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# Highly enantioselective alkylation of glycine methyl and ethyl ester derivatives under phase-transfer conditions: its synthetic advantage

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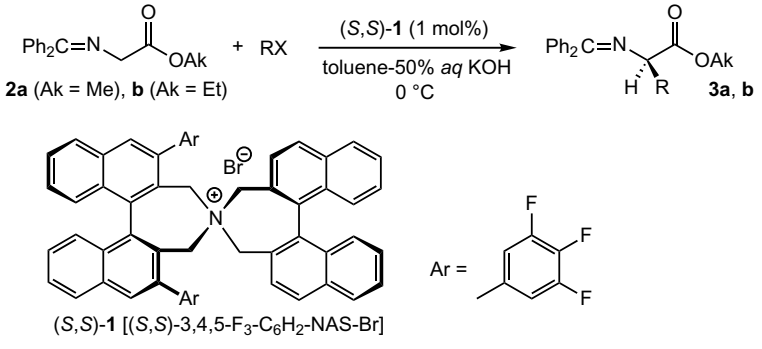
**Abstract**—Phase-transfer alkylation of the benzophenone Schiff base of glycine methyl or ethyl ester (**2**) was found to be catalyzed by 3,4,5-$F_3$-$C_6H_2$-NAS-Br [(*S*,*S*)-**1**] with high efficiency and excellent enantioselectivity. This procedure allows facile derivatization of the resulting alkylation products to other synthetically useful chiral building blocks.


The phase-transfer catalytic asymmetric functionalization of protected glycine derivatives has certainly gained solid success through recent extensive studies on the development of new catalysts and modification of the reaction conditions, providing practical procedures for the asymmetric synthesis of both natural and unnatural α-amino acids.[1] In almost all the reaction systems reported to date, however, use of *tert*-butyl ester seems essential primarily to avoid hydrolysis under the basic conditions and, more importantly, to achieve sufficient enantioselectivity;[1,2] this leads to inevitable difficulty in the substrate preparation and particularly in additional functionalizations. During the course of our efforts on the molecular design of chiral $C_2$-symmetric quaternary ammonium salts and their applications,[1f,3] we fortunately found that the distinct ability of 3,4,5-$F_3$-$C_6H_2$-NAS-Br [(*S*,*S*)-**1**][3b] as a chiral phase-transfer catalyst made it feasible to attain excellent enantioselectivity with glycine methyl and ethyl ester derivatives, providing the first solution to this problem (Scheme 1).

Vigorous stirring of a mixture of **2a**[2,4], benzyl bromide (1.2 equiv), and (*S*,*S*)-**1**[3b] (1 mol%) in toluene–50% KOH aqueous solution (volume ratio = 3:1) at 0 °C for 3 h resulted in formation of the corresponding benzylation product **3a** (R = $CH_2Ph$) in 82% yield and,




**Scheme 1.**

*Keywords*: Alkylation; Chiral quaternary ammonium bromide; Phase-transfer catalysis; Schiff base of glycine ethyl ester.
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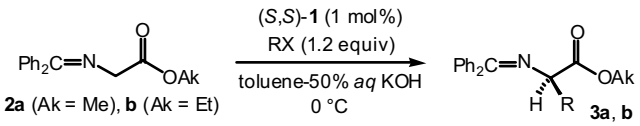
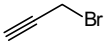
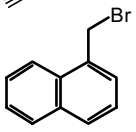
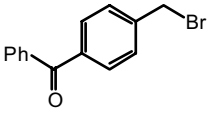
**Table 1.** Catalytic asymmetric alkylation of **2** under phase-transfer conditions with (*S*,*S*)-**1** as catalyst[a]



