		0, 24	91	95 (*R*)
15	**3a**	CH_3CH_2I[e]	0, 24	12	88 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv. of RX in the presence of 1 mol% of **3** in 50% aq. KOH/toluene (volume ratio = 1:3) under the given reaction conditions.

[b] Isolated yield.

[c] Enantiopurity of **15** 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.[2a]

[e] Use of 5 equiv. of alkyl halide.

dibromo-6,6′-dichlorobinaphthyl ether **8**[5] is selectively converted to (*S*)-4,4′-diphenyl-6,6′-dichlorobinaphthyl ether **9** 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 **10** which is cleaved with BBr_3 to furnish (*S*)-4,4′-diphenylbinaphthol **11** in 79% overall yield. Transformation of **11** to **3b** via **12**, **13**, and **4b** was accomplished in a similar manner as described above.

The synthetic potential of these catalysts **3a** and **3b** was evaluated by the asymmetric phase-transfer alkylation of benzophenone imine glycine *tert*-butyl ester **14** under ordinary phase-transfer conditions. Thus,

treatment of protected glycine derivative **14** with benzyl bromide (1.2 equiv.) and 50% aqueous KOH/toluene (volume ratio = 1:3) under the influence of 1 mol% **3a** at 0°C for 3.5 h resulted in formation of α-phenylalanine derivative **15** ($R = CH_2Ph$) in 85% yield with 92% ee.[6] When we use 4,4′-diphenylbinaphthyl derivative **3b**, similar reactivity and selectivity (82% yield; 90% ee) was observed in the asymmetric benzylation of glycine derivative **14**.

Since the observed enantioselectivity is not excellent with **3a** or **3b**, we then prepared 4,4′,6,6′-tetrakis(3,5-diphenylphenyl)binaphthyl analogue **3c** as shown in Scheme 4.[7] Thus, (*S*)-bis-triflate **16** (Ar = 3,5-diphenylphenyl) can be prepared in a similar manner as described in Scheme 2 and Ref. 4, and then converted by catalytic $Pd(OAc)_2$, dppp, *i*-Pr_2NEt, CO (gas), and MeOH to the corresponding (*S*)-dicarboxylic acid methyl ester **17**, which is further reduced with $LiAlH_4$ to give (*S*)-diol **18**. Bromination of **16** with BBr_3 afforded (*S*)-dibromide **4c** which is reacted with aqueous ammonia in CH_3CN to furnish the desired spiro-type (*S*,*S*)-ammonium bromide **3c**. This carbonylation/reduction route is also applicable to the synthesis of **3d**.

The asymmetric benzylation of glycine derivative **14** was effected with new catalysts **3c** and **3d** to furnish the alkylation product **15** ($R = CH_2Ph$) with higher enantioselectivity (96–97% ee) under similar phase-transfer conditions. Other selected examples are also included in Table 1.

In conclusion, we have developed several new and efficient catalysts **3a**–**d**, via a simplified catalyst preparation, for effecting asymmetric phase-transfer alkylation of glycine derivative **14**.

Acknowledgements

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6. The catalyst **3a** was recovered in ~50% yield, suggesting the partial decomposition of **3a** under the phase-transfer conditions. In contrast, catalyst **1** having 3,3-diaryl substituents is stable and gives higher recovery yield than **3**. See Ref. 2c.
7. Because of the difficulty for 4,4′,6,6′-tetrakis(3,5-diphenylphenyl)binaphthyl analogue in radical bromination as shown in Scheme 2, we developed a new synthetic route to **4c** as indicated in Scheme 4.