Molecular Design of a C_2-Symmetric Chiral Phase-Transfer Catalyst for Practical Asymmetric Synthesis of α-Amino Acids

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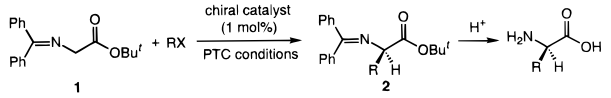
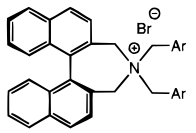
Despite the increasing importance and usefulness of phase transfer catalysis (PTC) in synthetic organic reactions,[1] catalytic asymmetric synthesis utilizing chiral phase-transfer catalysts remains poorly studied.[2−4] Yet, since the pioneering work of O'Donnell et al. in 1989, asymmetric synthesis of α-amino acids by phase-transfer enantioselective alkylation of a prochiral protected glycine derivative **1** using a chiral catalyst has provided an attractive method for the preparation of both natural and unnatural amino acids.[5] Recently, the Corey[6] and Lygo groups[7] independently reported an impressive departure from the previous results in terms of enantioselectivity and general applicability. However, almost all of the elaborated chiral phase-transfer catalysts reported so far have been restricted to *cinchona* alkaloid derivatives, which unfortunately constitutes a major difficulty in rationally designing and fine-tuning catalysts to attain sufficient reactivity and selectivity for various chemical transformations under phase-transfer catalyzed conditions.[3,4] In this paper, we wish to describe a new, rational approach to this subject, i.e., the molecular design of a C_2-symmetric chiral quaternary ammonium salt and its successful application to the highly efficient, catalytic enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base **1** under mild phase-transfer conditions.

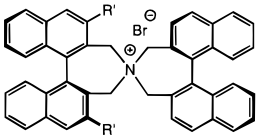


1 **2**

We employed a binaphthyl structure as a basic chiral unit and first synthesized C_2-symmetric chiral quaternary ammonium salts of type **3** from commercially available (*S*)-binaphthol in a six-step sequence as shown in Scheme 1.[8] Evaluation of the potential of the catalyst in the asymmetric phase-transfer alkylation of **1** using 1 mol % of **3a**, benzyl bromide (1.2 equiv), and 50% aqueous KOH/toluene (volume ratio = 1:3.25) at 0 °C for 6 h resulted in a disappointingly small induction (21% ee) with 34% yield of **2** (R = CH_2Ph). Changing the aryl group of the catalyst to α-naphthyl (**3b**) brought only a slight increase of the enantiomeric excess (29% ee). These results prompted us to design structurally more rigid chiral spiro ammonium salts of type **4** which can be readily assembled, also illustrated in Scheme 1.[8] In the presence of 1 mol % of **4a** under otherwise similar reaction conditions, the benzylation of **1** proceeded smoothly at 0 °C to furnish product **2** (R = CH_2Ph) in 73% yield after 6 h and the enantiomeric excess was dramatically improved (79% ee). Noteworthy is the fact that the beneficial effect of 3,3′-bisaryl substituents (R′) of the catalysts on the reactivity as well as on the enantioselectivity was greatly appreciated in this case. For instance, the benzylation of **1** under the influence of **4b** (1 mol %) was completed within 30 min at 0 °C, producing the alkylation product **2** (R = CH_2Ph) in 81% yield, whose enantiomeric purity was determined to be 89% ee. Use of **4c** as catalyst further increased the enantioselectivity to 96% ee (95% yield) for the benzylation.



3a (Ar = Ph), **b** (Ar = α-Np)



4a (R′ = H), **b** (R′ = Ph), **c** (R′ = β-Np)

Table 1 summarizes the results obtained for the alkylation of **1** with various alkyl halides using 1 mol % of catalyst **4c**. Enantioselectivities observed herein generally exceeded 90% ee, indicating the remarkable potential and generality of the present asymmetric system. It should be noted that none of the double alkylation products was obtained under the reaction conditions. The use of 50% NaOH as an aqueous phase brought a decrease of reactivity with similar enantioselectivity (52%, 95% ee for the benzylation at 0 °C for 6 h).

The primary structure of the parent chiral spiro quaternary ammonium salt **4a** was successfully verified by single-crystal X-ray diffraction analysis as shown in Figure 1.[9]

On the basis of the experimental findings as well as X-ray structure of the catalyst **4a**, the transition state in the catalytic enantioselective alkylation can be visualized as shown in Figure 2. The space-filling model of the catalyst **4c** is derived from the structure of **4a**. The conformation of the *E*-enolate of *tert*-butyl glycinate-benzophenone Schiff base **1** makes a good match for the molecular pocket of the chiral catalyst **4c**, and the *si*-face of the enolate can be effectively shielded by the binaphthyl and the β-naphthyl moieties. Consequently, alkyl halides could only approach the *re*-face of the enolate, producing the *R* isomer **2** in accord with the experimental finding.

In conclusion, we introduced a new axis by designing a phase transfer catalyst based on the C_2-symmetric chiral unit and

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(4) Quite recently, Shioiri reported successful results for PTC-catalyzed asymmetric reactions, see: (a) Arai, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2145. (b) Arai, S.; Hamaguchi, S.; Shioiri, T. *ibid.* **1998**, *39*, 2997. (c) Arai, S.; Tsuge, H.; Shioiri, T. *ibid.* **1998**, *39*, 7653. (d) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Chem. Commun.* **1999**, 49.

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(6) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (c) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.

(7) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *ibid.* **1999**, *40*, 1385. (c) Lygo, B. *ibid.* **1999**, *40*, 1389. For a recent impressive application to PTC-catalyzed asymmetric epoxidation, see: Lygo, B.; Wainwright, G. P. *Tetrahedron Lett.* **1998**, *39*, 1599.