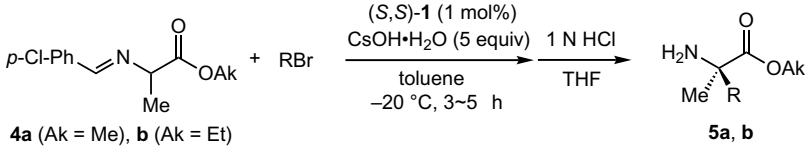

| Entry | Substrate | RX | React time (h) | % Yield[b] | % Ee[c] (config)[d] |
|---|---|---|---|---|---|
| 1 | **2a** | $PhCH_2Br$ | 3 | 82 | 97 (*R*) |
| 2 | **2a** |  | 3 | 72 | 94 (*R*) |
| 3 | **2b** | $PhCH_2Br$ | 2 | 96 | 98 (*R*) |
| 4 | **2b** |  | 2 | 81 | 96 (*R*) |
| 5[e] | **2b** |  | 3 | 72 | 95 (*R*) |
| 6 | **2b** |  | 2 | 99 | 97 (*R*) |
| 7 | **2b** |  | 2 | 99 | 94 (*R*) |
| 8[f] | **2b** | EtI | 3 | 75 | 93 (*R*) |

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of RX in the presence of 1 mol% of (*S*,*S*)-**1** in toluene–50% KOH aqueous solution at 0 °C for the given reaction time.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis of the alkylated imine using a chiral column [DAICEL Chiralcel OD (entries 1 and 3), OD-H (entries 2 and 5–7), Chiralpak AD (entry 4), and AD-H (entry 8)] with hexane–2-propanol as solvent.
[d] Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently prepared.[2a]
[e] With 2 mol% of the catalyst.
[f] Use of 5 equiv of alkyl halide and satd CsOH as a basic phase at −15 °C.

surprisingly, the enantioselectivity reached 97% ee (entry 1 in Table 1). A similar tendency was observed in the allylation of **2a** (entry 2).[5] In addition, the benzylation of glycine ethyl ester-derived **2b**[2,4] furnished **3b** ($R = CH_2Ph$) in 96% yield with 98% ee (entry 3). Encouraged by these initial findings, we examined the alkylation of **2b** with other representative alkyl halides and the results summarized in Table 1 clearly demonstrate the general applicability of the present method.

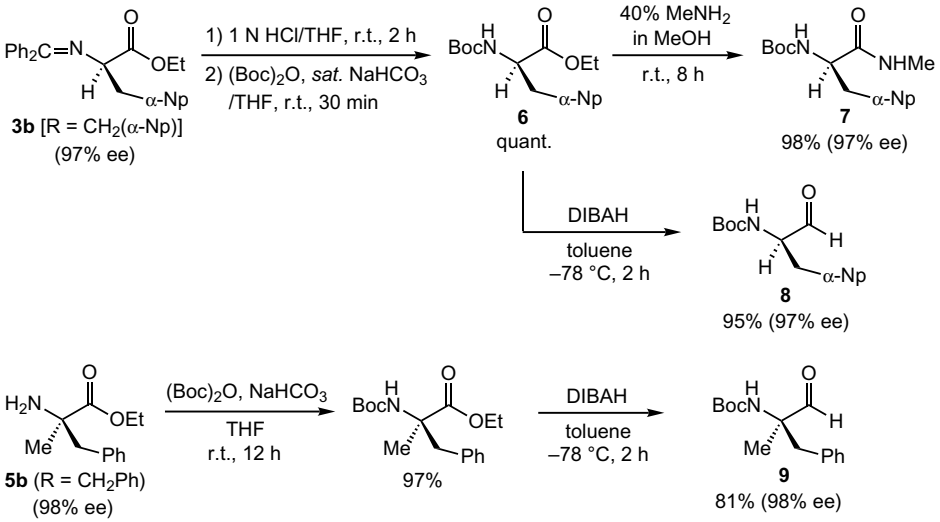
The chiral phase-transfer catalysis of (*S*,*S*)-**1**[3b] was also found to be quite effective for the asymmetric quaternization of the aldimine Schiff base of alanine methyl and ethyl esters (**4a** and **4b**) as exemplified in Scheme 2.[3a] In the benzylation of **4b**, amino ester **5b** ($R = CH_2Ph$) was obtained with 98% ee (82% yield), which was superior to that of **5a** in the reaction with **4a**, and high level of enantioselectivity was also observed when other alkyl halides such as α-naphthylmethyl bromide and *trans*-cinnamyl bromide were employed.