(8) For the spectroscopic characterization of the catalysts, see Supporting Information.

(9) The single-crystal of **4a** was obtained by recrystallization from acetonitrile/dichloromethane solvents. Crystal structure data for **4a**: $C_{48}H_{32}N_3Br$, $M_w = 730.70$, orthorhombic, space group $I2_12_12_1$, $a = 14.6723(9)$ Å, $b = 25.127(1)$ Å, $c = 10.8390(5)$ Å, $V = 3996.1(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.214$ gcm^{-3}, $R_1 = 0.077$.

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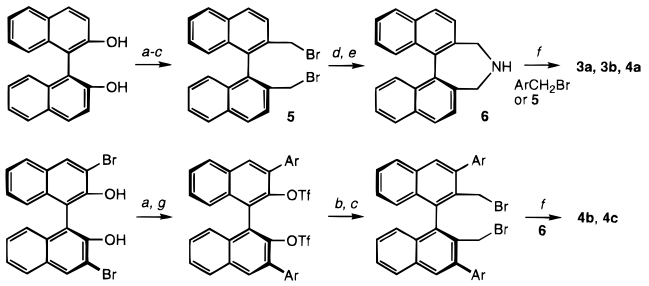
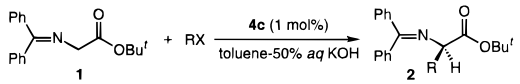
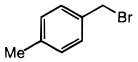
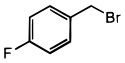
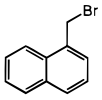
Scheme 1



[a] Tf_2O, Et_3N, CH_2Cl_2. [b]MeMgI, $NiCl_2(PPh_3)_2$, ether. [c]NBS, benzoyl peroxide, cyclohexane. [d]Allylamine, MeCN. [e]$RhCl(PPh_3)_3$, MeCN−H_2O. [f]K_2CO_3, MeOH. [g]$ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_3PO_4, THF.

Table 1. Catalytic Enantioselective Phase-Transfer Alkylation[a]



entry	RX	condition (°C, h)	% yield [b]	% ee [c] (config) [d]
1	$PhCH_2Br$	0, 0.5	95	96 (*R*)
2	CH_3I [e]	0, 8	64	90 (*R*)
3	CH_3CH_2I [e]	0, 10	41	95 (*R*)
4		0, 1	84	94 (*R*)
5		0, 1	82	93 (*R*)
6		0, 1	90	95 (*R*)
7		0, 0.5	80	96 (*R*)
8		0, 1	81	96 (*R*)
9		0, 1.5	60	96 (*R*)

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of RX in the presence of 1 mol % of **4c** in 50% aqueous KOH/toluene (volume ratio = 1:3.25) under the given reaction conditions. [b]Isolated yield. [c]Enantiopurity of **2** was determined by HPLC analysis of the alkylated imine using a chiral column [DAICEL Chiralcel OD (entries 1−6, 8, and 9) and Chiralpak AD (entry 7)] 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.[5] [e]Use of 5 equiv of alkyl halide.

demonstrated its potential in an application to asymmetric synthesis of α-amino acids. Steric and/or electronic manipulation of the catalyst should further enhance the reactivity and selectivity, which obviously emphasizes the unequivocal advantage of our approach for the development of new, yet practical phase-transfer catalyzed enantioselective reaction systems.

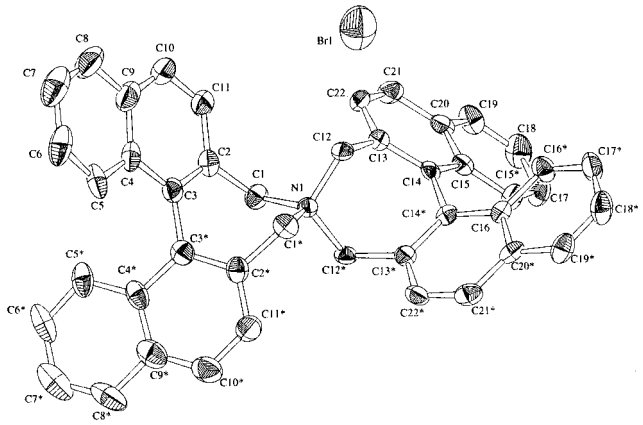


Figure 1. ORTEP diagram of the catalyst **4a**. The solvent molecules (MeCN) and all hydrogen atoms are omitted for clarity.

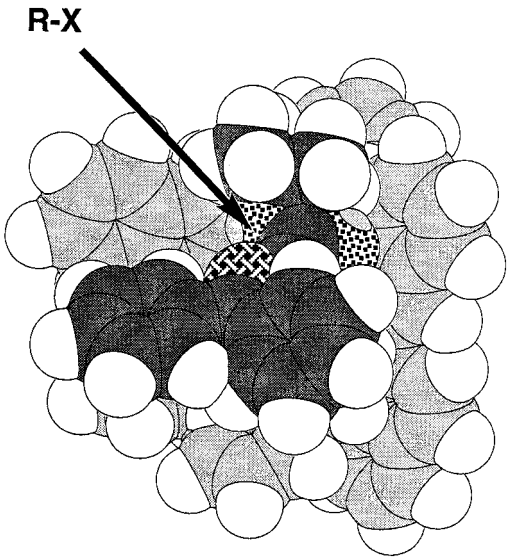


Figure 2. The space-filling model of a plausible transition-state structure of a chiral spiro ammonium *E*-enolate derived from **4c** and **1**.

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Supporting Information Available: Representative experimental procedure as well as spectroscopic characterization of catalyst **4** and all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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