The synthetic advantage of the amenability of glycine methyl and ethyl ester derivatives is quite obvious and highlighted by the well-established transformations as illustrated in Scheme 3. Acidic hydrolysis of the imine moiety of **3b** [$R = CH_2(\alpha\text{-Np})$] and reprotection with




**4a** R = $PhCH_2$ : 81%, 85% ee
**4b** R = $PhCH_2$ : 82%, 98% ee
($\alpha$-Np)$CH_2$ : 89%, 88% ee
$PhCH{=}CHCH_2$ : 80%, 82% ee

**Scheme 2.**




**Scheme 3.**

$(Boc)_2O$ afforded **6** quantitatively, which was readily transformed into the corresponding secondary amide **7** by simple treatment with excess methyl amine in methanol and α-amino aldehyde **8** with DIBAH in toluene,[6] respectively, without loss of enantiomeric excesses. Similarly, optically active α,α-dialkyl-α-amino ester **5b** ($R = CH_2Ph$) can be converted to the corresponding stereochemically stable α-amino aldehyde **9** in excellent chemical yield.[6,7]

In summary, we have shown that the efficient chiral phase-transfer catalysis of (*S*,*S*)-**1** enables highly enantioselective alkylation of methyl and ethyl esters of N-protected α-amino acids under mild conditions, greatly expanding the scope of this well-elaborated asymmetric methodology. Facile conversion of the resulting α-alkylated α-amino esters to the corresponding optically active α-amino amides and aldehydes represents the usefulness of this method.

## Acknowledgements

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## References and notes

1. For recent reviews, see: (a) Shioiri, T. In *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997, Chapter 14; (b) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; 2nd ed.; Wiley-VCH: New York, 2000, Chapter 10; (c) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, 2000; p 123; (d) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689; (e) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3; (f) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
2. Effect of ester group on the enantioselectivity has been documented. See: (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; (b) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277, See also Ref. 3b.
3. (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228; (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139; (c) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576; See also: (d) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519; (e) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339; (f) Ooi, T.; Doda, K.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273; (g) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716; (h) Ooi, T.; Uematsu, Y.; Maruoka, K. *Adv. Synth. Catal.* **2002**, *344*, 288; (i) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551; (j) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640; (k) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542; (l) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 579; (m) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796.
4. **2a** and **2b** have often been employed in the transition metal-catalyzed asymmetric allylic alkylations. For recent selected examples, see: (a) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933; (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256; (c) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197.
5. The 3,4,5-trifluorophenyl group as 3,3′-substituents (Ar) is crucial to attain excellent level of enantioselectivity as demonstrated by the following results of the allylation of **2a**; Ar = β-Np: 91%, 85% ee (0 °C, 1 h); Ar = 3,5-$Ph_2$-$C_6H_3$: 87%, 92% ee (0 °C, 1 h). This tendency is similar to that observed with *tert*-butyl glycinate benzophenone Schiff base [**2** (Ak = *t*-Bu)][3b].
6. For the vast synthetic utility of optically active α-amino aldehydes, see: (a) Tramontini, M. *Synthesis* **1982**, 605; (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, 149; (c) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935; (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835;

(e) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108.

7. Complete preservation of the enantiomeric excess was confirmed by the direct HPLC analysis for **7** and **9**. **7**: DAICEL Chiralcel OD, $\lambda = 300$ nm, hexane/EtOH = 50:1, flow rate = 0.5 mL/min, retention time: 29.6 min (*R*), 32.8 min (*S*); **9**: DAICEL Chiralcel OJ, $\lambda = 254$ nm, hexane/*i*-PrOH = 10:1, flow rate = 0.5 mL/min, retention time: 11.3 min (*R*), 12.3 min (*S*). The optical purity of **8** was determined after conversion to the corresponding protected α-amino alcohol with $NaBH_4$/MeOH; DAICEL Chiralpak AD-H, $\lambda = 300$ nm, hexane/EtOH = 15:1, flow rate = 0.5 mL/min, retention time: 22.4 min (*S*), 29.7 min (*R*).